PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2016/026655	08.04.2016	08.04.2015

International Patent Classification (IPC) or both national classification and IPC
INV. C07K14/725 C07K16/28 C12N5/0783 ADD. A61K39/00

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Offermann, Stefanie Telephone No. +49 89 2399-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2016/026655

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☒ furnished subsequent to the international filing date for the purposes of international search only:

      ☒ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 45-53

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 45-53

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-44

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-35, 39-41, 43, 44
	No:	Claims	1-4, 36-38, 42
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-44
Industrial applicability (IA)	Yes:	Claims	1-44
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

D1 WO 2014/130635 A1 (NOVARTIS AG [CH]; UNIV PENNSYLVANIA [US]; BROGDON JENNIFER [US]; GILL) 28 August 2014 (2014-08-28)

D2 Marco Ruella: "Novel Chimeric Antigen Receptor T Cells for the Treatment of CD19-Negative Relapses Occurring after CD19-Targeted Immunotherapies", Blood Journal 124, 4 December 2014 (2014-12-04), page 966, XP055291040, Retrieved from the Internet: URL:http://www.bloodjournal.org/content/124/21/966

D3 US 2014/271635 A1 (BROGDON JENNIFER [US] ET AL) 18 September 2014 (2014-09-18)

D4 KEICHIRO MIHARA ET AL: "Synergistic and persistent effect of T-cell immunotherapy with anti-CD19 or anti-CD38 chimeric receptor in conjunction with rituximab on B-cell non-Hodgkin lymphoma", BRITISH JOURNAL OF HAEMATOLOGY, vol. 151, no. 1, 1 October 2010 (2010-10-01), pages 37-46, XP055086001

D5 US 2014/099309 A1 (POWELL JR DANIEL J [US] ET AL) 10 April 2014 (2014-04-10)

D6 WO 2013/123061 A1 (SEATTLE CHILDREN S HOSPITAL D B A SEATTLE CHILDREN S RES INST [US]) 22 August 2013 (2013-08-22)

D7 Anonymous: "EP Vantage - ASH - Novartis, Juno, June and Rosenberg steal the T-cell show", EP vantage, 9 December 2014 (2014-12-09), XP055291048, Retrieved from the Internet: URL:http://epvantage.com/Universal/View.aspx?type=Story&id=546429&isEPVantage=yes

D8 W. HASO ET AL: "Anti-CD22-chimeric antigen receptors targeting B cell precursor acute lymphoblastic leukemia", BLOOD, 14 December 2012 (2012-12-14), XP055048750

Re Item IV

Lack of unity of invention

1 This Authority is of the opinion that the present application lacks unity, the following 4 (groups of) inventions have been identified:

I Claims 1-44 (all completely) related to means and methods for treating diseases linked with the (former) expression of CD19. Provided are therapies based on a combination of a CAR binding CD19 (CD19 CAR) with B-cell inhibitors, such as inhibitors (preferably CARs) binding to CD20 or CD22. Provided are as well therapies using B-cell inhibitors for treating patients who do not, only partially or not anymore respond to a CD19-inhibitor.

II Claim 45-47 (completely) related to methods of treating DLBCL by CD19 CAR expressing cells or a combination of CD19 CAR expressing cells and a PD1- or PD-L1-inhibitor

III Claims 48-50 (all completely) related to certain CD20-CARs, nucleic acid molecules encoding them and methods for using them in therapy

IV Claims 51-53 (all completely) related to certain CD22-CARs, nucleic acid molecules encoding them and methods for using them in therapy.

1.1 The reasons why said inventions are not so linked by a common inventive concept are as follows: **D1** (WO2014130635) discloses CD123-CARs and methods for using them in treatment of diseases associated with expression of CD123, in particular wherein the patient has previously received treatment with CD19 CAR and experienced a relapse with said anti-CD19-therapy (D1, claims 1, 91, 98-100). **D2** (Ruella et al., 2014) similarly describes CART (CAR-T-cells) targeting CD123 (CART123) for treating CD19-negative relapses after CD19 CAR-therapy. **D3** (US2014271635) discloses CD19 CARs comprising one of the sequences of present claim 14, *i.e.* any of SEQ ID NOs:1-12 of the present application. For example SEQ ID NO:1 of D3 corresponds 100% to SEQ ID NO:1 of the present application. D3 further discloses table 2 which comprises nearly all sequences presented in table 2 of the present application (see claims 12, 13 of the present application). D3 proposes to administer the CD19 CAR therapy following a B-cell ablative therapy, such as rituxan reacting with CD20. D3 also discloses the combination of the CD19 CAR therapy with *e.g.* a PD1-inhibitor (D3, claim 1, §337, 339). **D4** (Keichiro et al., 2010) describes the combination of CD19-CAR with rituximab, another CD20-inhibitor, for treating B-cell non-Hodgkin lymphoma. **D5** (US2014099309) discloses the combination of CARs targeting CD19, CD20, CD22 and ROR1; also compositions comprising the encoding nucleic acids and cells comprising the CARs are disclosed (D5, §186, claims 1, 11). **D6** (WO2013123061) discloses bispecific anti-CD19xCD20-CARs, T-cells transfected therewith and their use in therapy, such as treatment of cancer (D6, claims 1, 17, 98). **D7** (internet citation) relates to treatment with CD22 CARs, in particular in patients who relapsed after CD19 CAR-therapy, either due to loss of target cells or so-called CD19-positive relapses where levels of CART cells wane. **D8** (Haso et al., 2013) discloses CD22 CARs and

refers as well to CD19-negative relapses after treatment with blinatumomab (CD3/CD19 antibody). Improvement of CAR therapy by targeting multiple antigens is proposed.

1.2 The only concept linking the above identified inventions together are means and methods for treatment based on chimeric antigen receptors (CARs). This concept is widely known from the prior art, D1-D8 are only cited as examples. Thus, the technical problem underlying the present application is the provision of further means and methods for treatment based on CARs and CART-cells. This problem has individually been solved by the above identified inventions each characterized by its special technical feature, such as at least the use of a CD19 CAR (see argumentation with regard to claim 1 below) or any kind of B-cell inhibitor in diseases associated with expression of CD19 for invention group I, the treatment of DLBCL with CD19 CAR plus optionally additional agents for invention group II or the particular sequences for inventions III and IV. No further technical feature could be identified linking the individual inventions together. Consequently, there is a lack of unity and the different inventions not belonging to a common inventive concept are formulated as the different subjects on the communication pursuant to Article 17(3) PCT, each of the inventions relating to a different solution to the given problem. Search as well as the present opinion have, thus, been restricted to the first invention. Please consider the possibility that separate search strategies may lead to overlapping sets of documents. This can only be judged based on hindsight after the search effort has been spent and does not imply that such an additional search has not been cumbersome and did not require considerable additional effort.

1.3 It is further noted that in particular the first invention is considered to be a group of inventions, *i.e.* invention I/1 (claims 1, 2, 36-38, 42) related (mainly, for exception see below) to a combination of CD19 CAR with a B-cell inhibitor (not to forget the fact that CD19 is likewise a B-cell antigen) and invention I/2 (claims 3, 4) related to the use of a B-cell inhibitor in treating a patient who does not, only partially does or does not anymore respond to a CD19-inhibitor. In this case, the B-cell inhibitor, such as CD20 CAR might also be administered alone, the claims even do not exclude the probability that the fact of non-responding has *e.g.* be identified by genetic analysis. Thus, a further objection as to lack of unity might be raised in any upcoming phase.

1.3.1 For the sake of completeness, it is added that claim 1 also encompasses the administration of a cell expressing CD19 CAR alone: on the one hand in a patient group which has received a B-cell inhibitor, on the other hand due to the expression "*is about to receive one or more B-cell inhibitors*" which allows even the broad interpretation of claim 1 to relate to the use of only a cell expressing a CD19 CAR for treating diseases associated with expression of CD19.

1.4 Finally, the following is added: The application relates to a plurality of inventions, or groups of inventions, in the sense of Rule 13.1 PCT. They have been divided as defined above. If the Applicant pays additional fees for one (or more) not yet searched group(s) of invention(s), then the further search(es) may reveal further prior art that gives evidence of a further lack of unity 'a posteriori' within one (or more) of the not yet searched group(s). In such a case only the first invention in this (each of these) group(s) of inventions, which is considered to lack unity of invention, will be the subject of a search. No further invitation to pay further additional fees will be issued. This is because Article 17(3)(a) PCT stipulates that the ISA shall establish the International Search Report on those parts of the international application which relate to the invention first mentioned in the claims ('main invention') and for those parts which relate to inventions in respect of which the additional fees were paid. Neither the PCT nor the PCT guidelines provide a legal basis for further invitations to pay further additional search fees (W17/00, point 11 and W1/97, points 11-16). In such a case the non-searched claims may be the subject of one or more divisional applications after the application has entered the regional phase before the EPO (see W18/07, point 26).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Summary

The present first invention is related to means and methods for treating diseases linked with the (former) expression of CD19. Provided are therapies based on a combination of a CAR binding CD19 (CD19 CAR) with B-cell

inhibitors, such as inhibitors, preferably CARs, binding to CD20 or CD22. Provided are as well therapies using B-cell inhibitors for treating patients who do not, only partially or not anymore respond to a CD19-inhibitor.

2 Remark

Claims 2, 4 (and any claim dependent thereon) and claims 45-47, 50, 53 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT.

3 Novelty and clarity, inventive step

3.1 The subject-matter of at least claims 1-4, 36-38 and 42 cannot be considered novel in view of at least one of D1-D8. The respective dependent claims are likewise not considered novel and/or inventive in view of said documents, e.g. with regard to claims 12-14 it is referred to D3 (Article 33(2)/(3) PCT)

3.2 With regard to invention group 1, the present application discloses *e.g.* the fact that i) in relapsed ALL cancer patient, several B-antigens were expressed, including CD19, CD22, CD123 (Ex. 14), ii) almost all patient who became CD19-negative remained both CD22 and CD123-positive (Ex. 15), iii) the combination of anti-CD123 and anti-CD19 CAR T-cells is useful for the treatment and prevention of antigen-loss relapse (Ex. 17), iv) bicistronic expression of CD19 and CD123 CAR had a superior anti-leukemia effect compared to single CART treatment and pooled CART cells (Ex. 22); v) CART22 is effective against CD19-negative B-ALL in an animal model (Ex. 23). Thus, e.g. no other B-cell inhibitors than CARs were analysed, no data have been provided with regard to inhibitors to antigens other than CD20, CD22 and CD123, nothing has been shown with regard to CD19-negative diseases which are not negative after CD19 CAR treatment, *i.e* due to loss of the antigen (which is, however, also included in e.g. claim 3), no data are provided with regard to patient groups having received a B-cell inhibitor and are now treated with a CD19 CAR. Thus, in this regard, the technical problem cannot be considered to be solved (Article 33(3) PCT).

3.3 At present, starting *e.g.* from D5 as closest prior art for claims 15-21 which are directed to particular CD20/CD22/CD123 CARs, the difference is, presently, considered to be the sequence of the CARs. No particular effect can be linked to this difference. Thus, the technical problem is formulated as

the provision of further compositions for treating *e.g.* cancer using a combination of different CARs directed against different antigens of the cancer cells. The solution are the particular sequences provided which is considered as an arbitrary selection out of a huge pool of different possibilities (Article 33(3) PCT).

3.4 It is generally noted that the whole concept underlying the first invention group was known from the prior art, *i.e.* the fact that patients relapse with CD19-negative cancer after treatment with anti-CD19-CARs and that, thus, the targeting of multiple antigens is advantageous.

Re Item VI

Certain documents cited

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2016028896	25.2.2016	19.8.15	19.8.14
WO2016102965	30.6.16	23.12.15	24.12.14
WO2015075468	28.5.15	21.11.14	21.11.13

Re Item VIII

Certain observations on the international application

1 Claim 1 also also encompasses the administration of a cell expressing CD19 CAR alone: on the one hand in a patient group which has received a B-cell inhibitor, on the other hand due to the expression "*is about to receive one or more B-cell inhibitors*" which allows even the broad interpretation of claim 1 to relate to the use of a cell expressing a CD19 CAR only for treating diseases associated with expression of CD19 (Article 6 PCT).

2 The term "relapser" as used in claim 3 is unclear.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 October 2016 (13.10.2016)

WIPO | PCT

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(51) **International Patent Classification**:
C07K 14/725 (2006.01) *C12N 5/0783* (2010.01)
C07K 16/28 (2006.01) *A61K 39/00* (2006.01)

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(25) **Filing Language**: English

(26) **Publication Language**: English

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62/144,639	8 April 2015 (08.04.2015)	US
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62/207,255	19 August 2015 (19.08.2015)	US
62/263,423	4 December 2015 (04.12.2015)	US

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(74) **Agents**: **COLLAZO, Diana, M.** et al.; Lando & Anastasi, LLP, Riverfront Office Park, One Main Street, Suite 1100, Cambridge, MA 02142 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) **Date of publication of the international search report**:
10 November 2016

WO 2016/164731 A3

(54) **Title**: CD20 THERAPIES, CD22 THERAPIES, AND COMBINATION THERAPIES WITH A CD19 CHIMERIC ANTIGEN RECEPTOR (CAR) - EXPRESSING CELL

(57) **Abstract**: The invention provides compositions and methods for treating diseases associated with expression of CD19, e.g., by administering a recombinant T cell comprising the CD19 CAR as described herein, in combination with one or more B-cell inhibitors, e.g., inhibitors of one or more of CD1O, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a. The disclosure additionally features novel antigen binding domains and CAR molecules directed to CD20 and CD22, and uses, e.g., as monotherapies or in combination therapies. The invention also provides kits and compositions described herein.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
N2067-7072WO(PAT056		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2016/026655	8 April 2016 (08-04-2016)	8 April 2015 (08-04-2015)
Applicant		
NOVARTIS AG		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 8 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☒ **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant
      ☐ as selected by this Authority, because the applicant failed to suggest a figure
      ☐ as selected by this Authority, because this figure better characterizes the invention
   b. ☒ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/026655

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [ ] forming part of the international application as filed:

      [ ] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [X] furnished subsequent to the international filing date for the purposes of international search only:

      [X] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/026655

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-44

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/026655

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/725 C07K16/28 C12N5/0783
ADD. A61K39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/130635 A1 (NOVARTIS AG [CH]; UNIV PENNSYLVANIA [US]; BROGDON JENNIFER [US]; GILL) 28 August 2014 (2014-08-28)	3-35
Y	claims 1, 91, 98-100	1,2, 36-44
	----- -/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 July 2016	05/10/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Offermann, Stefanie

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Marco Ruella: "Novel Chimeric Antigen Receptor T Cells for the Treatment of CD19-Negative Relapses Occurring after CD19-Targeted Immunotherapies", Blood Journal 124, 4 December 2014 (2014-12-04), page 966, XP055291040, Retrieved from the Internet: URL:http://www.bloodjournal.org/content/124/21/966 [retrieved on 2016-07-25]	3-35
Y	the whole document	1,2, 36-44

X	US 2014/271635 A1 (BROGDON JENNIFER [US] ET AL) 18 September 2014 (2014-09-18)	1,2,5-35
Y	paragraphs [0337], [0339]; claim 1; table 2; sequences 1-12	3,4, 36-44

X	KEICHIRO MIHARA ET AL: "Synergistic and persistent effect of T-cell immunotherapy with anti-CD19 or anti-CD38 chimeric receptor in conjunction with rituximab on B-cell non-Hodgkin lymphoma", BRITISH JOURNAL OF HAEMATOLOGY, vol. 151, no. 1, 8 June 2010 (2010-06-08), pages 37-46, XP055086001, ISSN: 0007-1048, DOI: 10.1111/j.1365-2141.2010.08297.x	1,2,5-36
Y	the whole document	3,4, 36-44

X	US 2014/099309 A1 (POWELL JR DANIEL J [US] ET AL) 10 April 2014 (2014-04-10)	1,2,5-44
Y	paragraph [0186]; claims 1, 11	3,4

X	WO 2013/123061 A1 (SEATTLE CHILDREN S HOSPITAL D B A SEATTLE CHILDREN S RES INST [US]) 22 August 2013 (2013-08-22)	1,2,5-44
Y	claims 1, 17,98	3,4

X	Anonymous: "EP Vantage - ASH - Novartis, Juno, June and Rosenberg steal the T-cell show", EP vantage, 9 December 2014 (2014-12-09), XP055291048, Retrieved from the Internet: URL:http://epvantage.com/Universal/View.aspx?type=Story&id=546429&isEPVantage=yes [retrieved on 2016-07-25]	3-35
Y	the whole document	1,2, 36-44

	-/--	

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	W. HASO ET AL: "Anti-CD22-chimeric antigen receptors targeting B cell precursor acute lymphoblastic leukemia", BLOOD, 14 December 2012 (2012-12-14), XP055048750, ISSN: 0006-4971, DOI: 10.1182/blood-2012-06-438002	3-35
Y	the whole document	1,2, 36-44

T	E. ZAH ET AL: "T Cells Expressing CD19/CD20 Bispecific Chimeric Antigen Receptors Prevent Antigen Escape by Malignant B Cells", CANCER IMMUNOLOGY RESEARCH, vol. 4, no. 6, 8 April 2016 (2016-04-08), pages 498-508, XP055290967, US ISSN: 2326-6066, DOI: 10.1158/2326-6066.CIR-15-0231	

X,P	WO 2016/028896 A1 (NOVARTIS AG [CH]; UNIV PENNSYLVANIA [US]; BROGDON JENNIFER [US]; GILL) 25 February 2016 (2016-02-25) claims 1-102; examples 1-16	1-44

E	WO 2016/102965 A1 (UCL BUSINESS PLC [GB]; AUTOLUS LTD [GB]) 30 June 2016 (2016-06-30) claims 1-44; figures 1-17; example 1	1-44

X,P	WO 2015/075468 A1 (UCL BUSINESS PLC [GB]) 28 May 2015 (2015-05-28) claims 1-27; examples 1-14	1-44

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/026655

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014130635 A1	28-08-2014	EP 2958942 A1	30-12-2015
		TW 201446794 A	16-12-2014
		US 2014322212 A1	30-10-2014
		UY 35340 A	30-09-2014
		WO 2014130635 A1	28-08-2014
US 2014271635 A1	18-09-2014	AU 2014236098 A1	17-09-2015
		CA 2907100 A1	25-09-2014
		CN 105392888 A	09-03-2016
		EP 2970482 A1	20-01-2016
		JP 2016514462 A	23-05-2016
		KR 20150132850 A	26-11-2015
		SG 11201506603P A	29-09-2015
		TW 201512222 A	01-04-2015
		US 2014271635 A1	18-09-2014
		UY 35468 A	31-10-2014
		WO 2014153270 A1	25-09-2014
US 2014099309 A1	10-04-2014	US 2014099309 A1	10-04-2014
		WO 2014055657 A1	10-04-2014
WO 2013123061 A1	22-08-2013	AU 2013221672 A1	07-08-2014
		CA 2861491 A1	22-08-2013
		EP 2814846 A1	24-12-2014
		HK 1205144 A1	11-12-2015
		JP 2015513394 A	14-05-2015
		US 2015038684 A1	05-02-2015
		WO 2013123061 A1	22-08-2013
WO 2016028896 A1	25-02-2016	TW 201617367 A	16-05-2016
		US 2016068601 A1	10-03-2016
		WO 2016028896 A1	25-02-2016
WO 2016102965 A1	30-06-2016	NONE	
WO 2015075468 A1	28-05-2015	AU 2014351557 A1	26-05-2016
		AU 2014351558 A1	26-05-2016
		CA 2929984 A1	28-05-2015
		CA 2930215 A1	28-05-2015
		CN 105792840 A	20-07-2016
		EP 3071221 A1	28-09-2016
		EP 3071222 A1	28-09-2016
		EP 3071223 A1	28-09-2016
		KR 20160085347 A	15-07-2016
		KR 20160085348 A	15-07-2016
		SG 11201603479T A	30-05-2016
		SG 11201603484P A	30-05-2016
		WO 2015075468 A1	28-05-2015
		WO 2015075469 A1	28-05-2015
		WO 2015075470 A1	28-05-2015

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-44

   means and methods for treating diseases linked with the (former) expression of CD19. Provided are therapies based on a combination of a CAR binding CD19 (CD19 CAR) with B-cell inhibitors, such as inhibitors, preferably CARs, binding to CD20 or CD22. Provided are as well therapies using B-cell inhibitors for treating patients who do not, only partially or not anymore respond to a CD19-inhibitor.

   ---

2. claims: 45-47

   method of treating DLBCL by CD19 CAR expressing cells or a combination of CD19 CAR expressing cells and a PD1- or PD-L1-inhibitor

   ---

3. claims: 48-50

   certain CD20-CARs, nucleic acid molecules encoding them and methods for using them in therapy

   ---

4. claims: 51-53

   certain CD22-CARs, nucleic acid molecules encoding them and methods for using them in therapy.

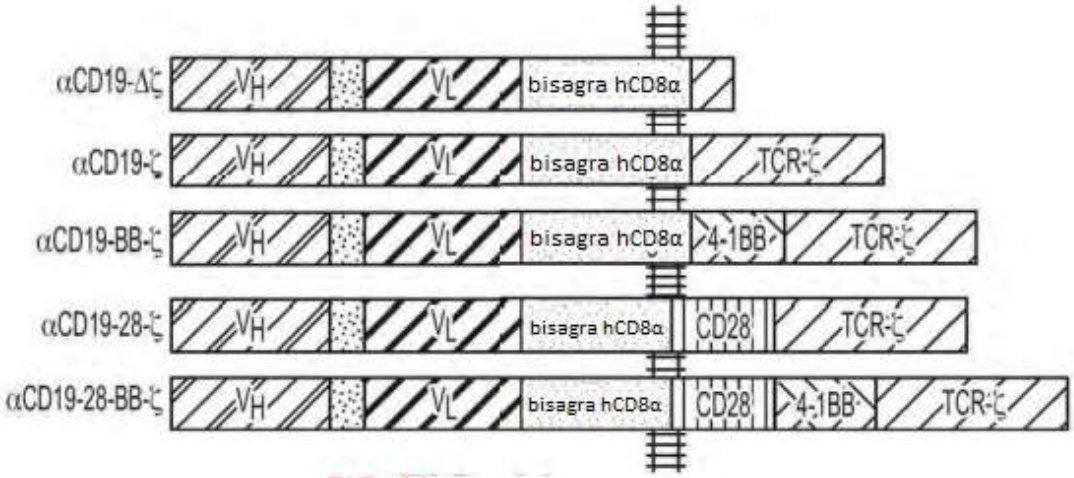

αCD19-Δζ
VH
VL
bisagra hCD8α
αCD19-ζ
TCR-ζ
αCD19-BB-ζ
4-1BB
αCD19-28-ζ
CD28
αCD19-28-BB-ζ

FIG. 1A

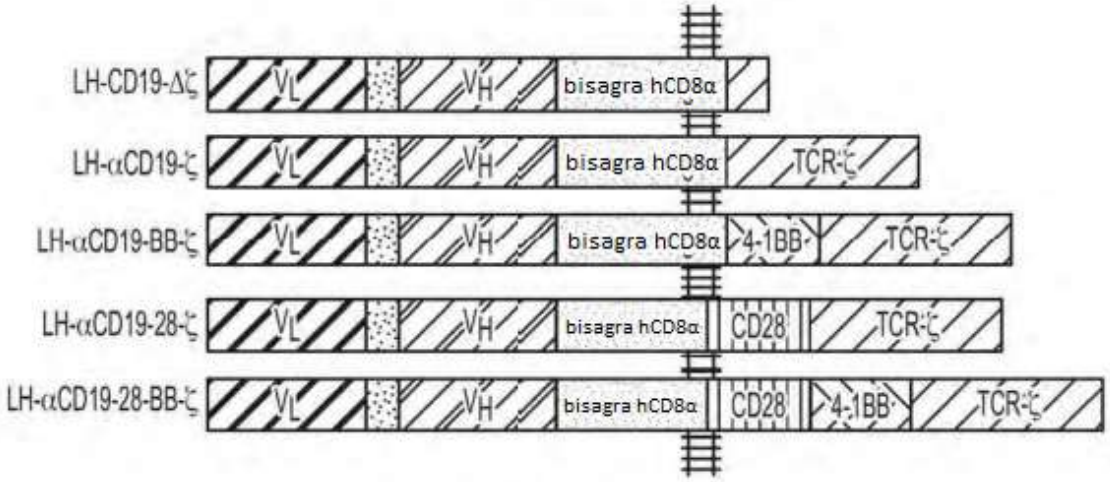

LH-CD19-Δζ
VL
VH
bisagra hCD8α
LH-αCD19-ζ
TCR-ζ
LH-αCD19-BB-ζ
4-1BB
LH-αCD19-28-ζ
CD28
LH-αCD19-28-BB-ζ

FIG. 1B

FIG. 2

Tinción de CD19

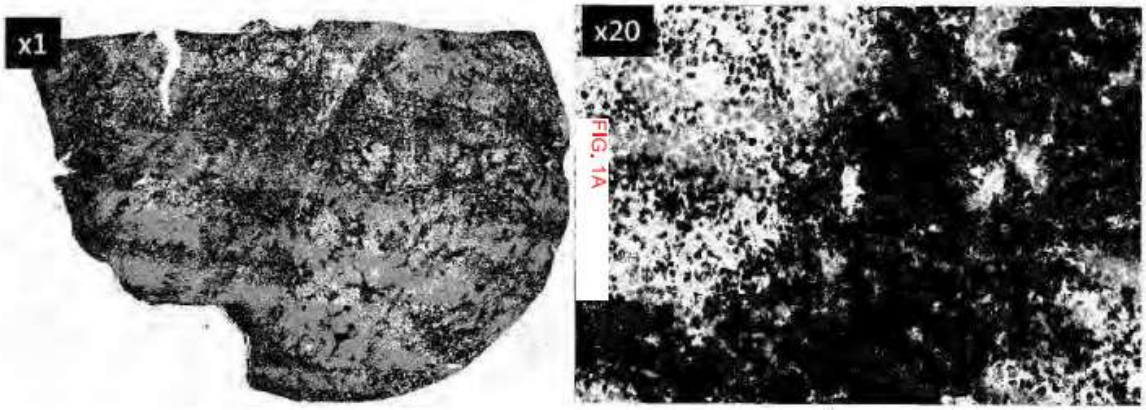


FIG. 1A

FIG. 3

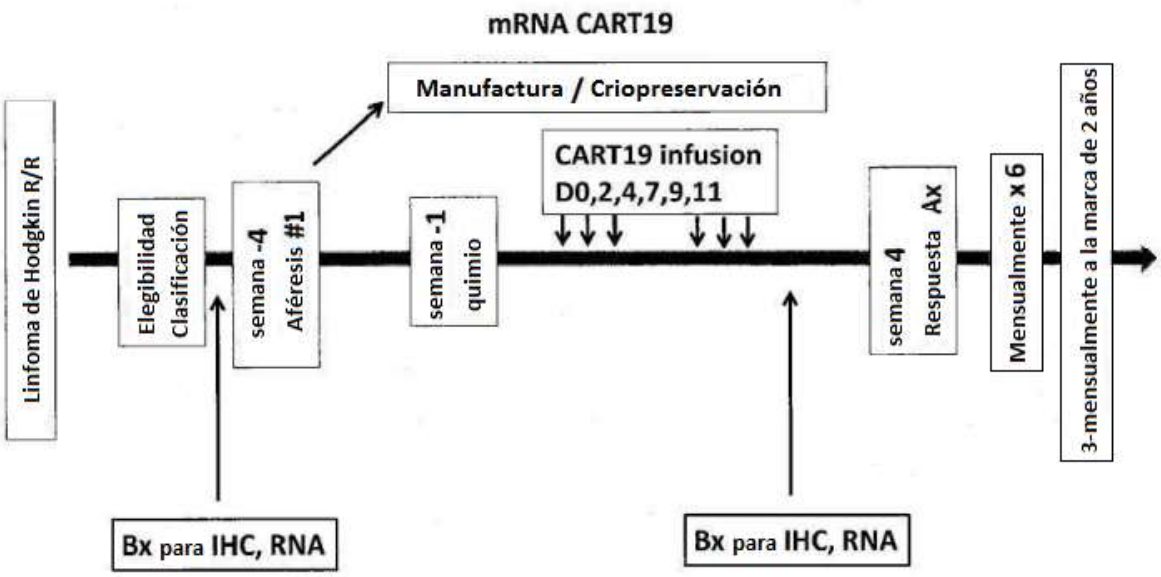

mRNA CART19
Manufactura / Criopreservación
CART19 infusion
D0,2,4,7,9,11
Linfoma de Hodgkin R/R
Elegibilidad
Clasificación
semana -4
Aféresis #1
semana -1
quimio
semana 4
Respuesta Ax
Mensualmente x 6
3-mensualmente a la marca de 2 años
Bx para IHC, RNA
Bx para IHC, RNA

FIG. 4

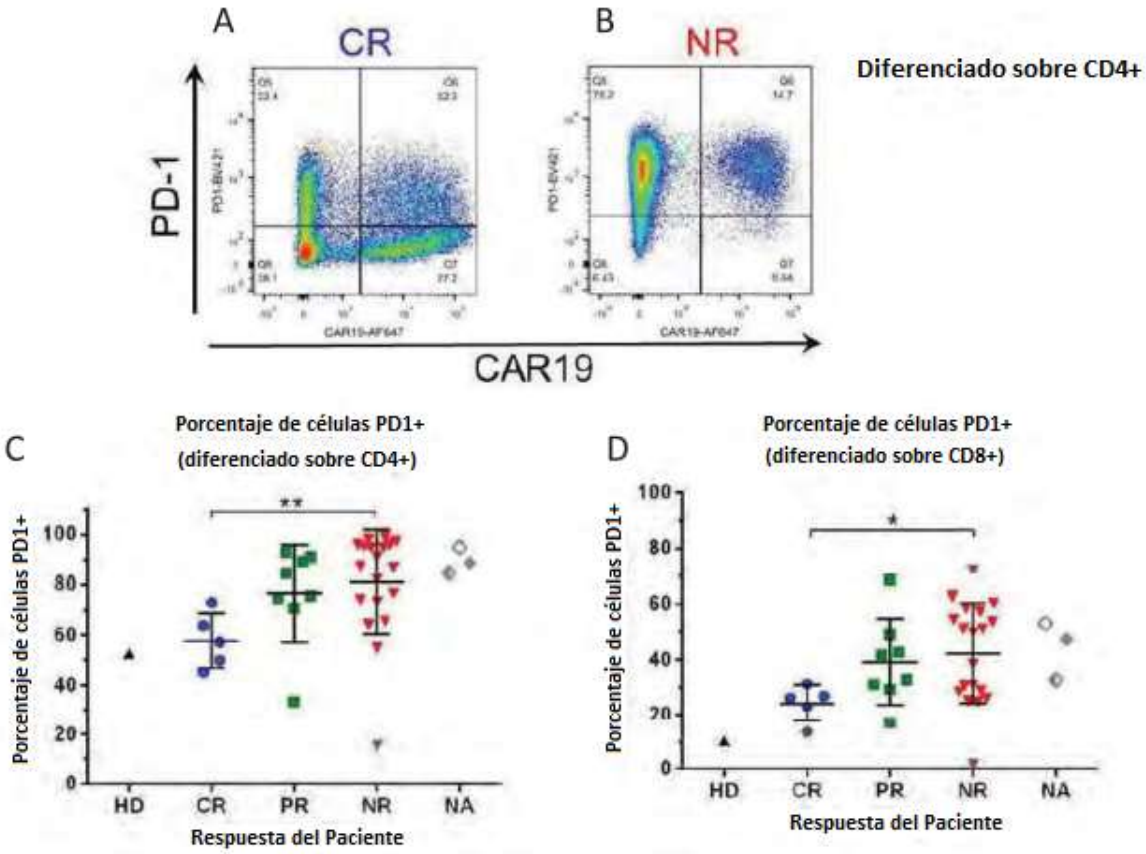

A
CR
B
NR
Diferenciado sobre CD4+
PD-1
CAR19
C
Porcentaje de células PD1+
(diferenciado sobre CD4+)
Porcentaje de células PD1+
HD
CR
PR
NR
NA
Respuesta del Paciente
D
Porcentaje de células PD1+
(diferenciado sobre CD8+)
Porcentaje de células PD1+
HD
CR
PR
NR
NA
Respuesta del Paciente

FIG. 5

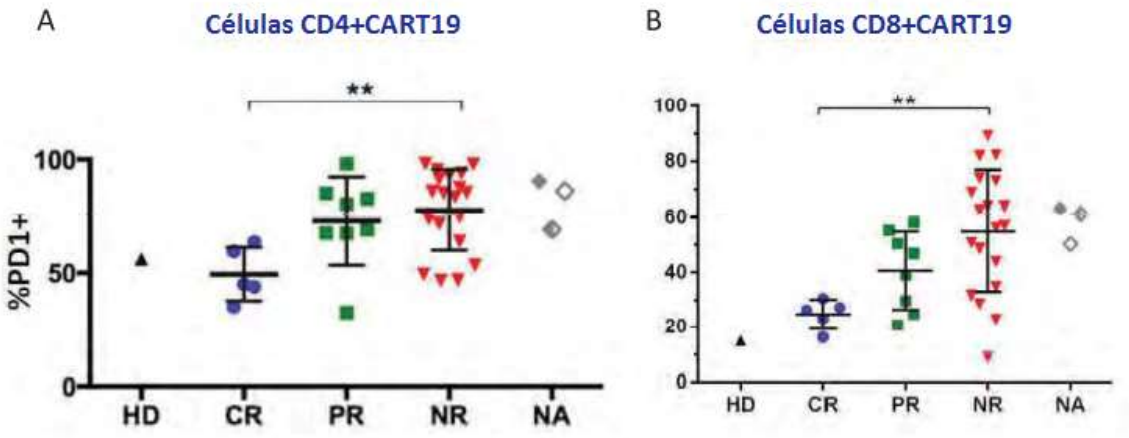

A
Células CD4+CART19
**
100
50
0
%PD1+
HD
CR
PR
NR
NA
B
Células CD8+CART19
**
100
80
60
40
20
0
HD
CR
PR
NR
NA

FIG. 6

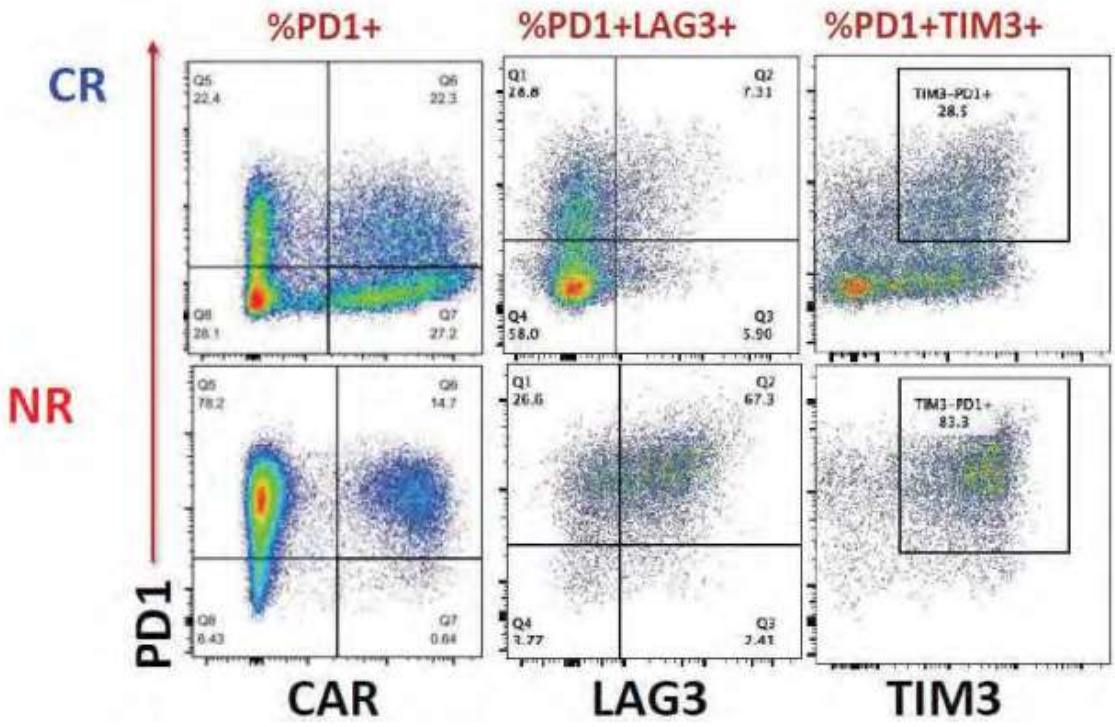

%PD1+
%PD1+LAG3+
%PD1+TIM3+
CR
NR
PD1
CAR
LAG3
TIM3
Q5
22.4
Q6
22.3
Q8
28.1
Q7
27.2
Q1
26.8
Q2
7.31
Q4
58.0
Q3
5.90
TIM3-PD1+
28.5
Q5
78.2
Q6
14.7
Q8
6.43
Q7
0.64
Q1
26.6
Q2
67.3
Q4
3.77
Q3
2.41
TIM3-PD1+
83.3

FIG. 7

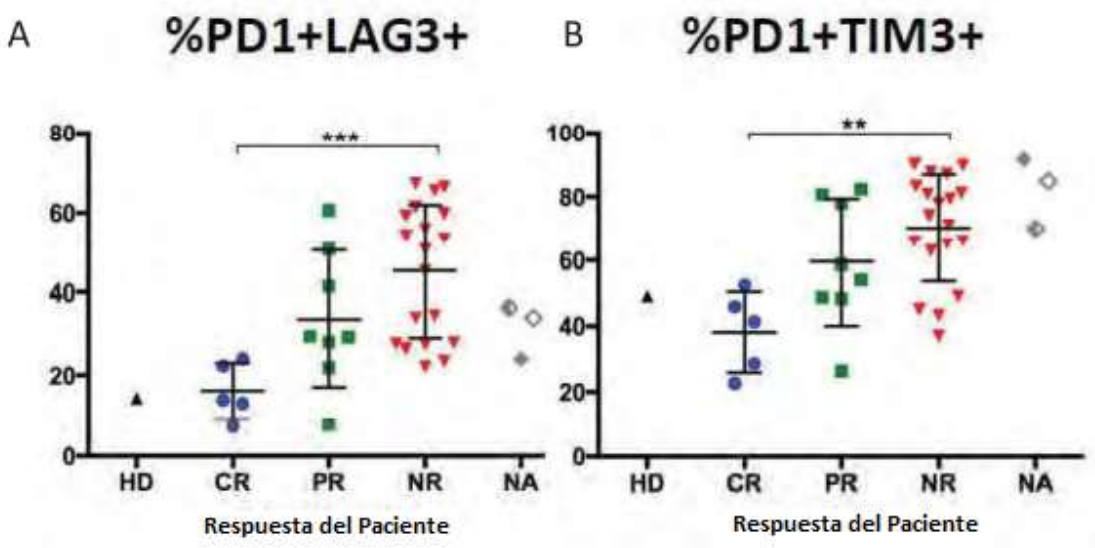

A
%PD1+LAG3+
***
80
60
40
20
0
HD
CR
PR
NR
NA
Respuesta del Paciente
B
%PD1+TIM3+
**
100
80
60
40
20
0
HD
CR
PR
NR
NA
Respuesta del Paciente

FIG. 8

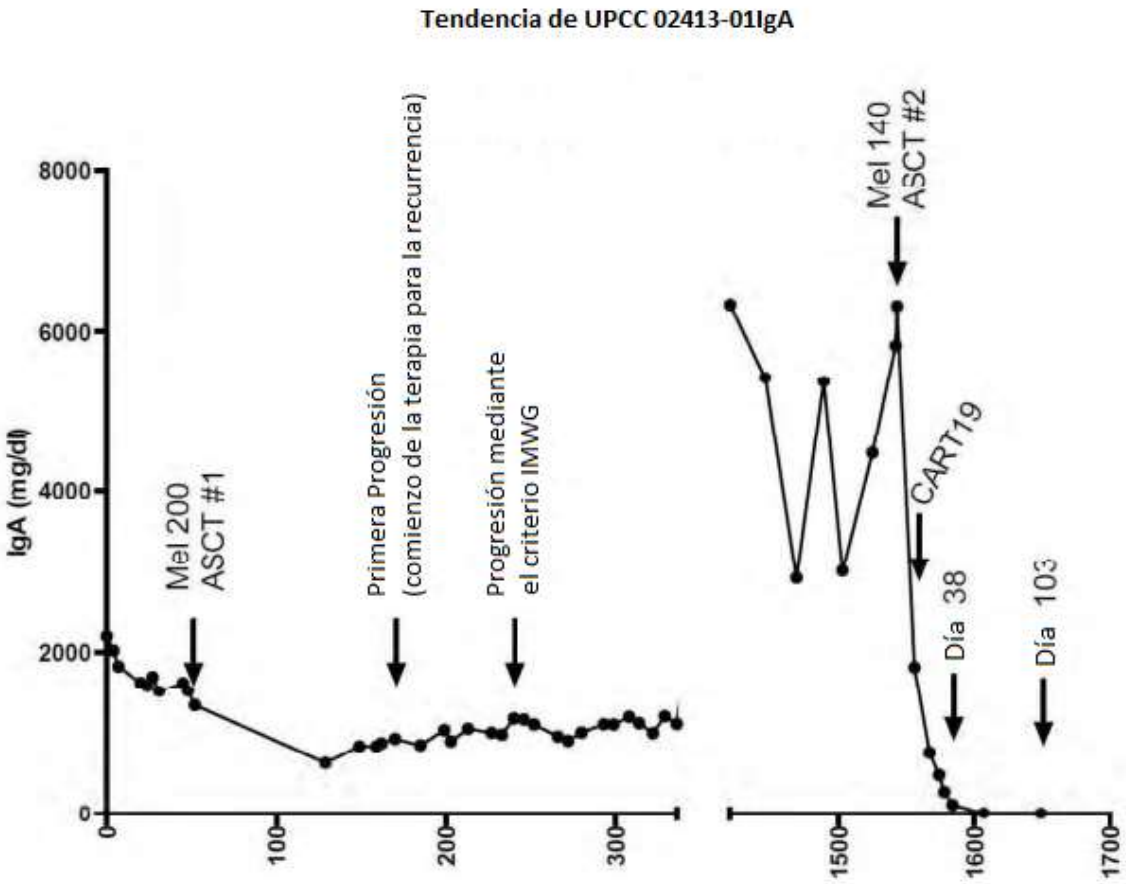

Tendencia de UPCC 02413-01IgA
IgA (mg/dl)
8000
6000
4000
2000
0
0
100
200
300
1500
1600
1700
Mel 200
ASCT #1
Primera Progresión
(comienzo de la terapia para la recurrencia)
Progresión mediante
el criterio IMWG
Mel 140
ASCT #2
CART19
Día 38
Día 103

FIG. 9

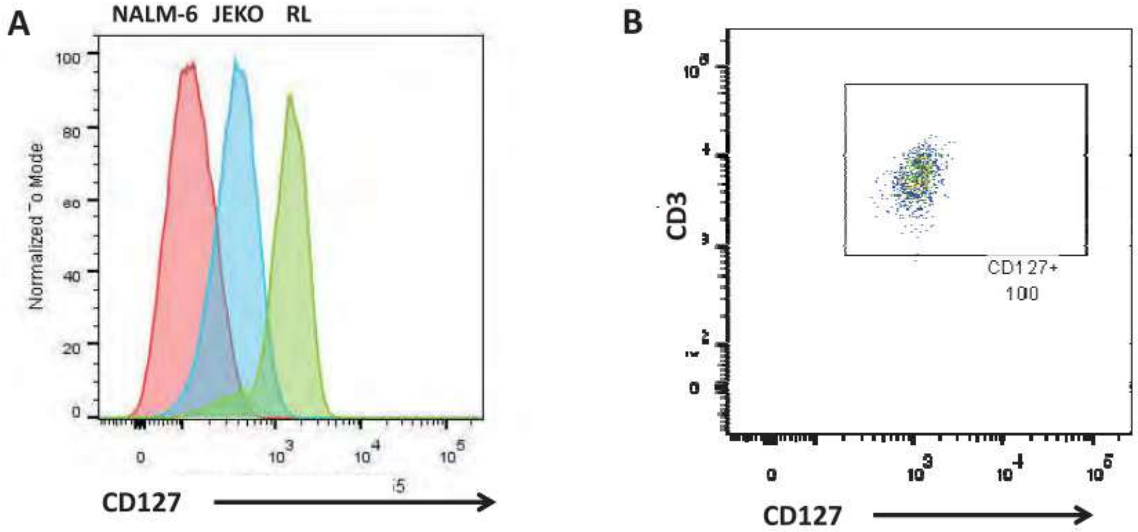

A
NALM-6 JEKO RL
Normalized To Mode
100
80
60
40
20
0
0
10^3
10^4
10^5
CD127
B
CD3
CD127+
100
0
10^3
10^4
10^5
CD127

FIG. 10

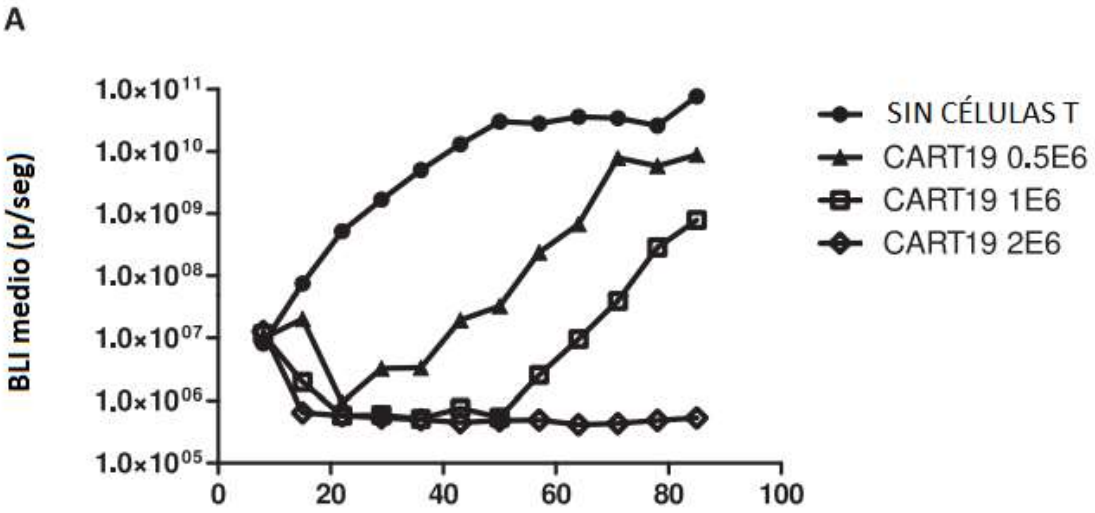

A
BLI medio (p/seg)
1.0×10^11
1.0×10^10
1.0×10^09
1.0×10^08
1.0×10^07
1.0×10^06
1.0×10^05
0
20
40
60
80
100
SIN CÉLULAS T
CART19 0.5E6
CART19 1E6
CART19 2E6

FIG. 10

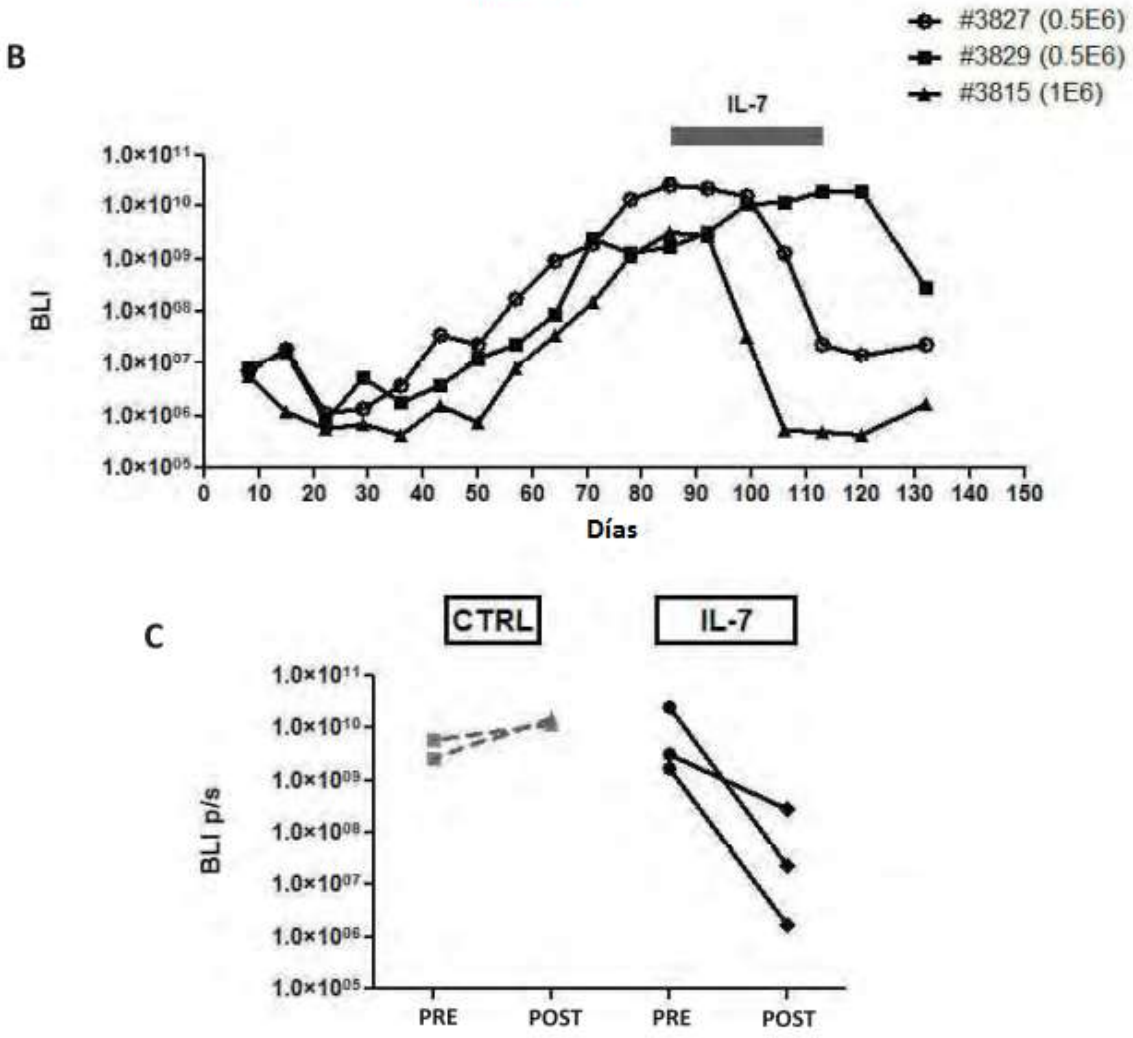

B
#3827 (0.5E6)
#3829 (0.5E6)
#3815 (1E6)
IL-7
BLI
1.0×10^11
1.0×10^10
1.0×10^09
1.0×10^08
1.0×10^07
1.0×10^06
1.0×10^05
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
Días
C
CTRL
IL-7
BLI p/s
1.0×10^11
1.0×10^10
1.0×10^09
1.0×10^08
1.0×10^07
1.0×10^06
1.0×10^05
PRE
POST
PRE
POST

FIG. 11

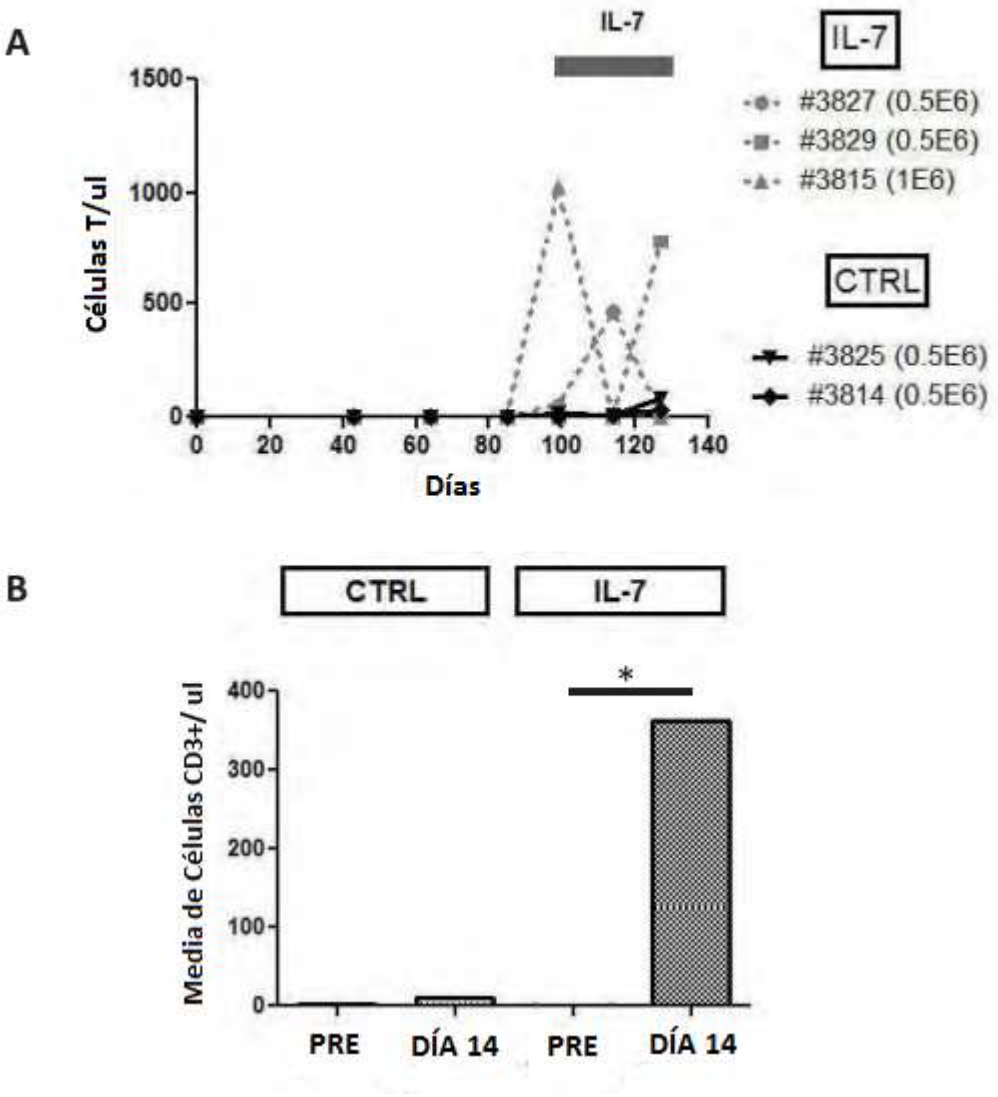

A
IL-7
IL-7
#3827 (0.5E6)
#3829 (0.5E6)
#3815 (1E6)
CTRL
#3825 (0.5E6)
#3814 (0.5E6)
Células T/ul
1500
1000
500
0
0
20
40
60
80
100
120
140
Días
B
CTRL
IL-7
*
Media de Células CD3+/ ul
400
300
200
100
0
PRE
DÍA 14
PRE
DÍA 14

FIG. 12

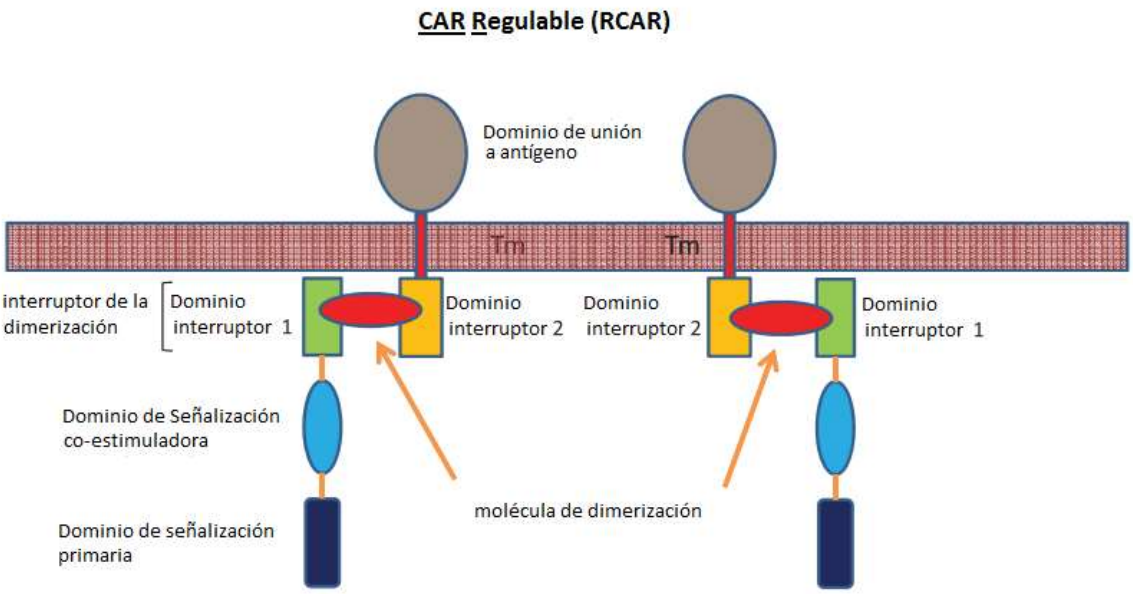

CAR Regulable (RCAR)
Dominio de unión a antígeno
Tm
Tm
interruptor de la dimerización
Dominio interruptor 1
Dominio interruptor 2
Dominio interruptor 2
Dominio interruptor 1
Dominio de Señalización co-estimuladora
molécula de dimerización
Dominio de señalización primaria

Figura 13
Diseño de la molécula biespecífica CD19/22 CAR



Figura 14

Ensayo NFAT CD19/CD22 biespecífico

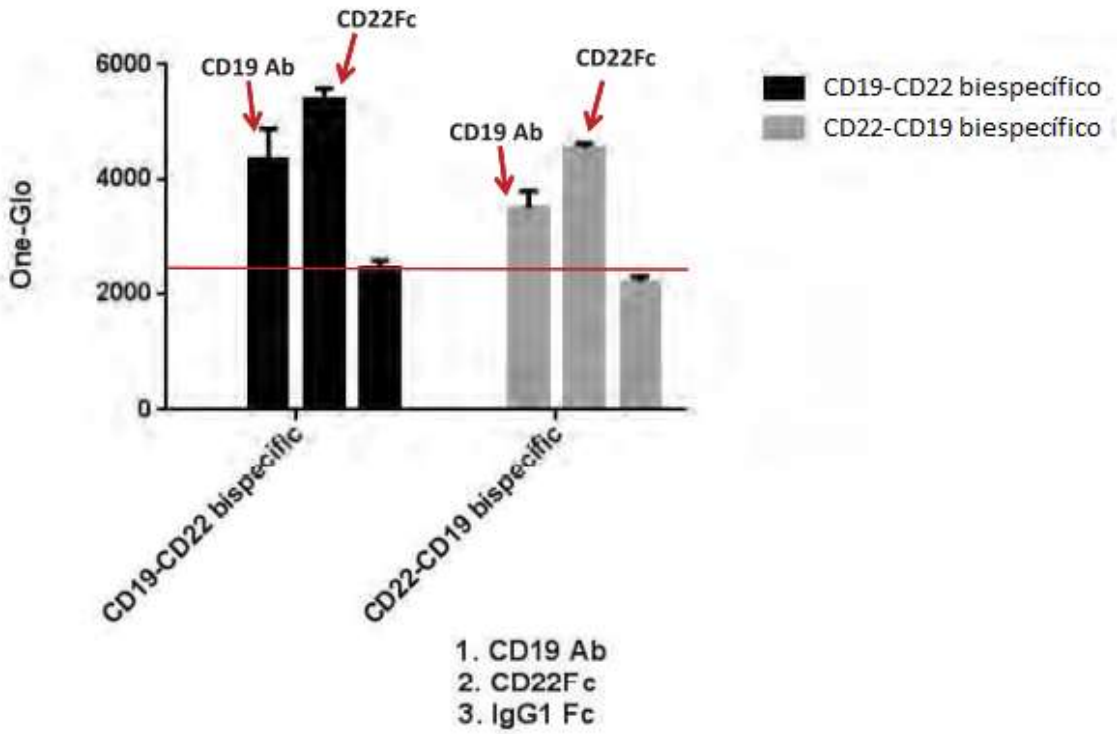


Fig. 15A

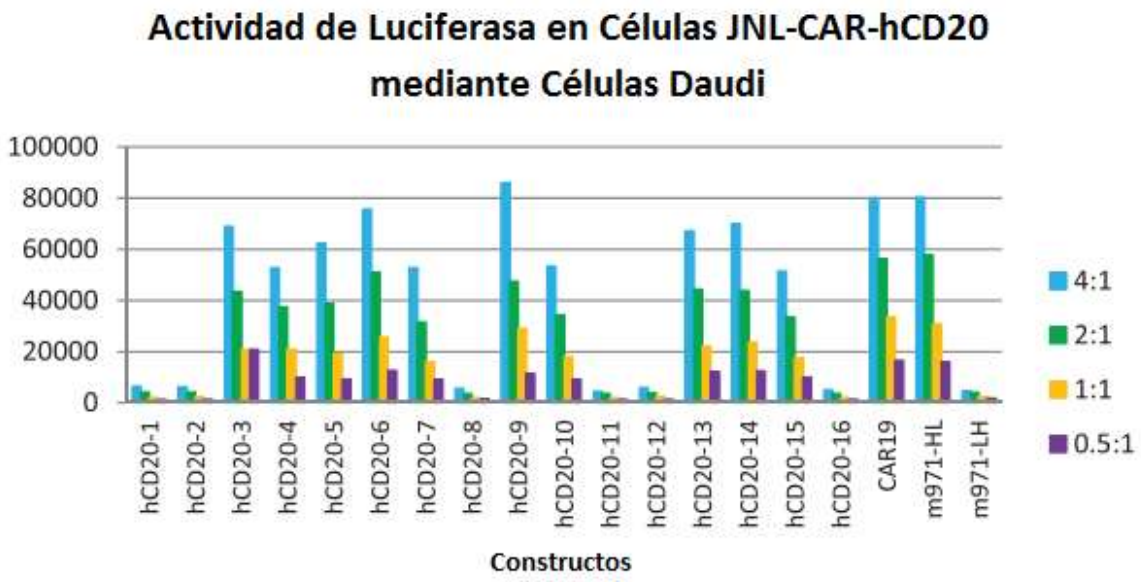

Actividad de Luciferasa en Células JNL-CAR-hCD20 mediante Células Daudi
100000
80000
60000
40000
20000
0
hCD20-1
hCD20-2
hCD20-3
hCD20-4
hCD20-5
hCD20-6
hCD20-7
hCD20-8
hCD20-9
hCD20-10
hCD20-11
hCD20-12
hCD20-13
hCD20-14
hCD20-15
hCD20-16
CAR19
m971-HL
m971-LH
Constructos
4:1
2:1
1:1
0.5:1

Fig. 15B

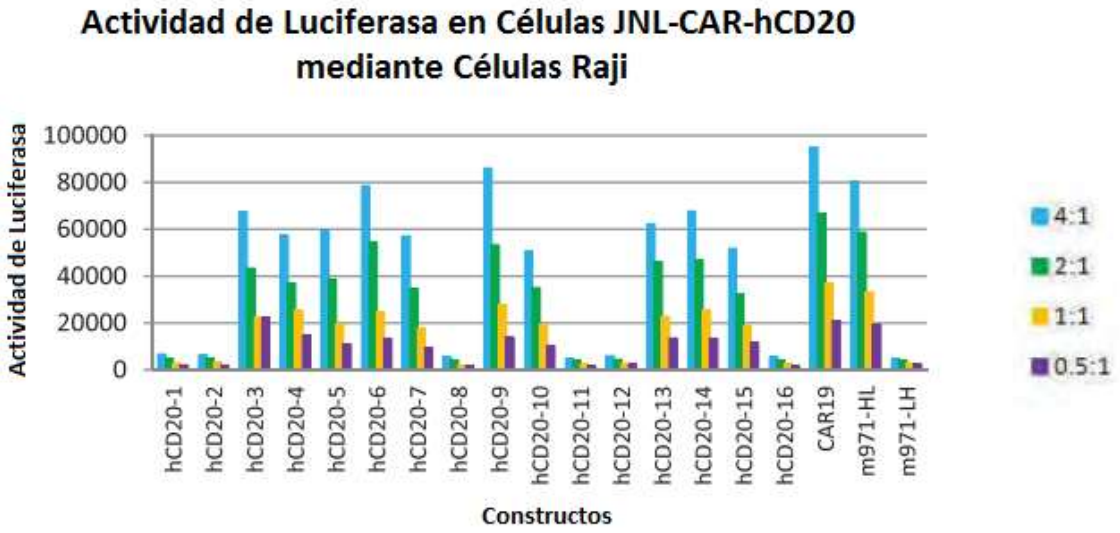

Actividad de Luciferasa en Células JNL-CAR-hCD20 mediante Células Raji
Actividad de Luciferasa
100000
80000
60000
40000
20000
0
hCD20-1
hCD20-2
hCD20-3
hCD20-4
hCD20-5
hCD20-6
hCD20-7
hCD20-8
hCD20-9
hCD20-10
hCD20-11
hCD20-12
hCD20-13
hCD20-14
hCD20-15
hCD20-16
CAR19
m971-HL
m971-LH
Constructos
4:1
2:1
1:1
0.5:1

Fig. 15C

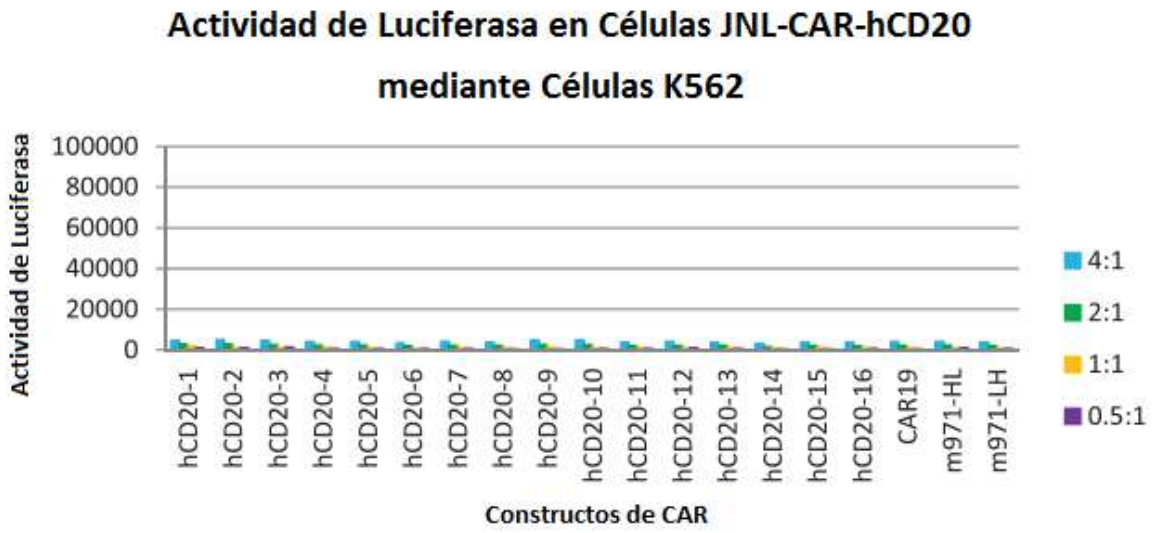

Actividad de Luciferasa en Células JNL-CAR-hCD20
mediante Células K562
Actividad de Luciferasa
100000
80000
60000
40000
20000
0
hCD20-1
hCD20-2
hCD20-3
hCD20-4
hCD20-5
hCD20-6
hCD20-7
hCD20-8
hCD20-9
hCD20-10
hCD20-11
hCD20-12
hCD20-13
hCD20-14
hCD20-15
hCD20-16
CAR19
m971-HL
m971-LH
Constructos de CAR
4:1
2:1
1:1
0.5:1

FIG. 16

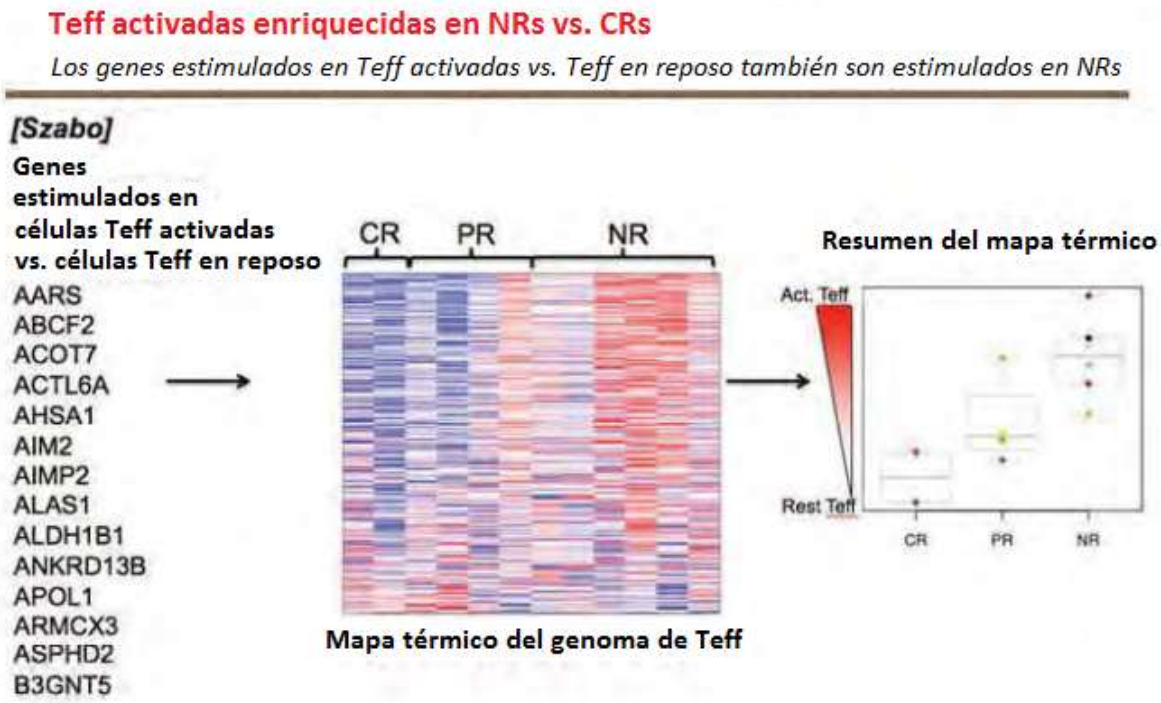

Teff activadas enriquecidas en NRs vs. CRs
Los genes estimulados en Teff activadas vs. Teff en reposo también son estimulados en NRs
[Szabo]
Genes estimulados en células Teff activadas vs. células Teff en reposo
AARS
ABCF2
ACOT7
ACTL6A
AHSA1
AIM2
AIMP2
ALAS1
ALDH1B1
ANKRD13B
APOL1
ARMCX3
ASPHD2
B3GNT5
CR
PR
NR
Mapa térmico del genoma de Teff
Resumen del mapa térmico
Act. Teff
Rest Teff
CR
PR
NR

FIG. 17

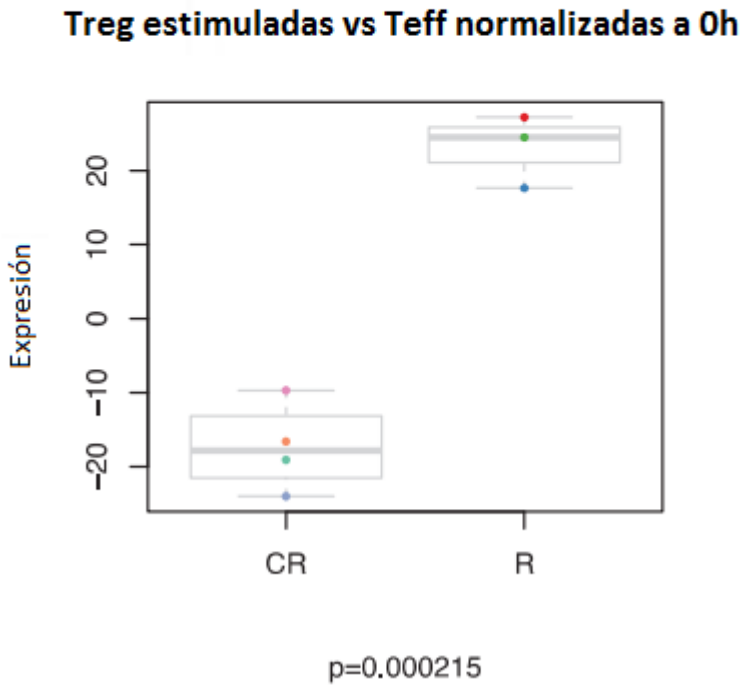

Treg estimuladas vs Teff normalizadas a 0h
Expresión
20
10
0
−10
−20
CR
R
p=0.000215

FIG. 18A

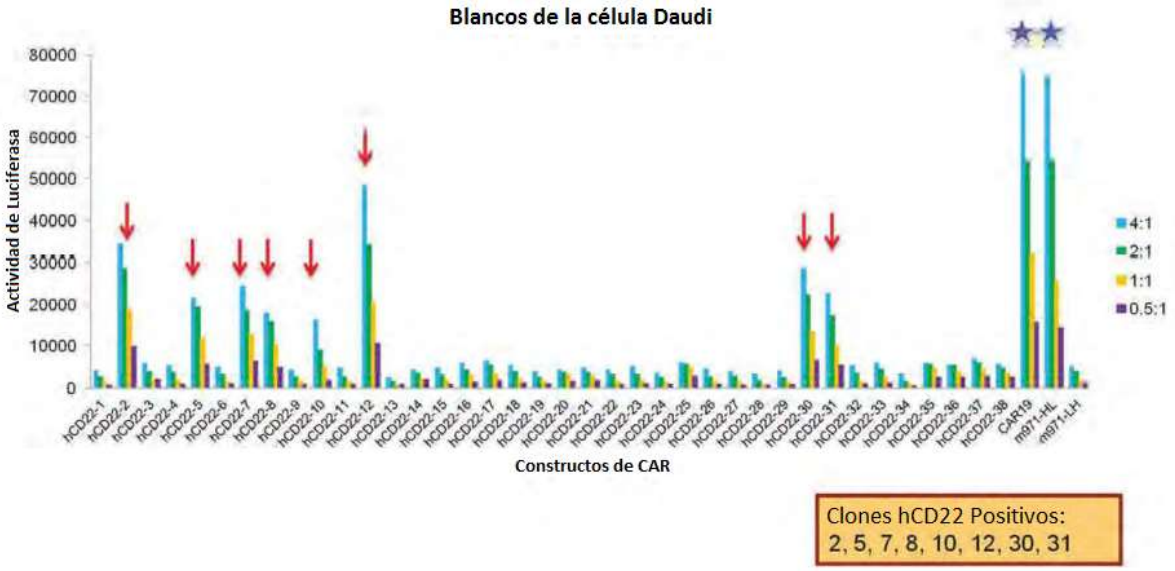

Blancos de la célula Daudi
Actividad de Luciferasa
80000
70000
60000
50000
40000
30000
20000
10000
0
4:1
2:1
1:1
0.5:1
Constructos de CAR
Clones hCD22 Positivos:
2, 5, 7, 8, 10, 12, 30, 31

FIG. 18B

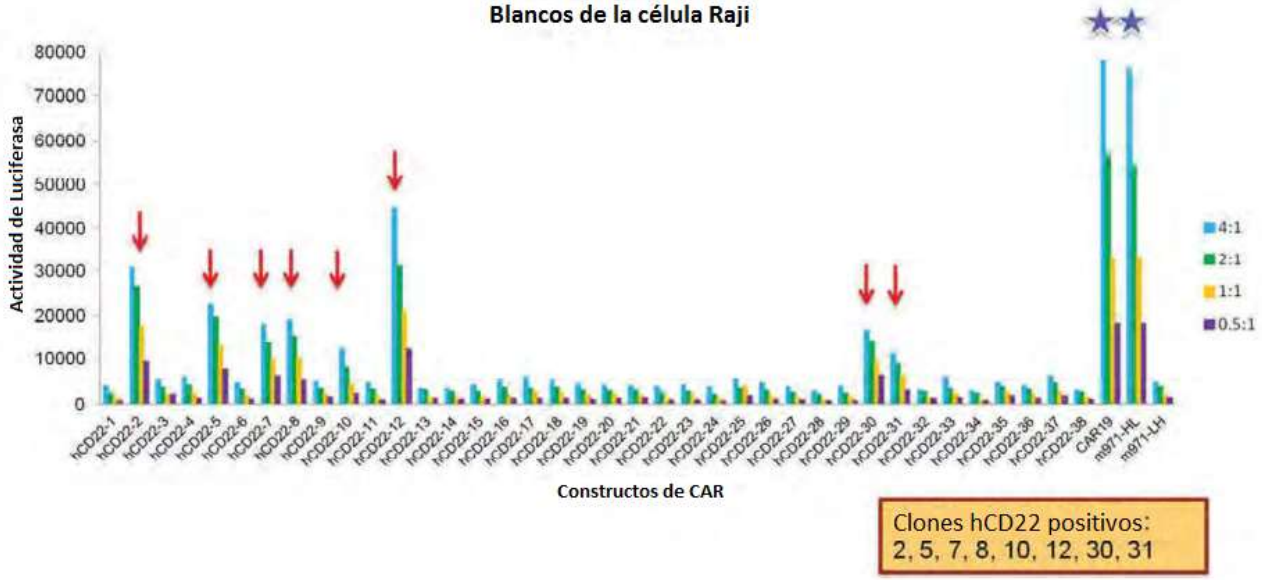

Blancos de la célula Raji
Actividad de Luciferasa
80000
70000
60000
50000
40000
30000
20000
10000
0
4:1
2:1
1:1
0.5:1
hCD22-1
hCD22-2
hCD22-3
hCD22-4
hCD22-5
hCD22-6
hCD22-7
hCD22-8
hCD22-9
hCD22-10
hCD22-11
hCD22-12
hCD22-13
hCD22-14
hCD22-15
hCD22-16
hCD22-17
hCD22-18
hCD22-19
hCD22-20
hCD22-21
hCD22-22
hCD22-23
hCD22-24
hCD22-25
hCD22-26
hCD22-27
hCD22-28
hCD22-29
hCD22-30
hCD22-31
hCD22-32
hCD22-33
hCD22-34
hCD22-35
hCD22-36
hCD22-37
hCD22-38
CAR19
m971-HL
m971-LH
Constructos de CAR
Clones hCD22 positivos:
2, 5, 7, 8, 10, 12, 30, 31

FIG. 18C

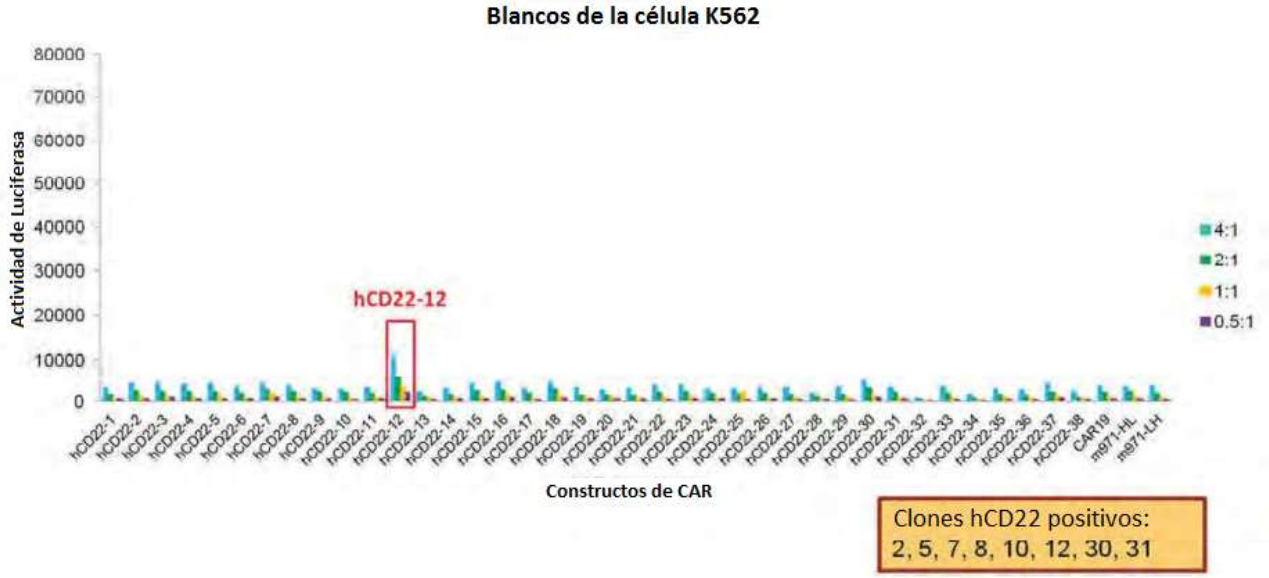

Blancos de la célula K562
Actividad de Luciferasa
80000
70000
60000
50000
40000
30000
20000
10000
0
hCD22-12
4:1
2:1
1:1
0.5:1
hCD22-1
hCD22-2
hCD22-3
hCD22-4
hCD22-5
hCD22-6
hCD22-7
hCD22-8
hCD22-9
hCD22-10
hCD22-11
hCD22-12
hCD22-13
hCD22-14
hCD22-15
hCD22-16
hCD22-17
hCD22-18
hCD22-19
hCD22-20
hCD22-21
hCD22-22
hCD22-23
hCD22-24
hCD22-25
hCD22-26
hCD22-27
hCD22-28
hCD22-29
hCD22-30
hCD22-31
hCD22-32
hCD22-33
hCD22-34
hCD22-35
hCD22-36
hCD22-37
hCD22-38
CAR19
m971-HL
m971-LH
Constructos de CAR
Clones hCD22 positivos:
2, 5, 7, 8, 10, 12, 30, 31

FIG. 19

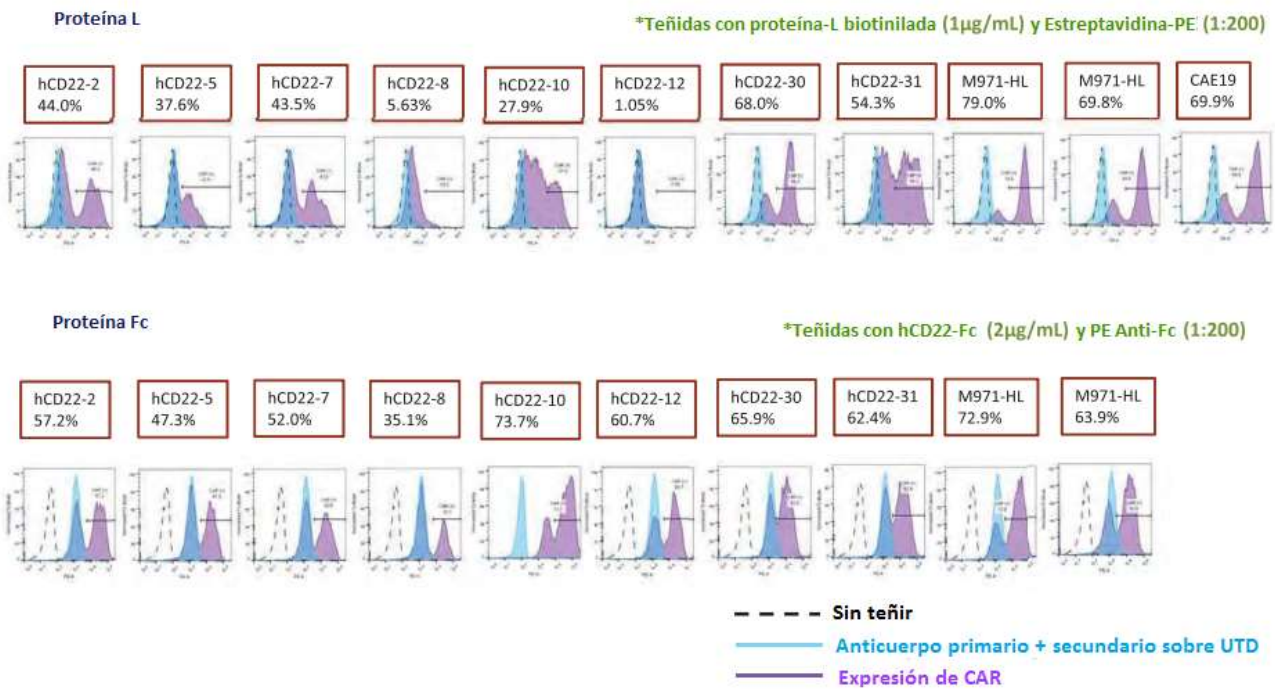

Proteína L
*Teñidas con proteína-L biotinilada (1µg/mL) y Estreptavidina-PE (1:200)
hCD22-2 44.0%
hCD22-5 37.6%
hCD22-7 43.5%
hCD22-8 5.63%
hCD22-10 27.9%
hCD22-12 1.05%
hCD22-30 68.0%
hCD22-31 54.3%
M971-HL 79.0%
M971-HL 69.8%
CAE19 69.9%
Proteína Fc
*Teñidas con hCD22-Fc (2µg/mL) y PE Anti-Fc (1:200)
hCD22-2 57.2%
hCD22-5 47.3%
hCD22-7 52.0%
hCD22-8 35.1%
hCD22-10 73.7%
hCD22-12 60.7%
hCD22-30 65.9%
hCD22-31 62.4%
M971-HL 72.9%
M971-HL 63.9%
Sin teñir
Anticuerpo primario + secundario sobre UTD
Expresión de CAR

FIG. 20A

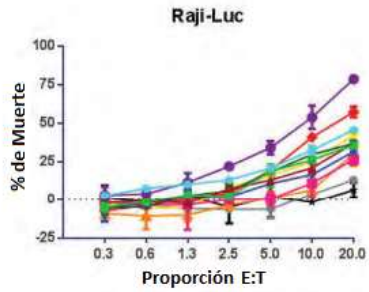


FIG. 20B

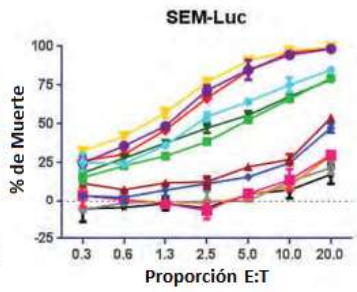


FIG. 20C

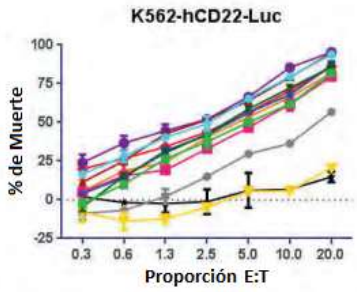


FIG. 20D

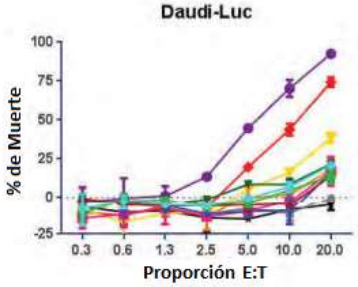


FIG. 20E

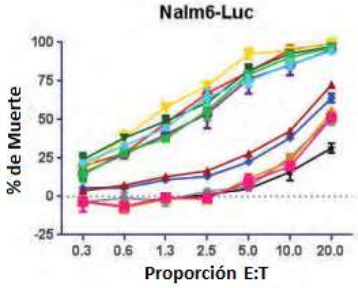


FIG. 20F

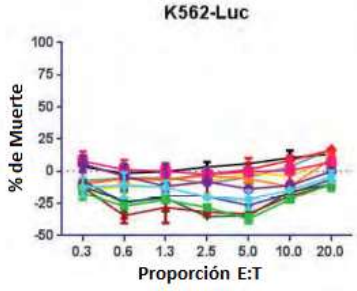




FIG. 21A

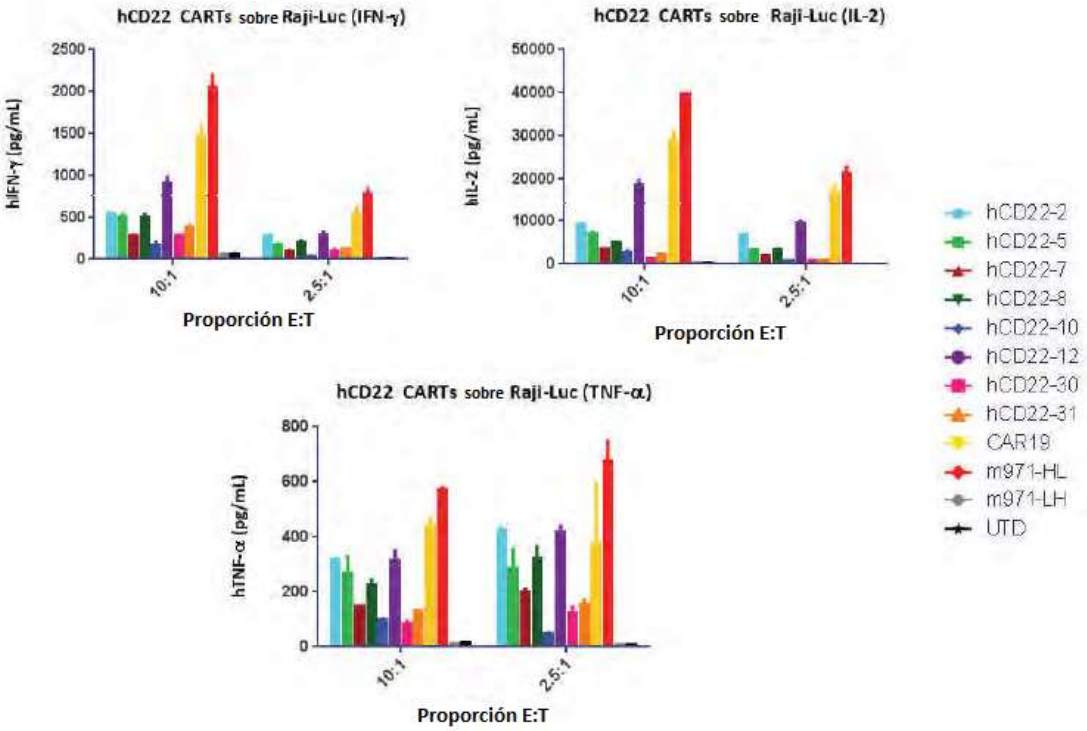

hCD22 CARTs sobre Raji-Luc (IFN-γ)
hIFN-γ (pg/mL)
2500
2000
1500
1000
500
0
10:1
2.5:1
Proporción E:T
hCD22 CARTs sobre Raji-Luc (IL-2)
hIL-2 (pg/mL)
50000
40000
30000
20000
10000
0
10:1
2.5:1
Proporción E:T
hCD22 CARTs sobre Raji-Luc (TNF-α)
hTNF-α (pg/mL)
800
600
400
200
0
10:1
2.5:1
Proporción E:T
hCD22-2
hCD22-5
hCD22-7
hCD22-8
hCD22-10
hCD22-12
hCD22-30
hCD22-31
CAR19
m971-HL
m971-LH
UTD

FIG. 21B

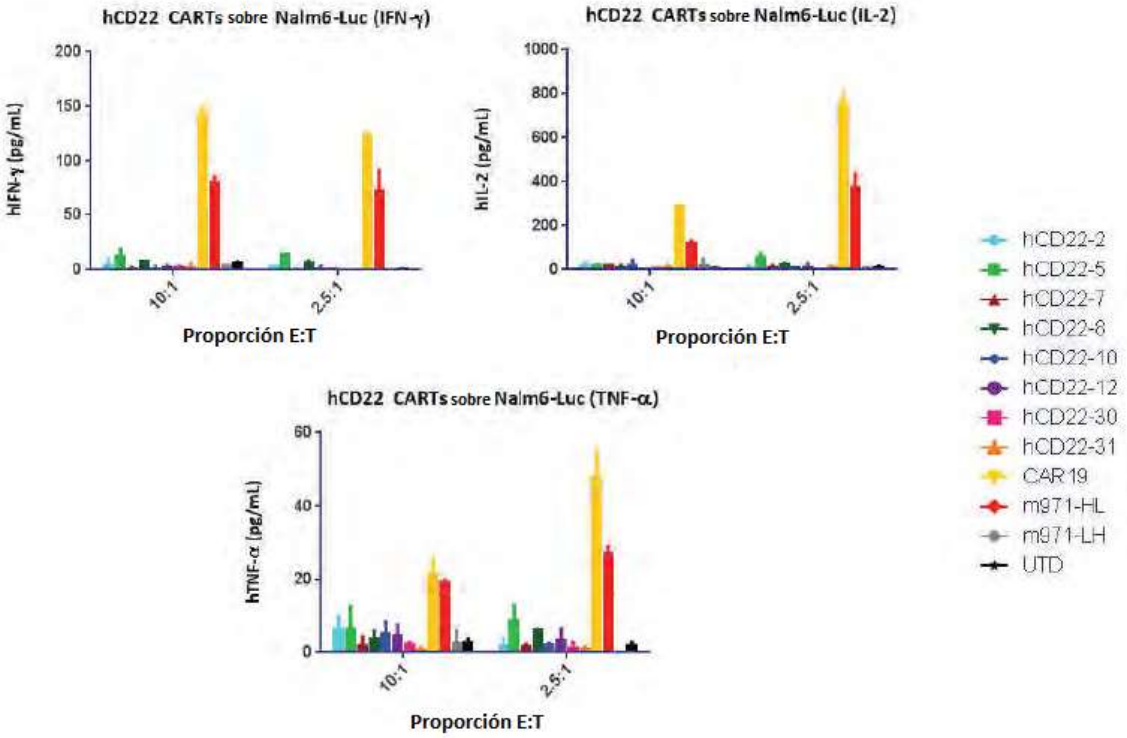

hCD22 CARTs sobre Nalm6-Luc (IFN-γ)
hIFN-γ (pg/mL)
200
150
100
50
0
10:1
2.5:1
Proporción E:T
hCD22 CARTs sobre Nalm6-Luc (IL-2)
hIL-2 (pg/mL)
1000
800
600
400
200
0
10:1
2.5:1
Proporción E:T
hCD22 CARTs sobre Nalm6-Luc (TNF-α)
hTNF-α (pg/mL)
60
40
20
0
10:1
2.5:1
Proporción E:T
hCD22-2
hCD22-5
hCD22-7
hCD22-8
hCD22-10
hCD22-12
hCD22-30
hCD22-31
CAR19
m971-HL
m971-LH
UTD

FIG. 21C

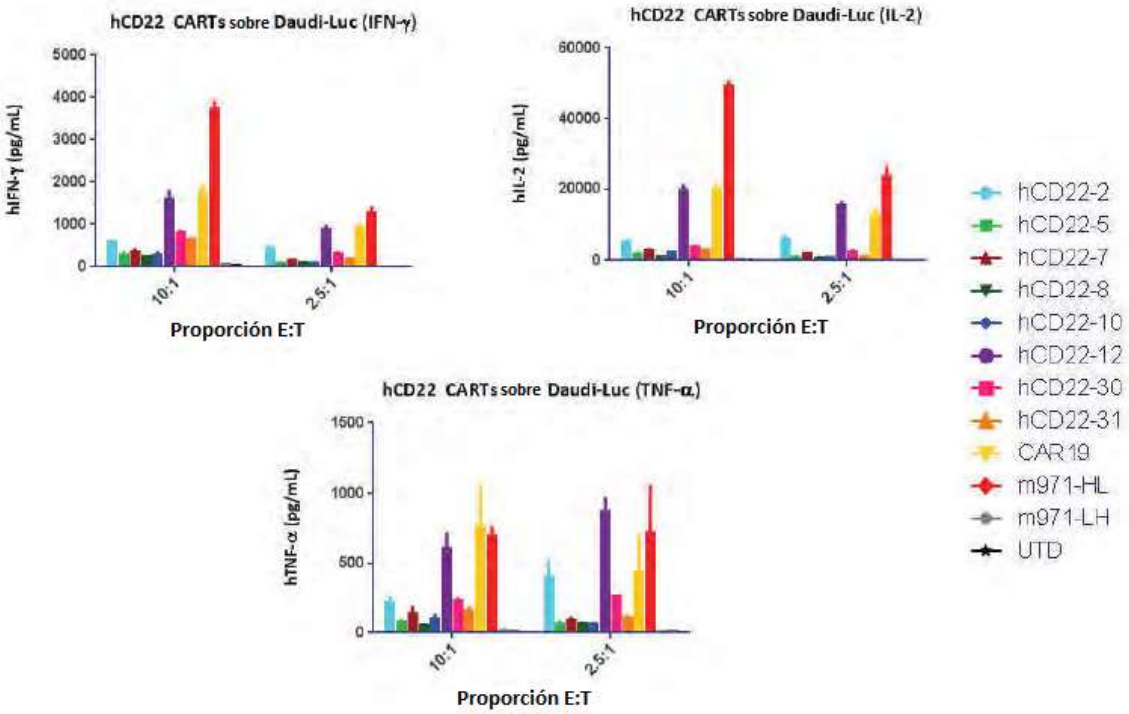

hCD22 CARTs sobre Daudi-Luc (IFN-γ)
hIFN-γ (pg/mL)
5000
4000
3000
2000
1000
0
10:1
2.5:1
Proporción E:T
hCD22 CARTs sobre Daudi-Luc (IL-2)
hIL-2 (pg/mL)
60000
40000
20000
0
10:1
2.5:1
Proporción E:T
hCD22 CARTs sobre Daudi-Luc (TNF-α)
hTNF-α (pg/mL)
1500
1000
500
0
10:1
2.5:1
Proporción E:T
hCD22-2
hCD22-5
hCD22-7
hCD22-8
hCD22-10
hCD22-12
hCD22-30
hCD22-31
CAR19
m971-HL
m971-LH
UTD

FIG. 21D

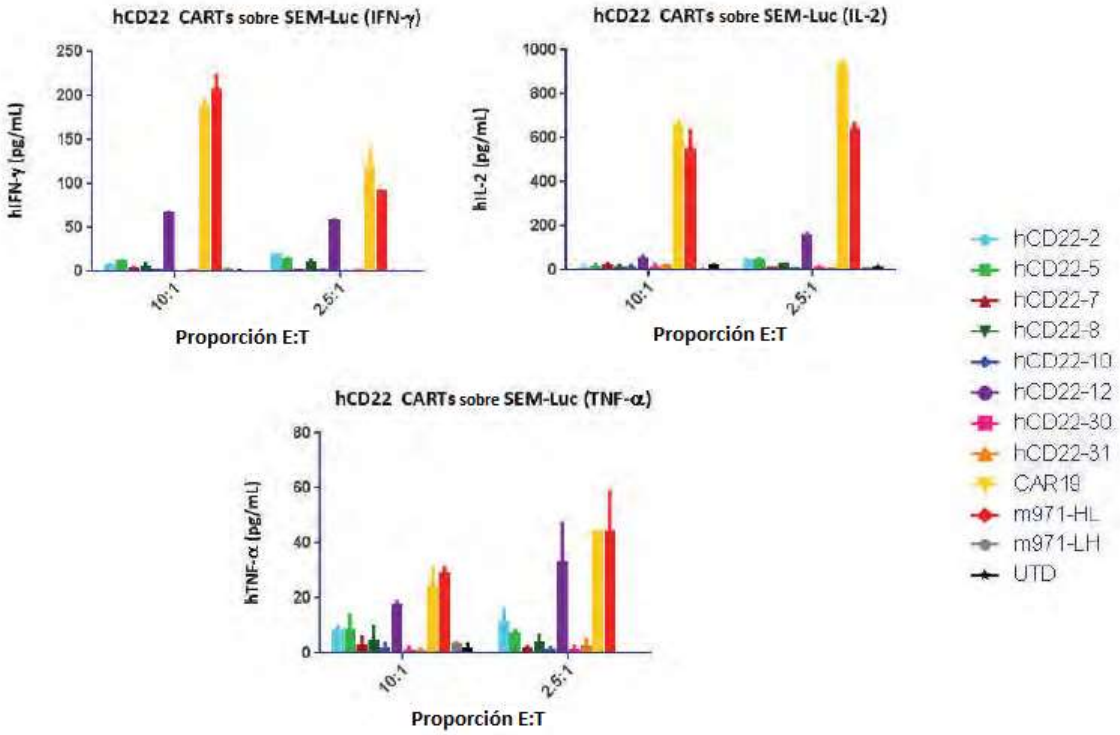

hCD22 CARTs sobre SEM-Luc (IFN-γ)
hIFN-γ (pg/mL)
250
200
150
100
50
0
10:1
2.5:1
Proporción E:T
hCD22 CARTs sobre SEM-Luc (IL-2)
hIL-2 (pg/mL)
1000
800
600
400
200
0
10:1
2.5:1
Proporción E:T
hCD22 CARTs sobre SEM-Luc (TNF-α)
hTNF-α (pg/mL)
80
60
40
20
0
10:1
2.5:1
Proporción E:T
hCD22-2
hCD22-5
hCD22-7
hCD22-8
hCD22-10
hCD22-12
hCD22-30
hCD22-31
CAR19
m971-HL
m971-LH
UTD

FIG. 21E

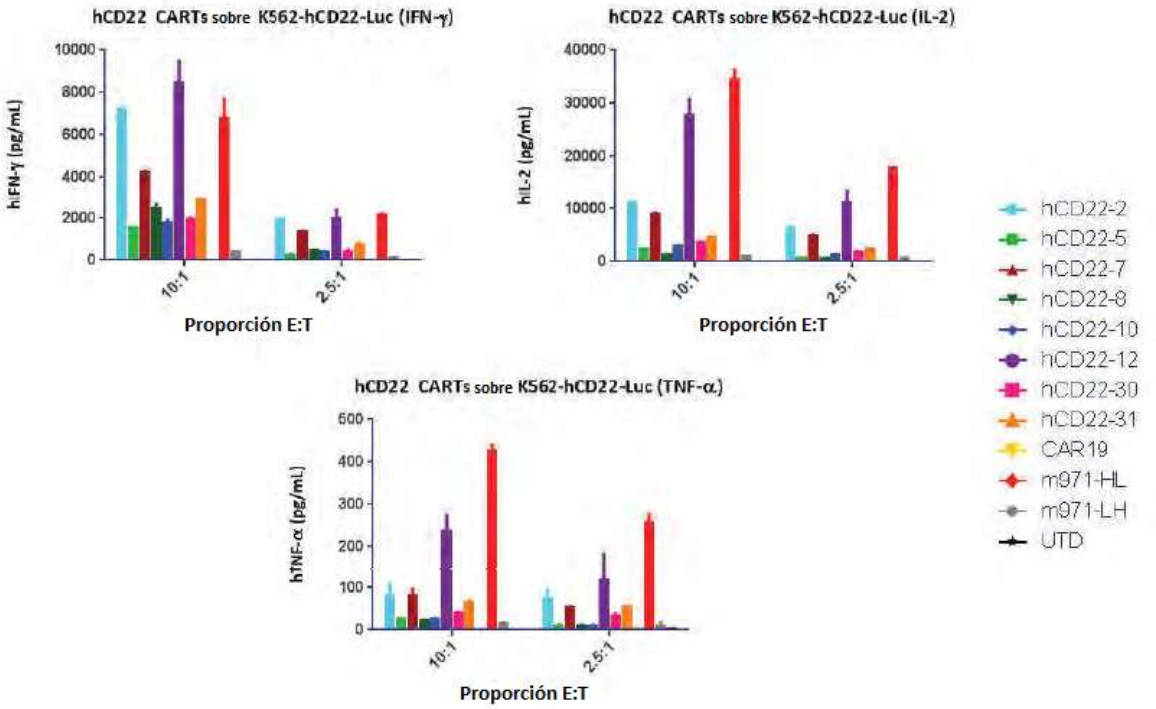

hCD22 CARTs sobre K562-hCD22-Luc (IFN-γ)
hIFN-γ (pg/mL)
10000
8000
6000
4000
2000
0
10:1
2.5:1
Proporción E:T
hCD22 CARTs sobre K562-hCD22-Luc (IL-2)
hIL-2 (pg/mL)
40000
30000
20000
10000
0
10:1
2.5:1
Proporción E:T
hCD22 CARTs sobre K562-hCD22-Luc (TNF-α)
hTNF-α (pg/mL)
600
400
300
200
100
0
10:1
2.5:1
Proporción E:T
hCD22-2
hCD22-5
hCD22-7
hCD22-8
hCD22-10
hCD22-12
hCD22-30
hCD22-31
CAR19
m971-HL
m971-LH
UTD

FIG. 21F

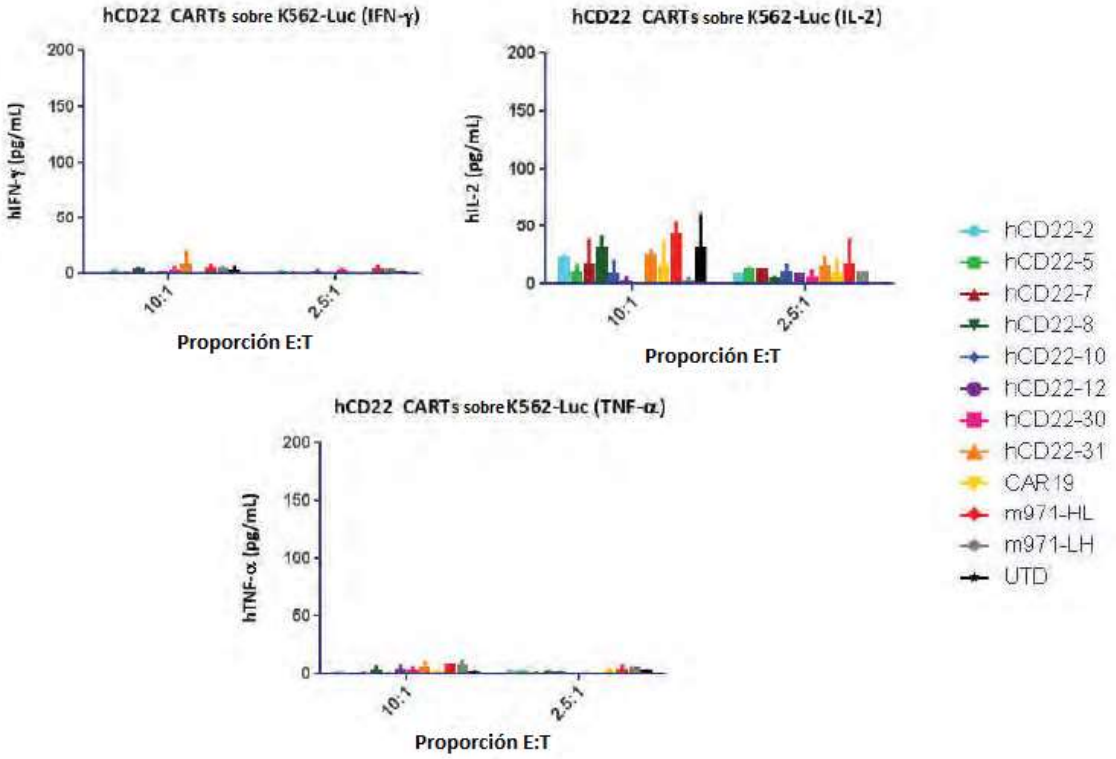

hCD22 CARTs sobre K562-Luc (IFN-γ)
hIFN-γ (pg/mL)
200
150
100
50
0
10:1
2.5:1
Proporción E:T
hCD22 CARTs sobre K562-Luc (IL-2)
hIL-2 (pg/mL)
200
150
100
50
0
10:1
2.5:1
Proporción E:T
hCD22 CARTs sobre K562-Luc (TNF-α)
hTNF-α (pg/mL)
200
150
100
50
0
10:1
2.5:1
Proporción E:T
hCD22-2
hCD22-5
hCD22-7
hCD22-8
hCD22-10
hCD22-12
hCD22-30
hCD22-31
CAR19
m971-HL
m971-LH
UTD

FIG. 22

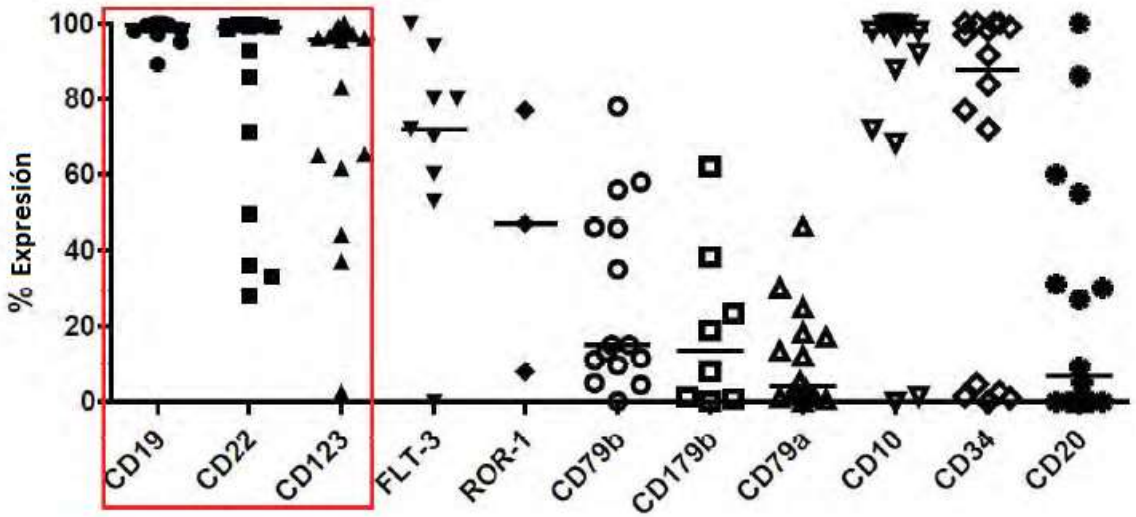

% Expresión
100
80
60
40
20
0
CD19
CD22
CD123
FLT-3
ROR-1
CD79b
CD179b
CD79a
CD10
CD34
CD20

FIG. 23

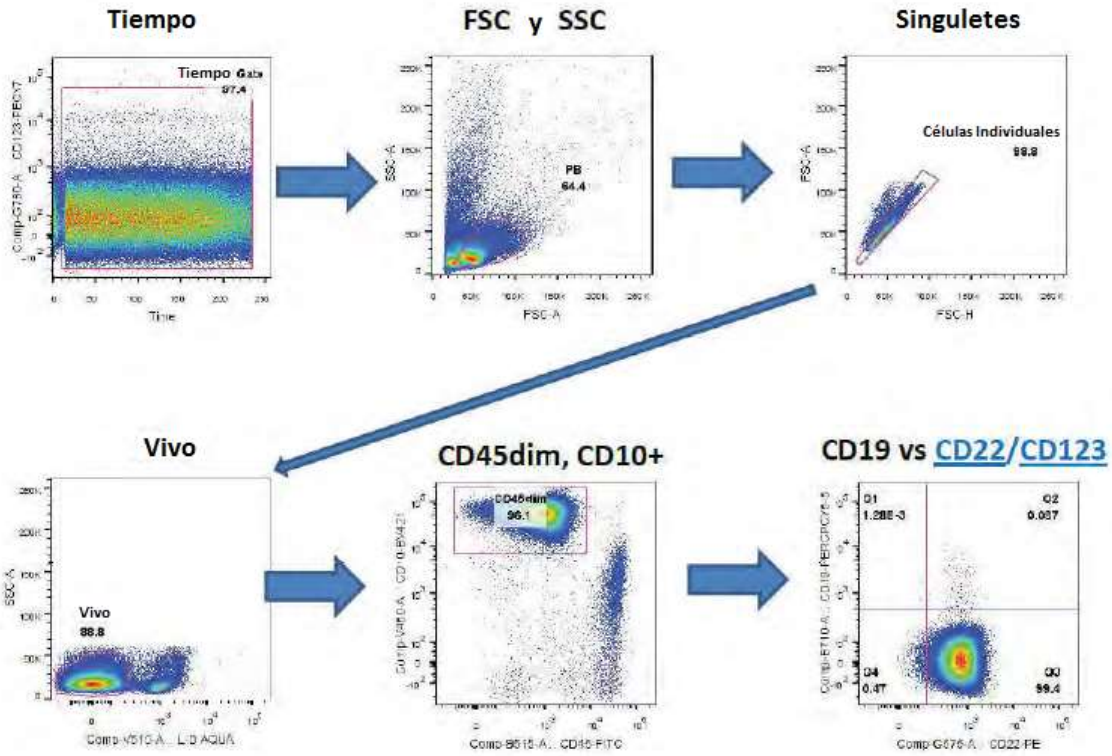

Tiempo
FSC y SSC
Singuletes
Tiempo Gate
97.4
PB
64.4
Células Individuales
99.9
Vivo
CD45dim, CD10+
CD19 vs CD22/CD123
Vivo
88.8
CD45dim
96.1
Q1
1.28E-3
Q2
0.087
Q4
0.47
Q3
99.4

FIG. 24

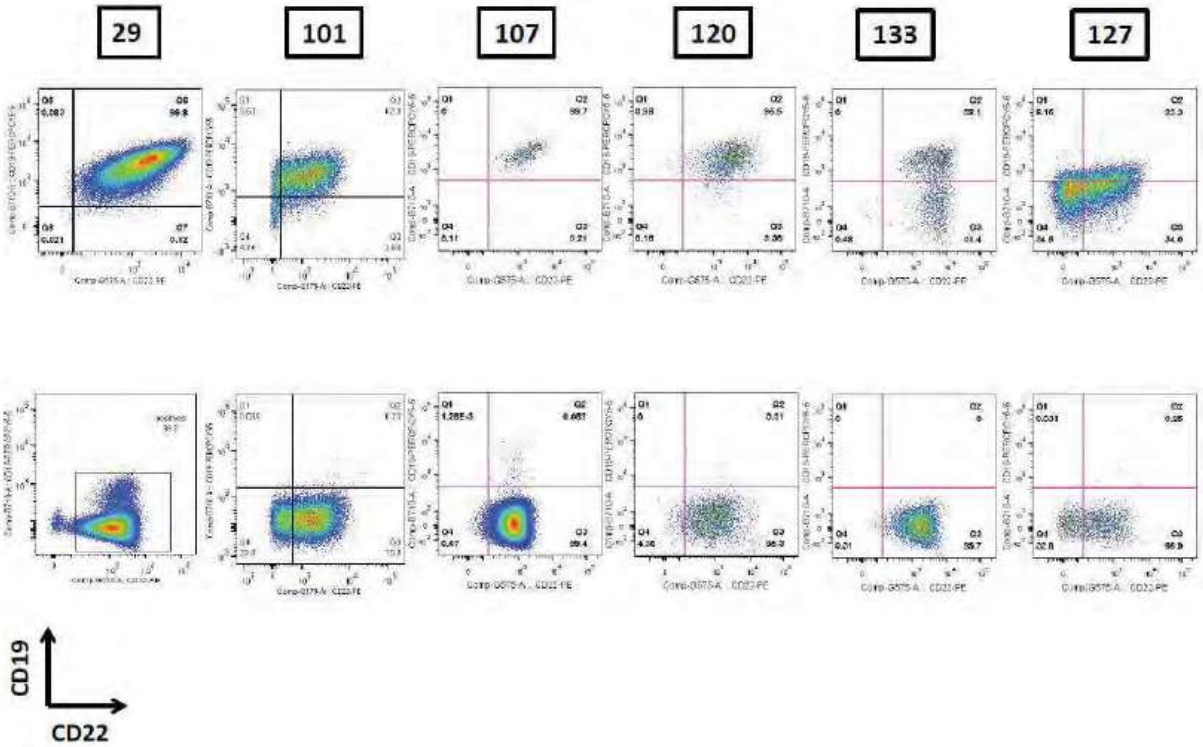


FIG. 25

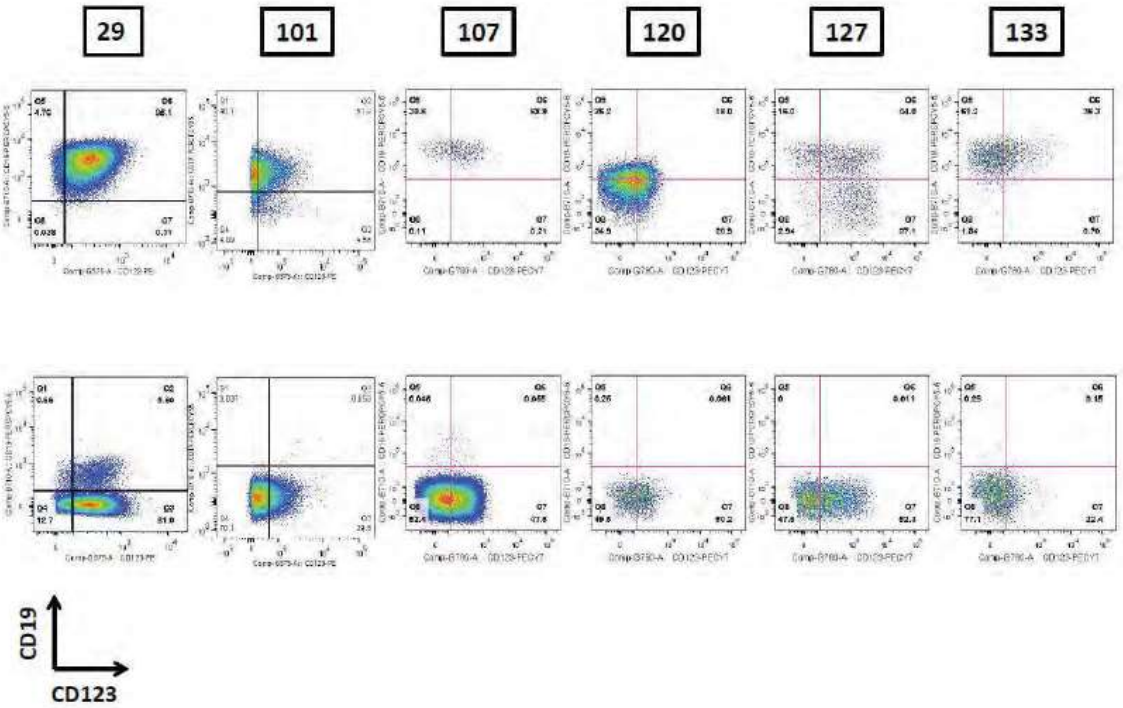


FIG. 26

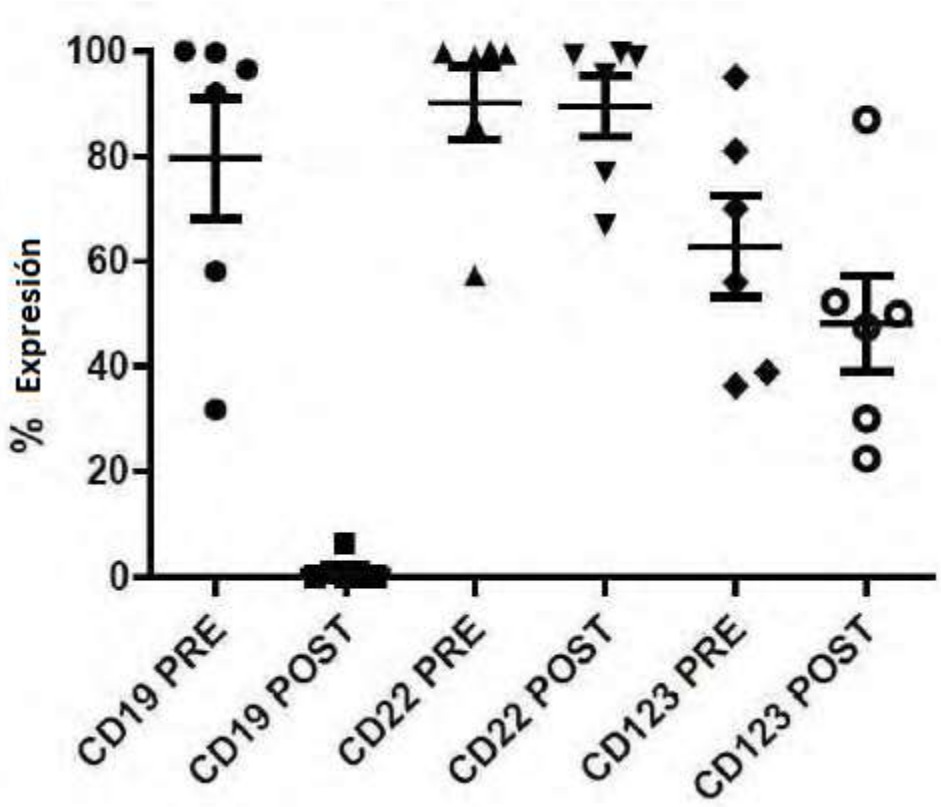

100
80
60
40
20
0
% Expresión
CD19 PRE
CD19 POST
CD22 PRE
CD22 POST
CD123 PRE
CD123 POST

FIG. 27

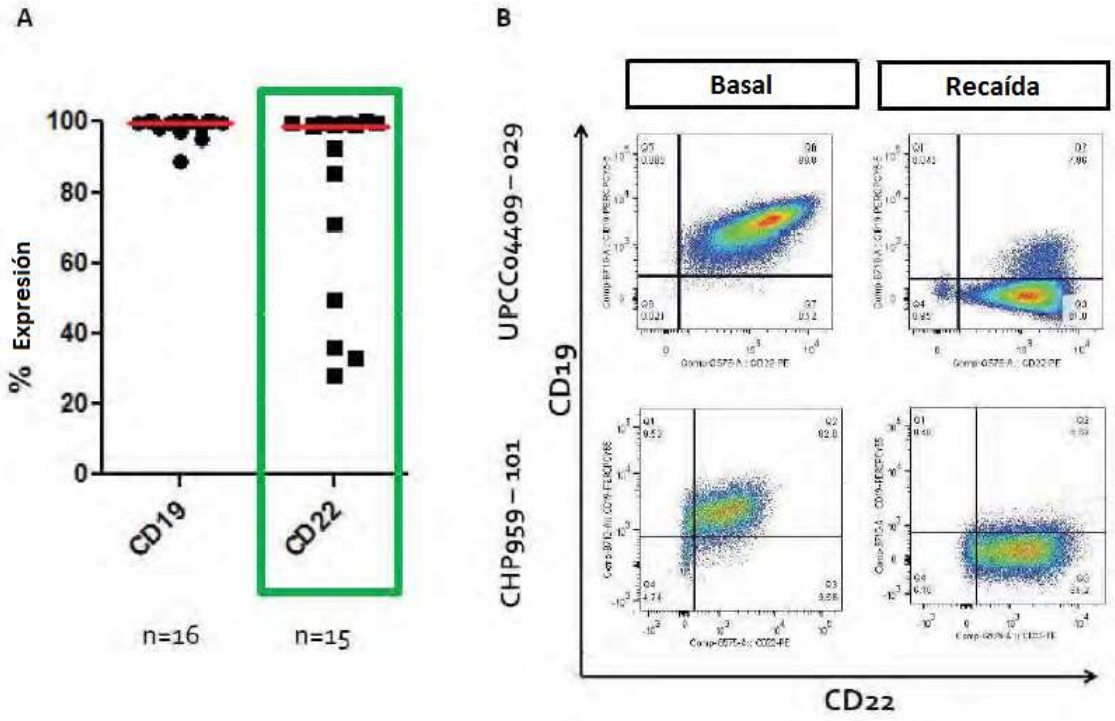

A
% Expresión
100
80
60
40
20
0
CD19
CD22
n=16
n=15
B
Basal
Recaída
UPCC04409 – 029
CHP959 – 101
CD19
CD22

FIG. 28

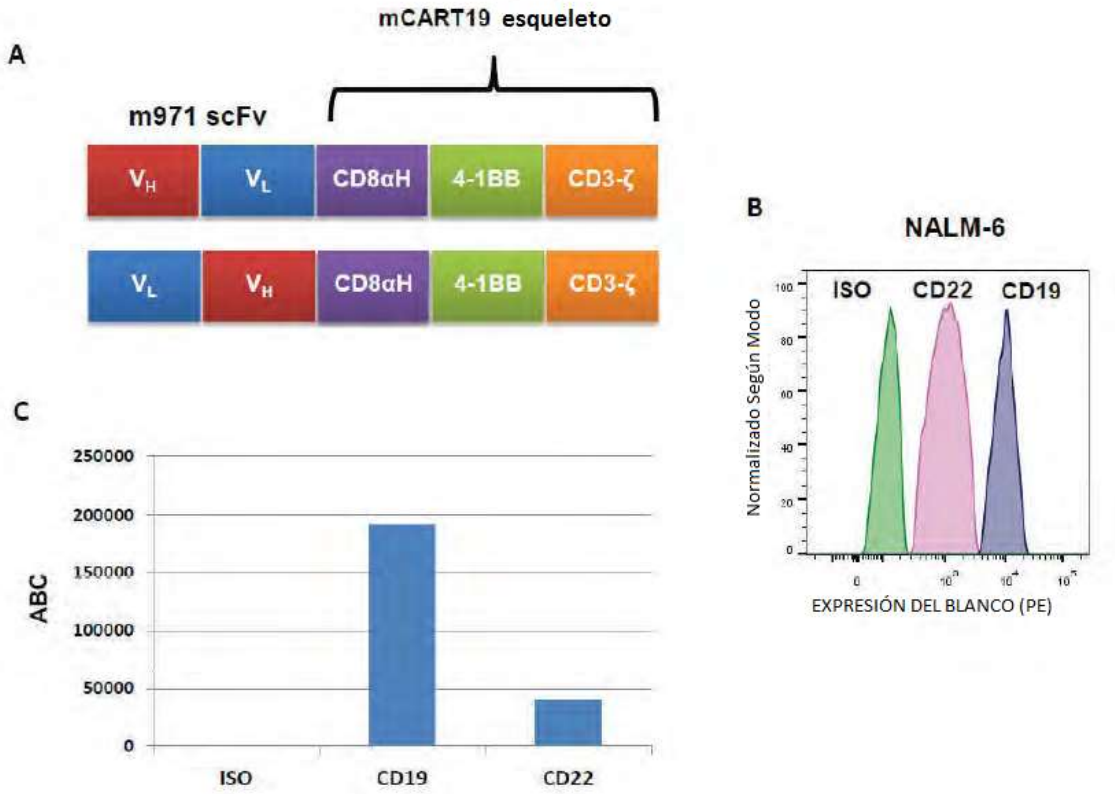
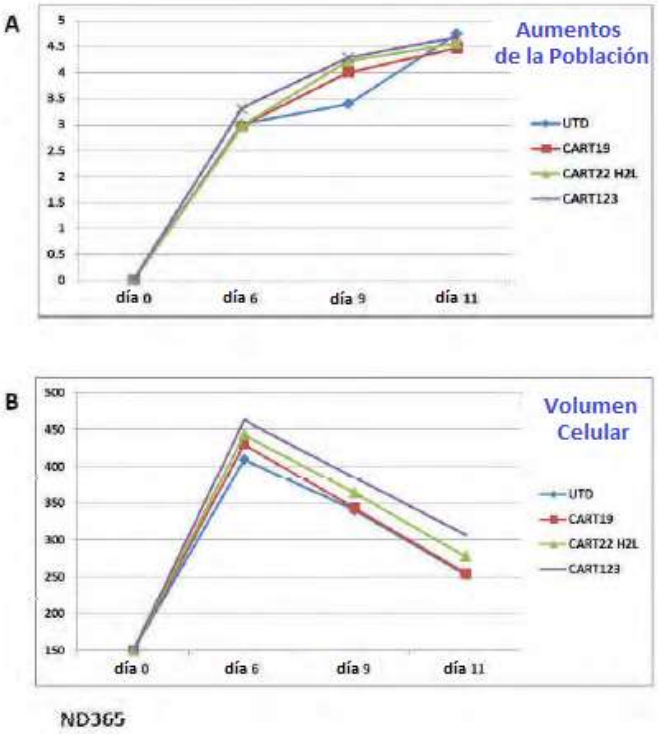

A
mCART19 esqueleto
m971 scFv
V_H
V_L
CD8αH
4-1BB
CD3-ζ
V_L
V_H
CD8αH
4-1BB
CD3-ζ
B
NALM-6
ISO
CD22
CD19
Normalizado Según Modo
EXPRESIÓN DEL BLANCO (PE)
C
ABC
250000
200000
150000
100000
50000
0
ISO
CD19
CD22

FIG. 29


A
Aumentos de la Población
UTD
CART19
CART22 H2L
CART123
día 0
día 6
día 9
día 11
B
Volumen Celular
UTD
CART19
CART22 H2L
CART123
día 0
día 6
día 9
día 11
ND365

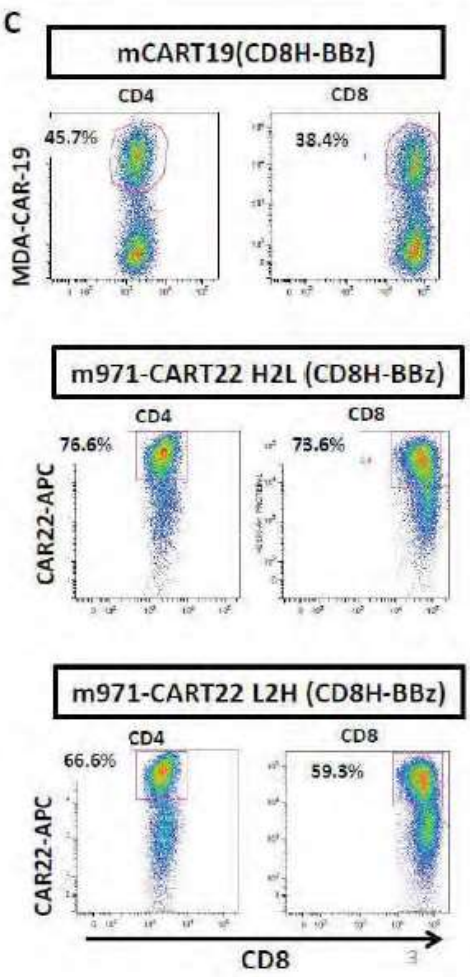
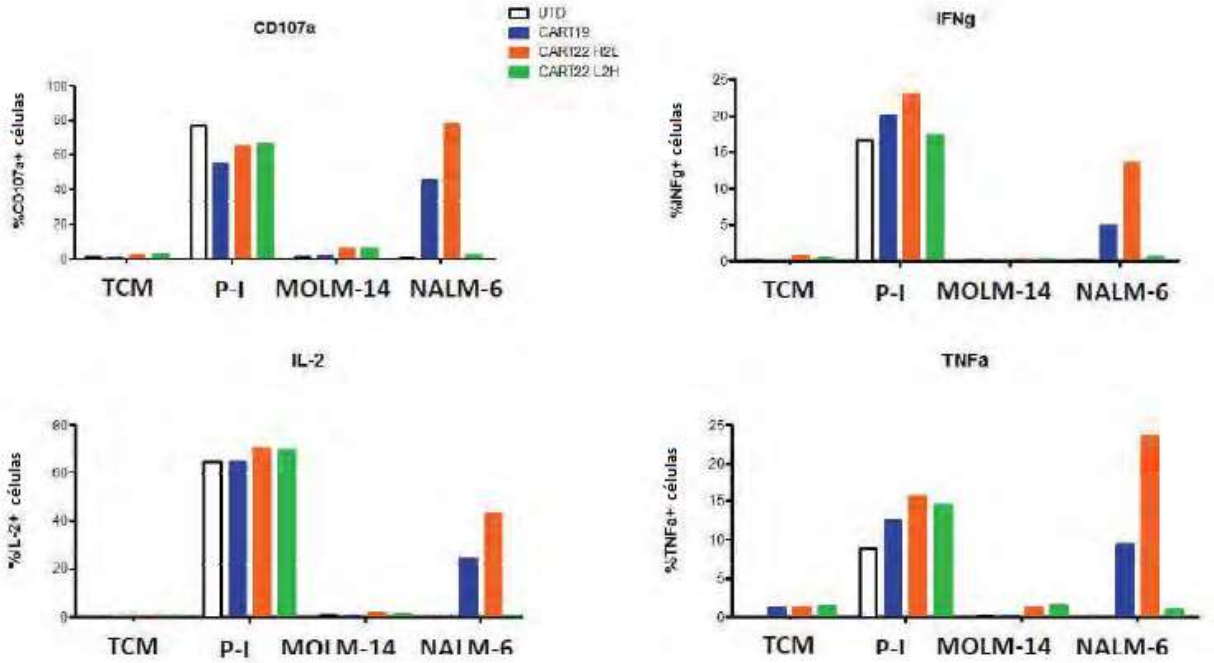

C
mCART19(CD8H-BBz)
CD4
CD8
MDA-CAR-19
45.7%
38.4%
m971-CART22 H2L (CD8H-BBz)
CD4
CD8
CAR22-APC
76.6%
73.6%
m971-CART22 L2H (CD8H-BBz)
CD4
CD8
CAR22-APC
66.6%
59.3%
CD8

FIG. 30



Todos los valores están comparados de manera estadísticamente significativa frente a UTD

FIG. 31

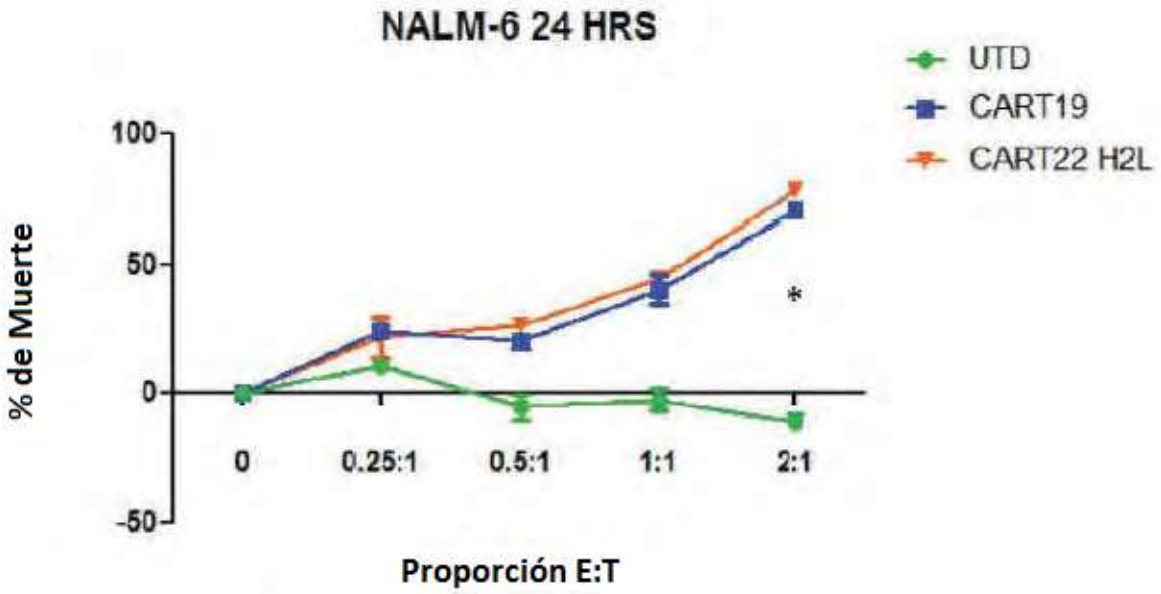

NALM-6 24 HRS
UTD
CART19
CART22 H2L
% de Muerte
100
50
0
-50
0
0.25:1
0.5:1
1:1
2:1
*
Proporción E:T

FIG. 32

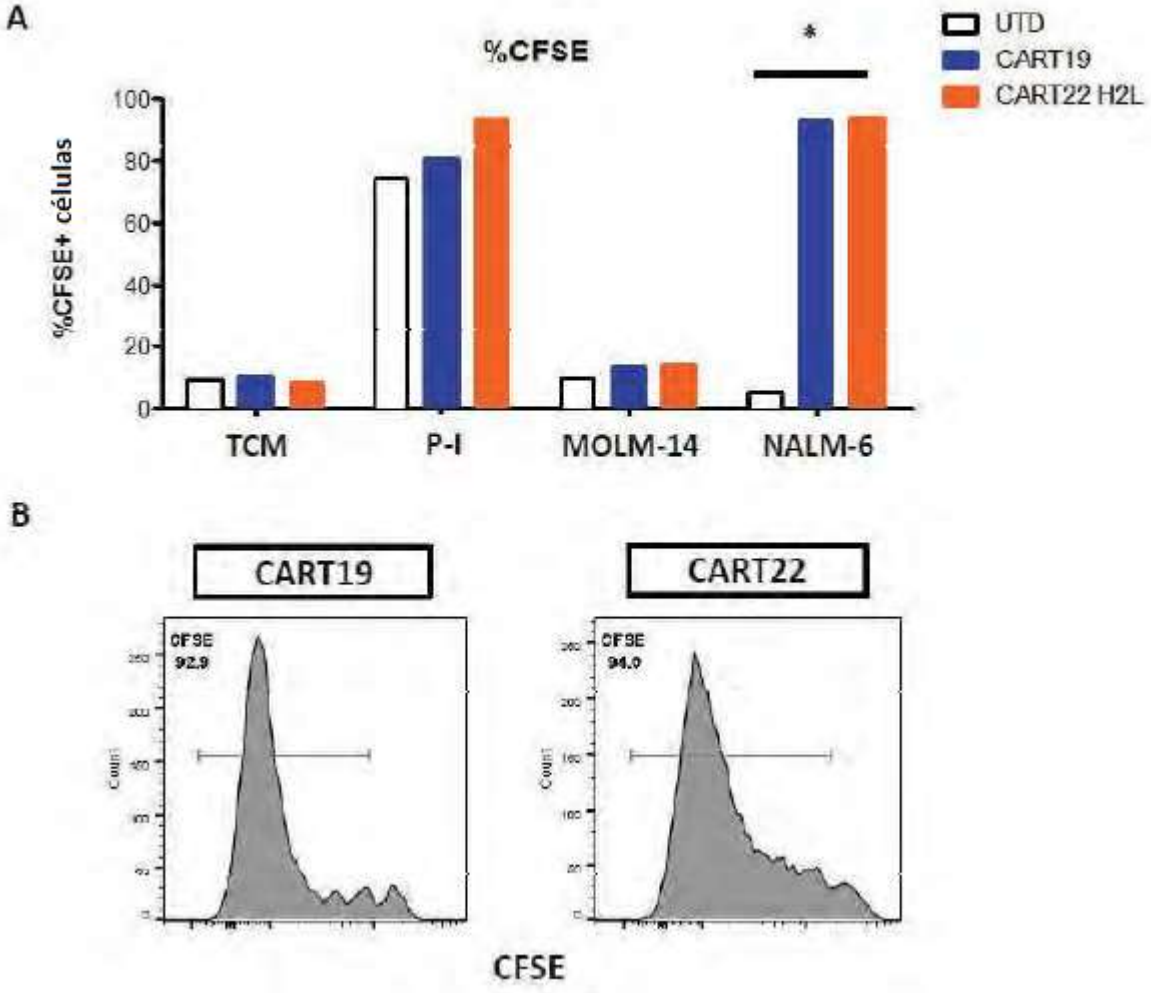
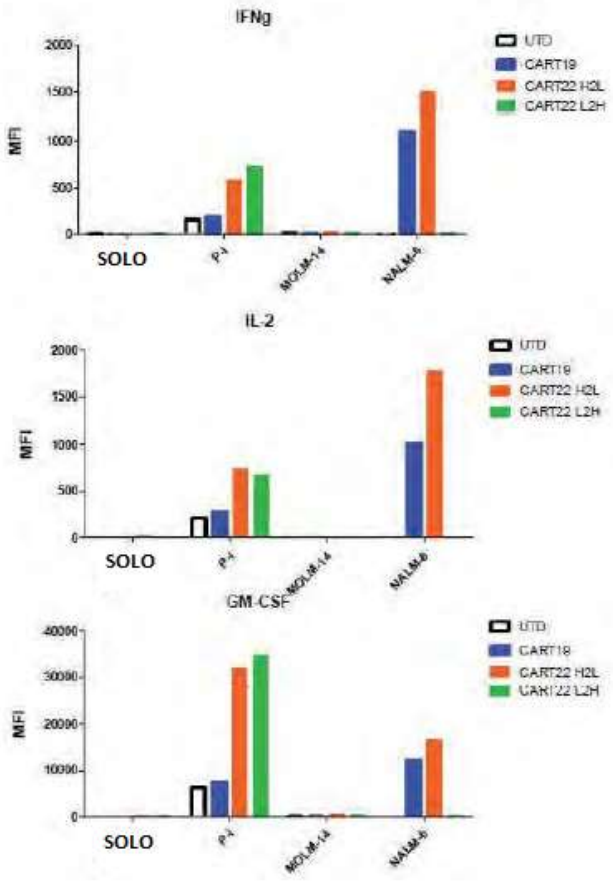
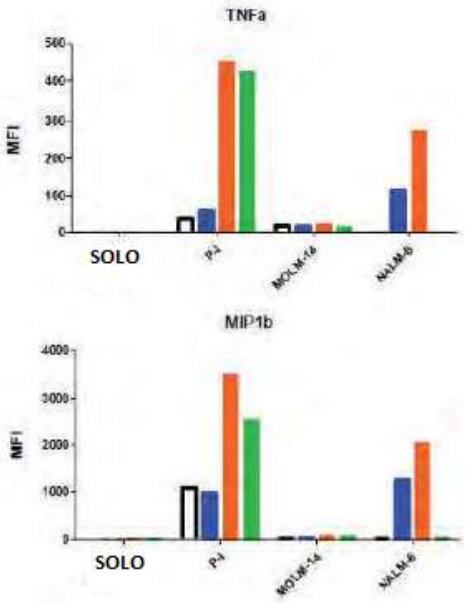

A
%CFSE
*
UTD
CART19
CART22 H2L
%CFSE+ células
100
80
60
40
20
0
TCM
P-I
MOLM-14
NALM-6
B
CART19
CART22
CFSE 92.9
CFSE 94.9
Count
CFSE

FIG. 33





Todos los valores están comparados de manera estadísticamente significativa frente a UTD

FIG. 34

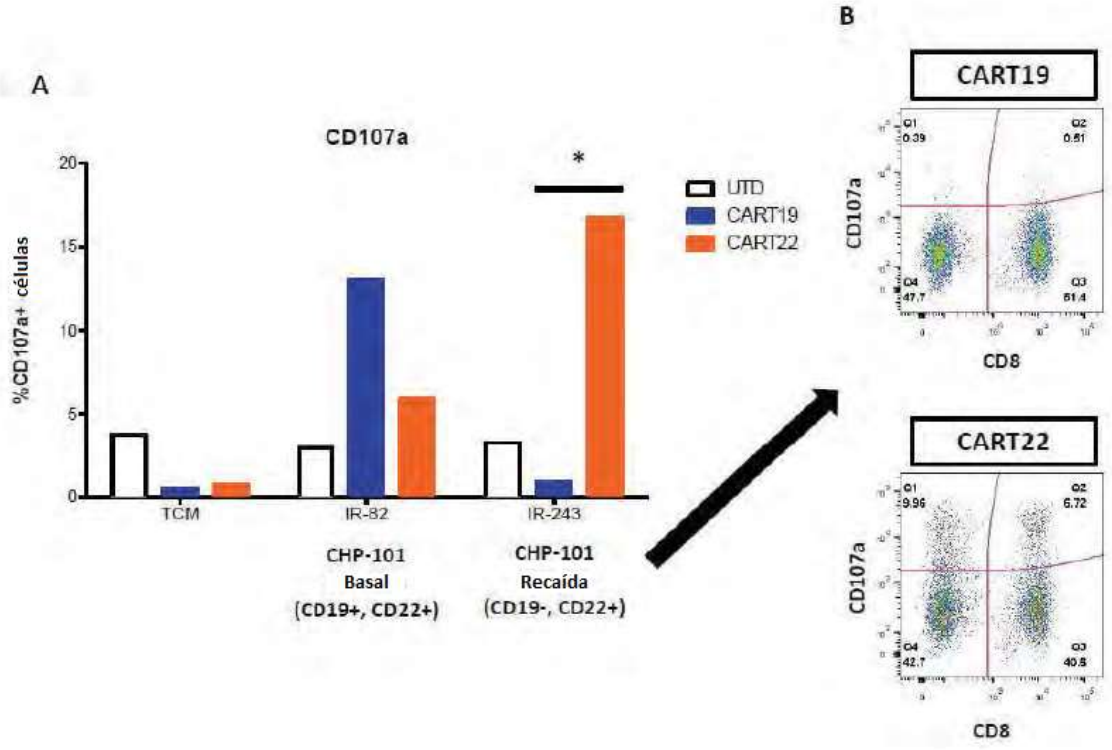

A
CD107a
%CD107a+ células
20
15
10
5
0
*
UTD
CART19
CART22
TCM
IR-82
IR-243
CHP-101
Basal
(CD19+, CD22+)
CHP-101
Recaída
(CD19-, CD22+)
B
CART19
CD107a
CD8
Q1
0.39
Q2
0.81
Q4
47.7
Q3
51.4
CART22
CD107a
CD8
Q1
9.96
Q2
6.72
Q4
42.7
Q3
40.6

FIG. 35

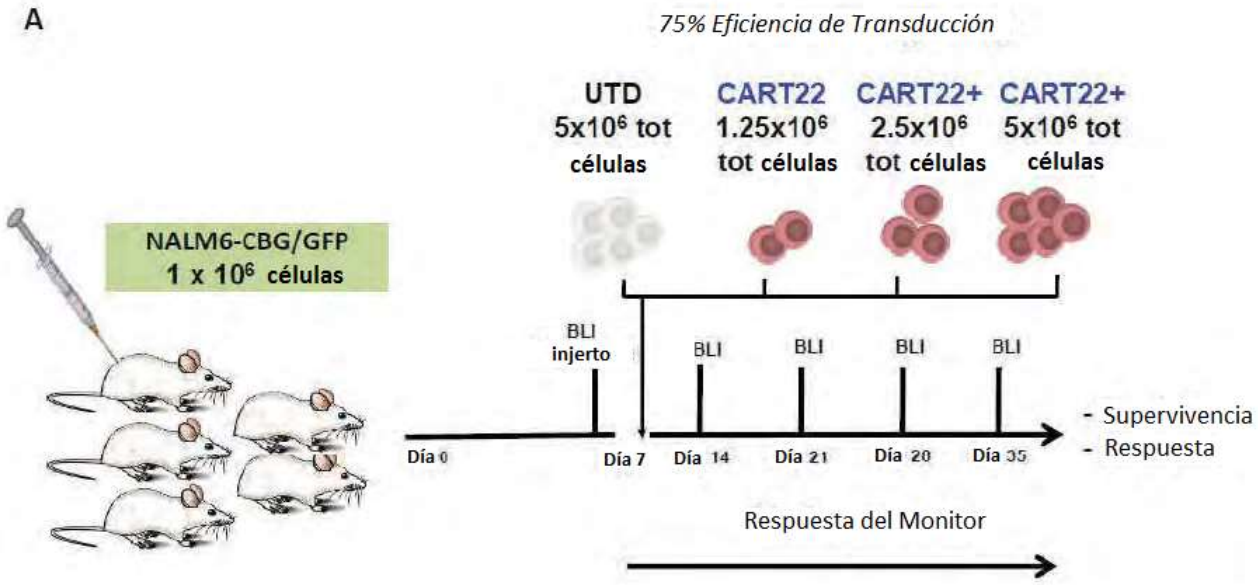
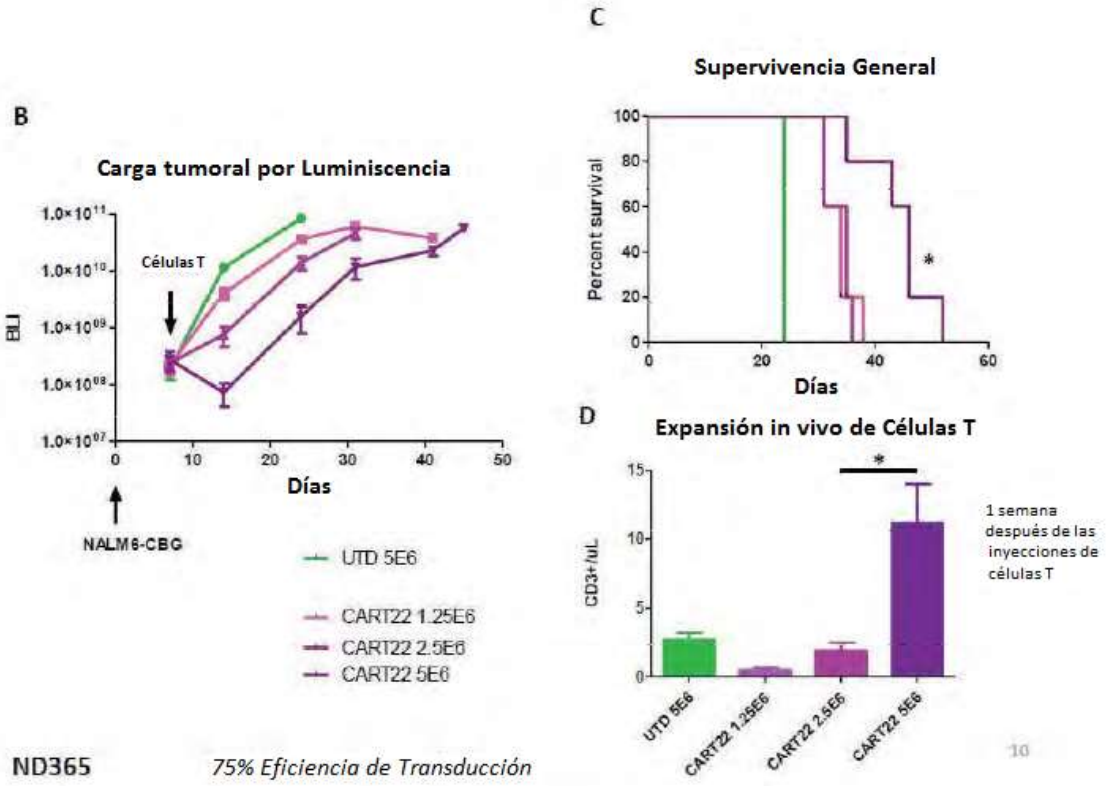

A
75% Eficiencia de Transducción
UTD
5x10⁶ tot células
CART22
1.25x10⁶ tot células
CART22+
2.5x10⁶ tot células
CART22+
5x10⁶ tot células
NALM6-CBG/GFP
1 x 10⁶ células
BLI injerto
BLI
BLI
BLI
BLI
Día 0
Día 7
Día 14
Día 21
Día 28
Día 35
- Supervivencia
- Respuesta
Respuesta del Monitor

FIG. 35



ND365 *75% Eficiencia de Transducción*

FIG. 36

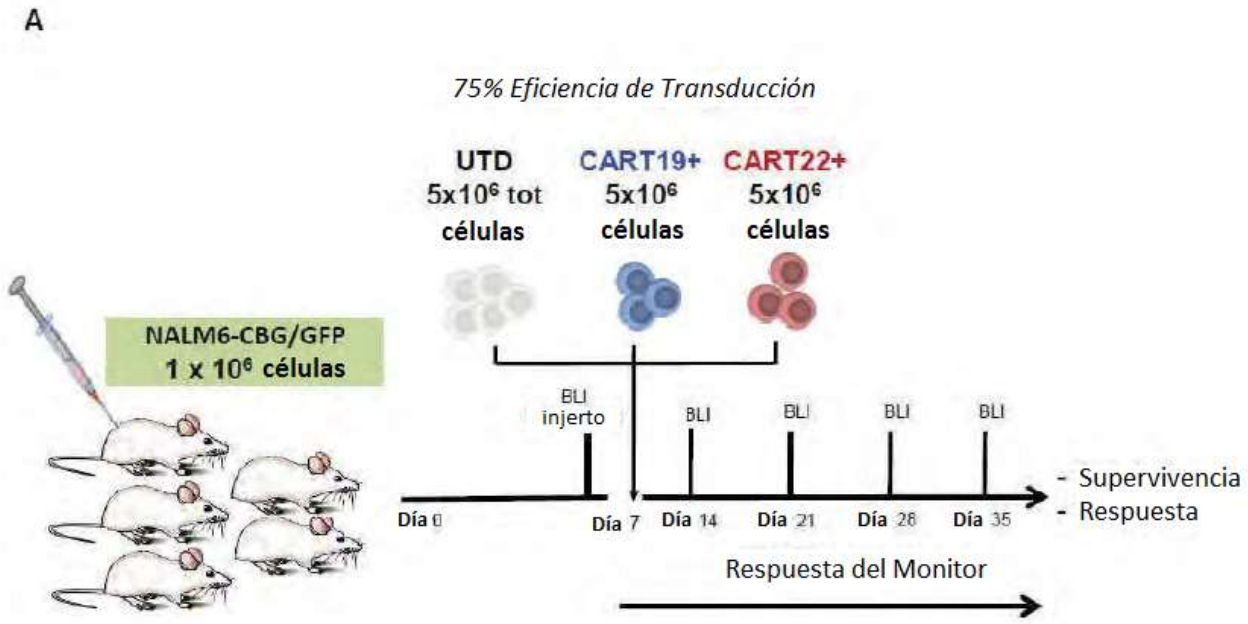
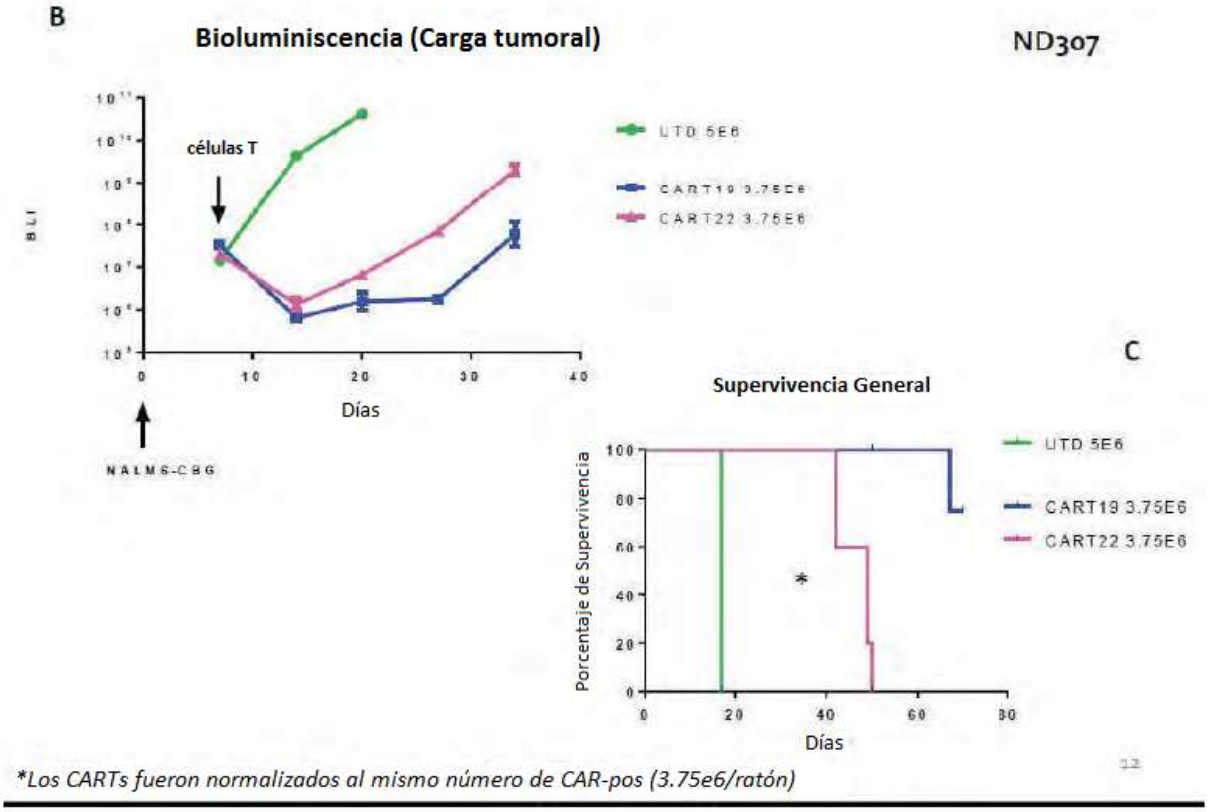

A
75% Eficiencia de Transducción
UTD
5x10⁶ tot
células
CART19+
5x10⁶
células
CART22+
5x10⁶
células
NALM6-CBG/GFP
1 x 10⁶ células
BLI
injerto
BLI
BLI
BLI
BLI
Día 0
Día 7
Día 14
Día 21
Día 28
Día 35
- Supervivencia
- Respuesta
Respuesta del Monitor

FIG. 36



**Los CARTs fueron normalizados al mismo número de CAR-pos (3.75e6/ratón)*

FIG. 37

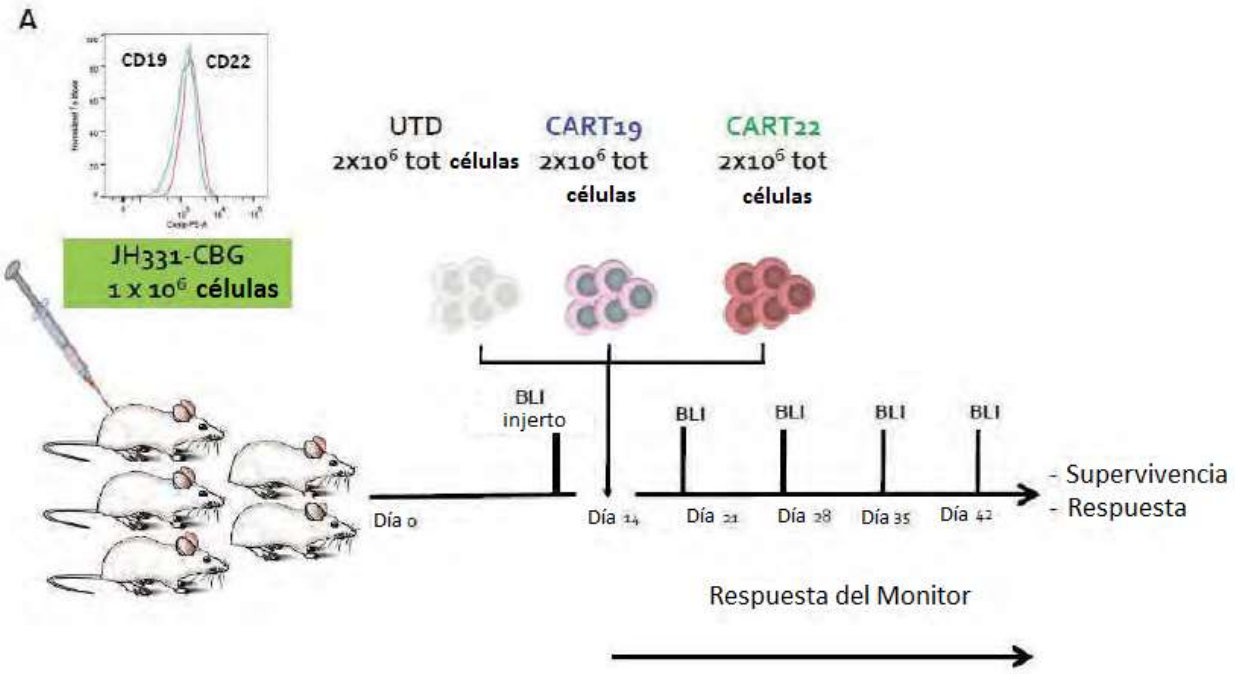

A
CD19
CD22
JH331-CBG
1 x 10⁶ células
UTD
2x10⁶ tot células
CART19
2x10⁶ tot
células
CART22
2x10⁶ tot
células
BLI
injerto
BLI
BLI
BLI
BLI
Día 0
Día 14
Día 21
Día 28
Día 35
Día 42
- Supervivencia
- Respuesta
Respuesta del Monitor

FIG. 37

B

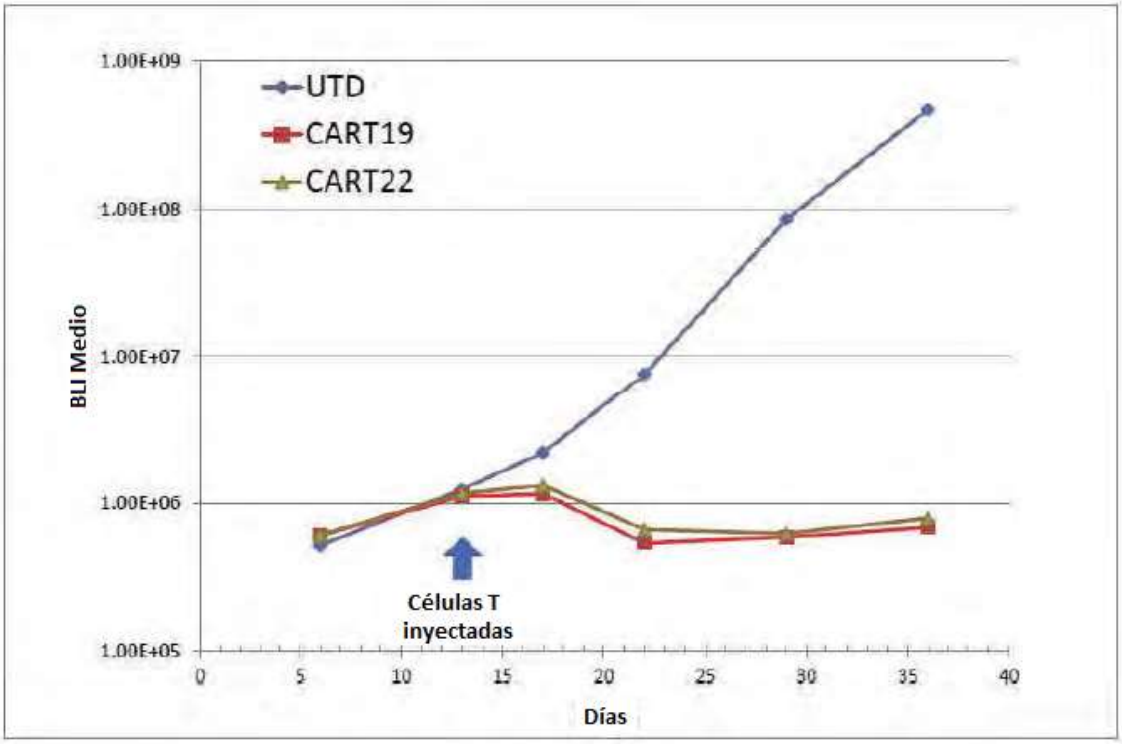

1.00E+09
1.00E+08
1.00E+07
1.00E+06
1.00E+05
BLI Medio
UTD
CART19
CART22
Células T
inyectadas
0
5
10
15
20
25
30
35
40
Días

FIG. 38A

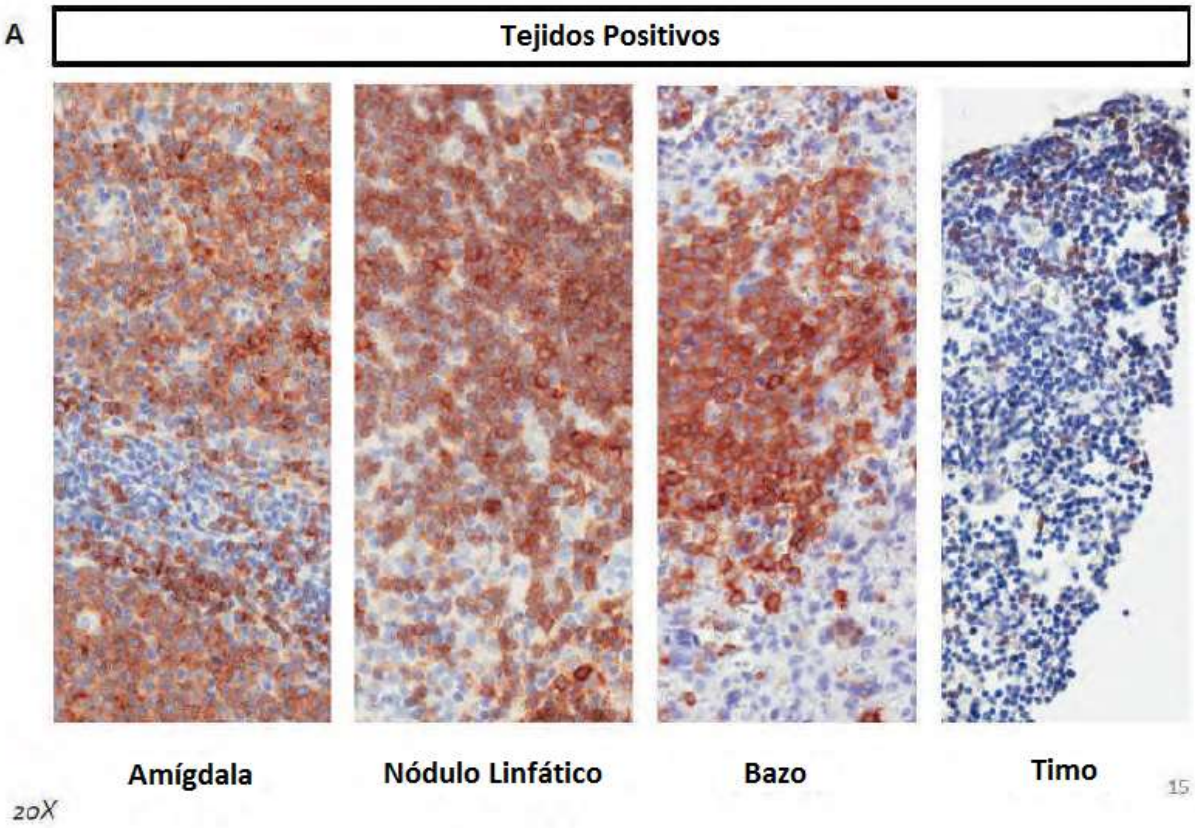

A
Tejidos Positivos
Amígdala
Nódulo Linfático
Bazo
Timo
20X

FIG. 38B

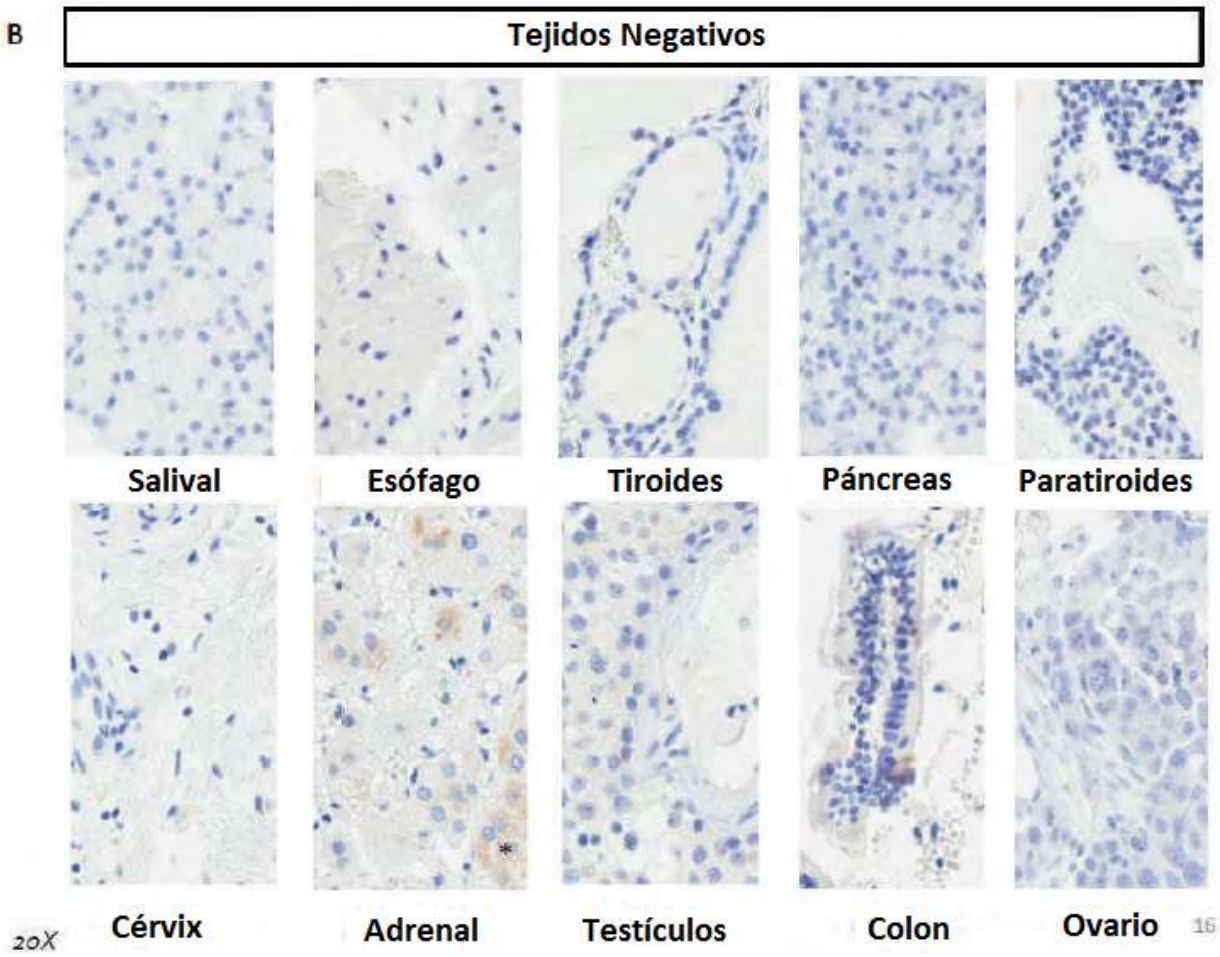

B
Tejidos Negativos
Salival
Esófago
Tiroides
Páncreas
Paratiroides
Cérvix
Adrenal
Testículos
Colon
Ovario
20X
16

FIG. 38B

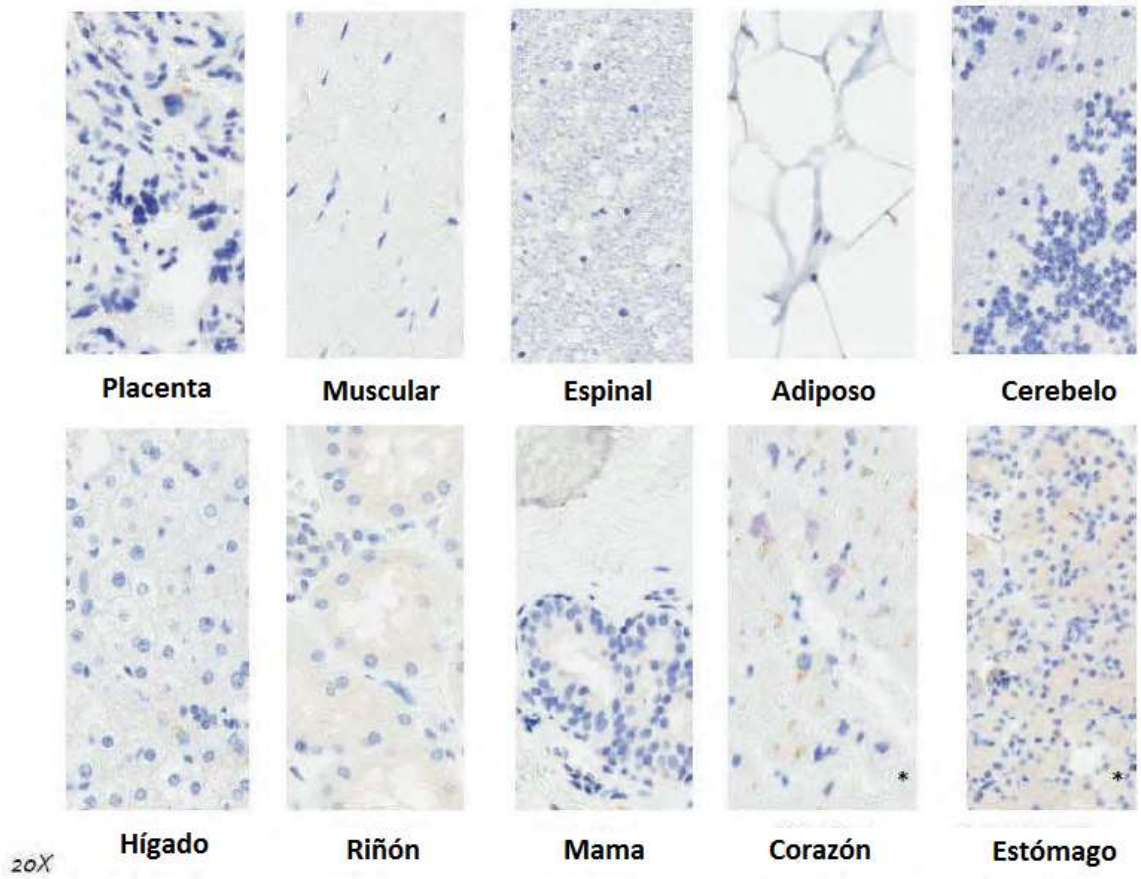

Placenta
Muscular
Espinal
Adiposo
Cerebelo
Hígado
Riñón
Mama
Corazón
Estómago
20X

FIG. 38B

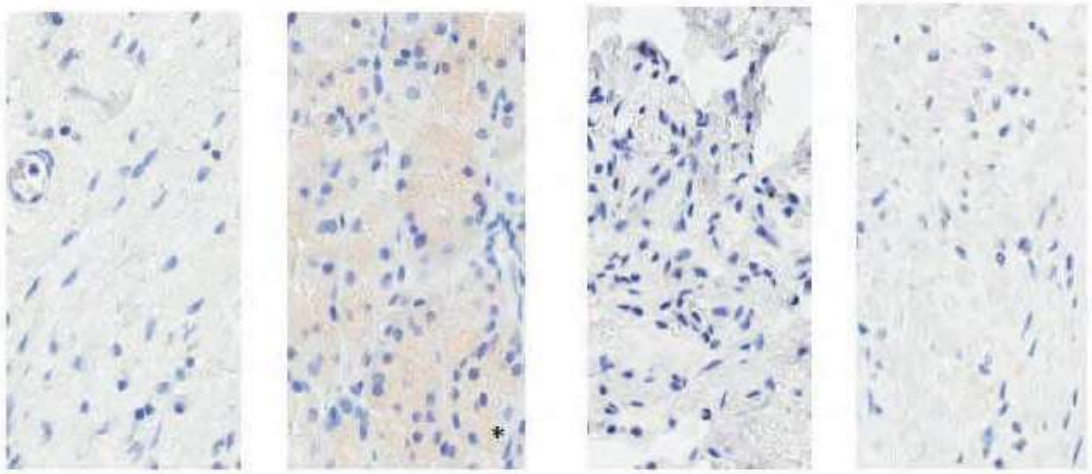


FIG. 38C

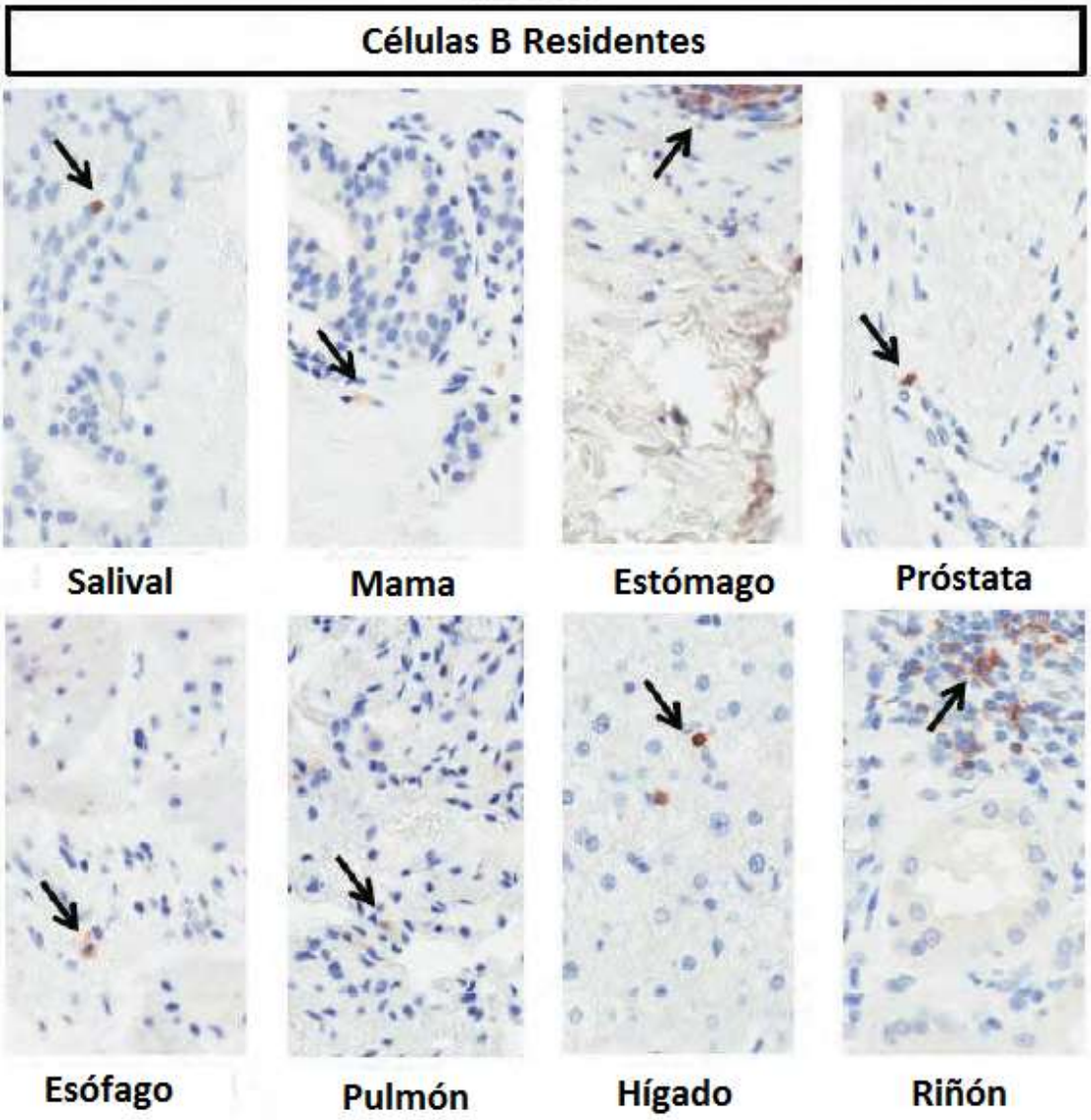
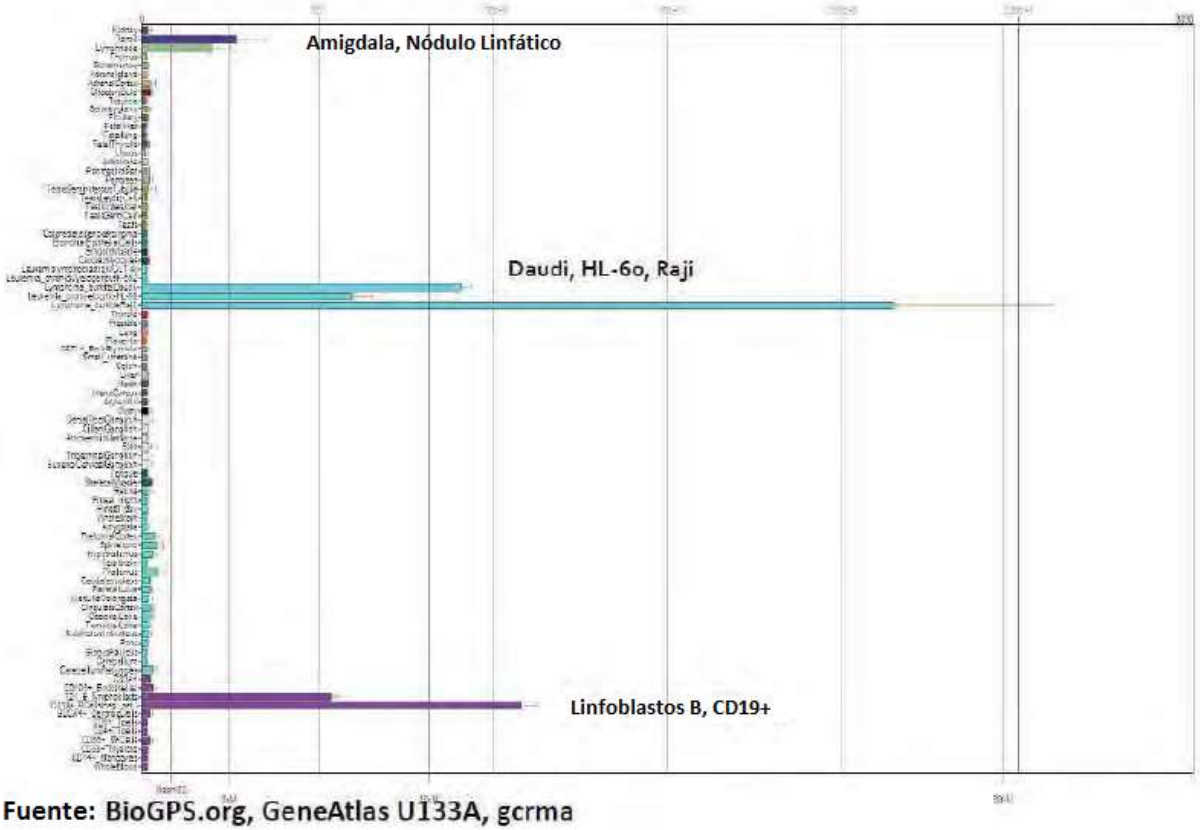

Células B Residentes
Salival
Mama
Estómago
Próstata
Esófago
Pulmón
Hígado
Riñón

FIG. 39



Fuente: BioGPS.org, GeneAtlas U133A, gcrma

FIG. 40

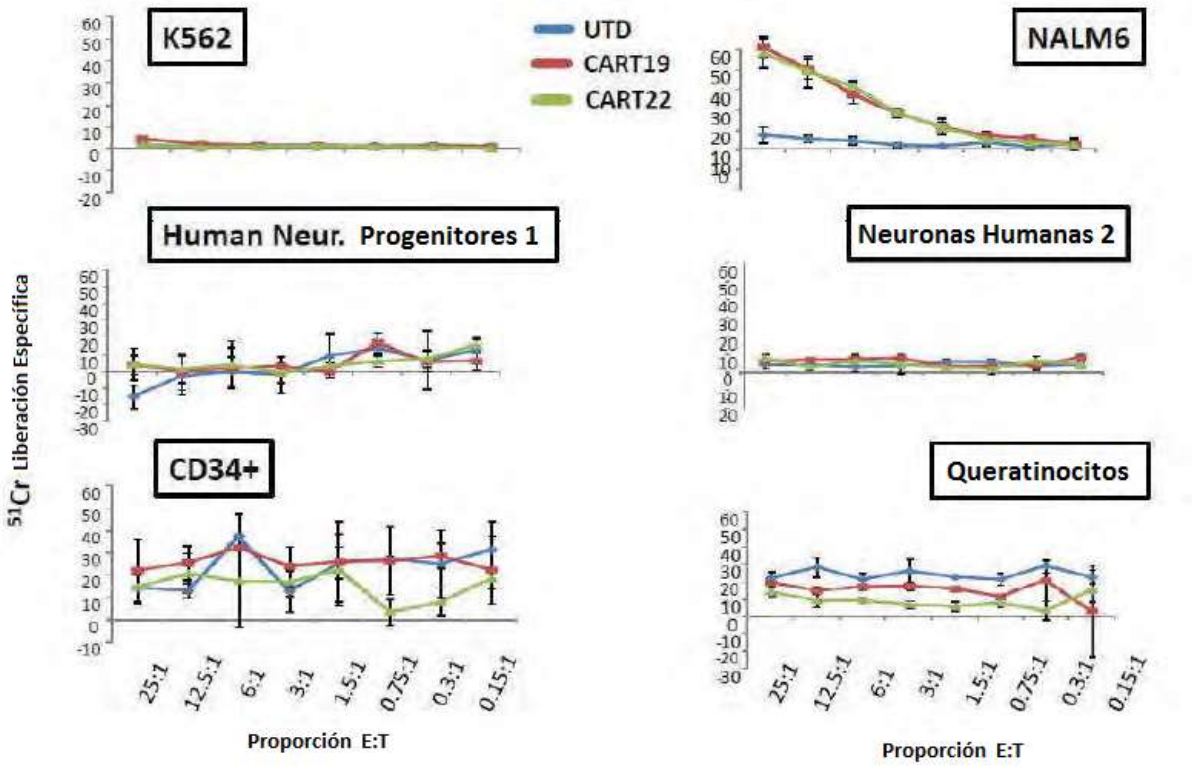

K562
UTD
CART19
CART22
NALM6
Human Neur. Progenitores 1
Neuronas Humanas 2
CD34+
Queratinocitos
^{51}Cr Liberación Específica
25:1
12.5:1
6:1
3:1
1.5:1
0.75:1
0.3:1
0.15:1
Proporción E:T
Proporción E:T

FIG. 41

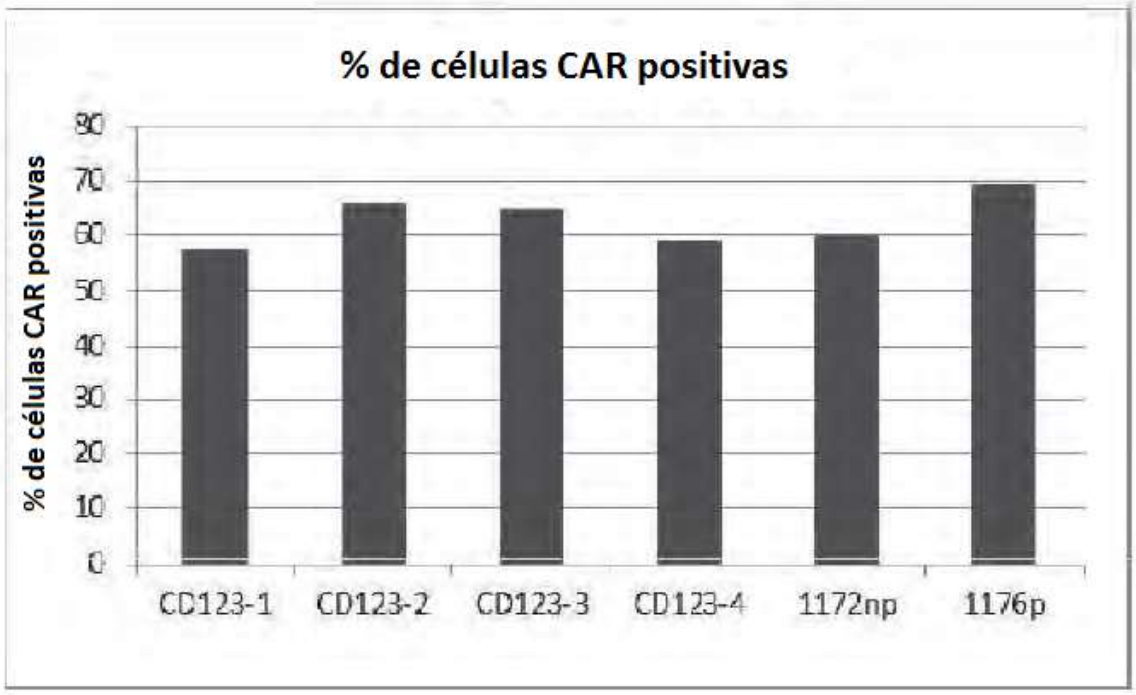

% de células CAR positivas
% de células CAR positivas
80
70
60
50
40
30
20
10
0
CD123-1
CD123-2
CD123-3
CD123-4
1172np
1176p

FIG. 42A: CD123-K562

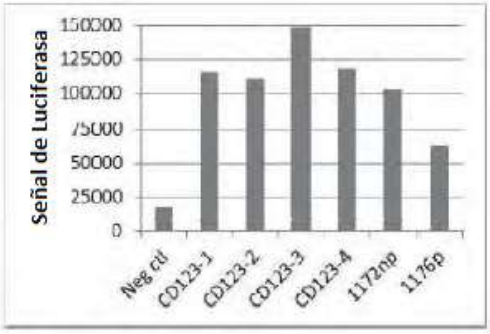


FIG. 42B: MOLM13

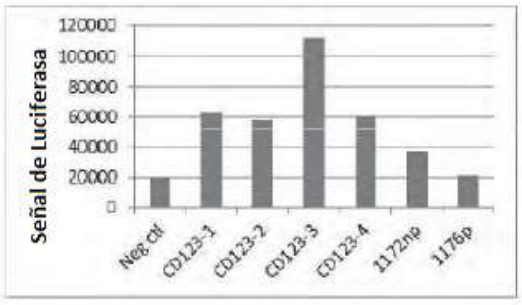


FIG. 42C: K562

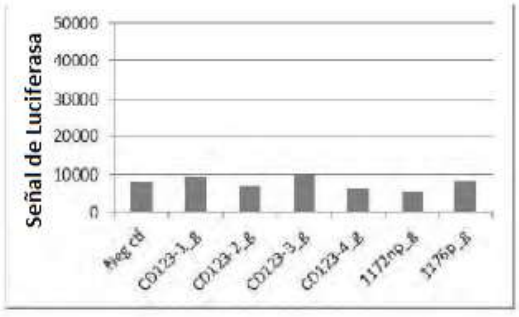


FIG. 43A

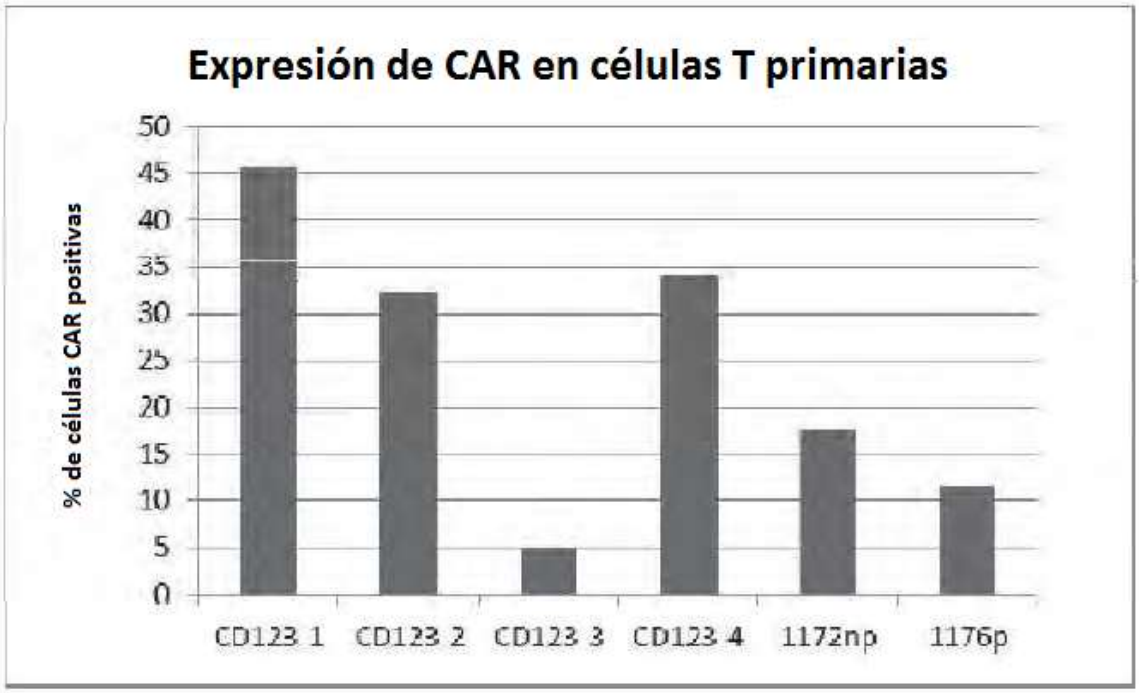

Expresión de CAR en células T primarias
% de células CAR positivas
50
45
40
35
30
25
20
15
10
5
0
CD123 1
CD123 2
CD123 3
CD123 4
1172np
1176p

FIG. 43B

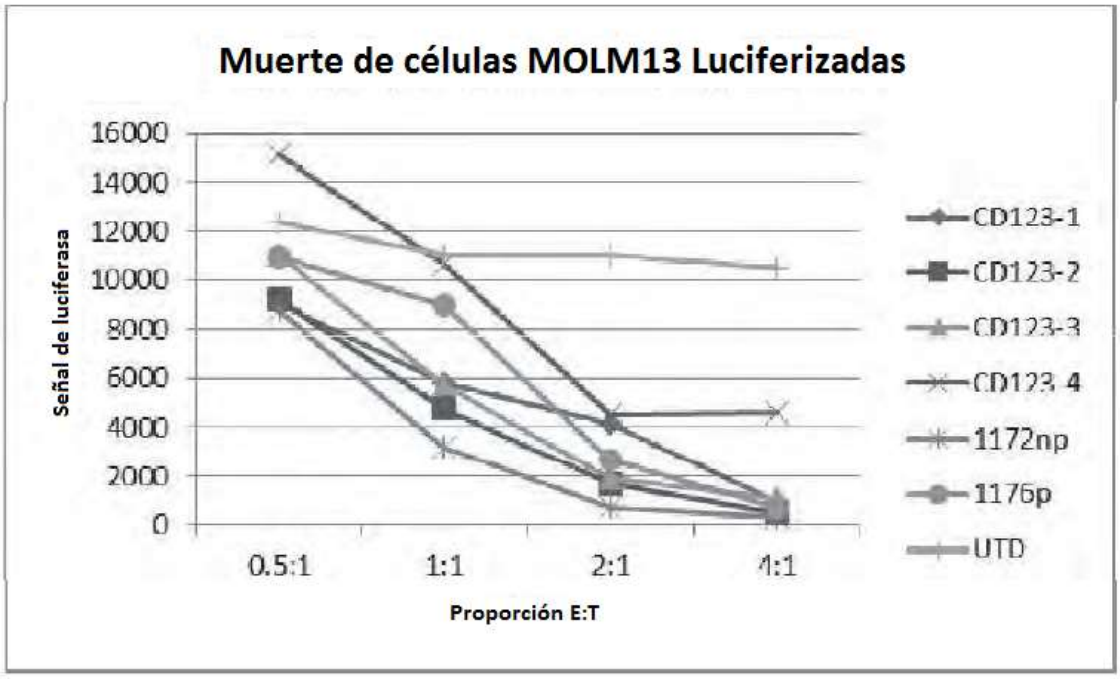

Muerte de células MOLM13 Luciferizadas
Señal de luciferasa
16000
14000
12000
10000
8000
6000
4000
2000
0
0.5:1
1:1
2:1
4:1
Proporción E:T
CD123-1
CD123-2
CD123-3
CD123-4
1172np
1176p
UTD

FIG. 44A

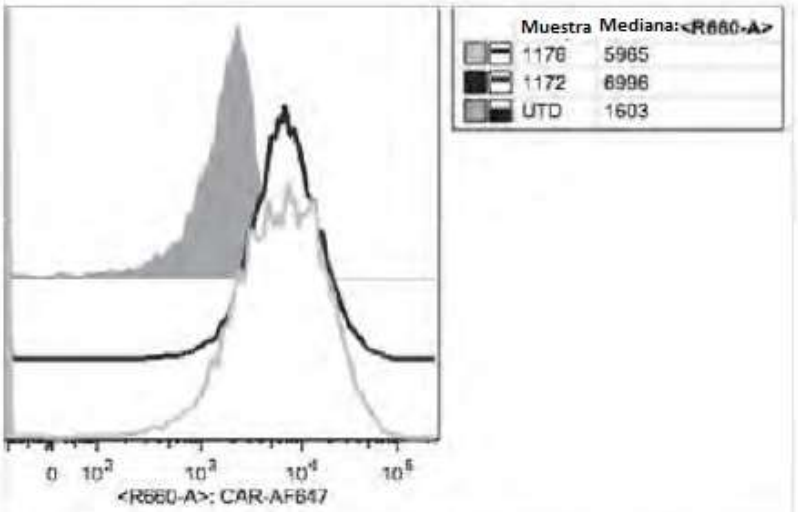


FIG. 44B

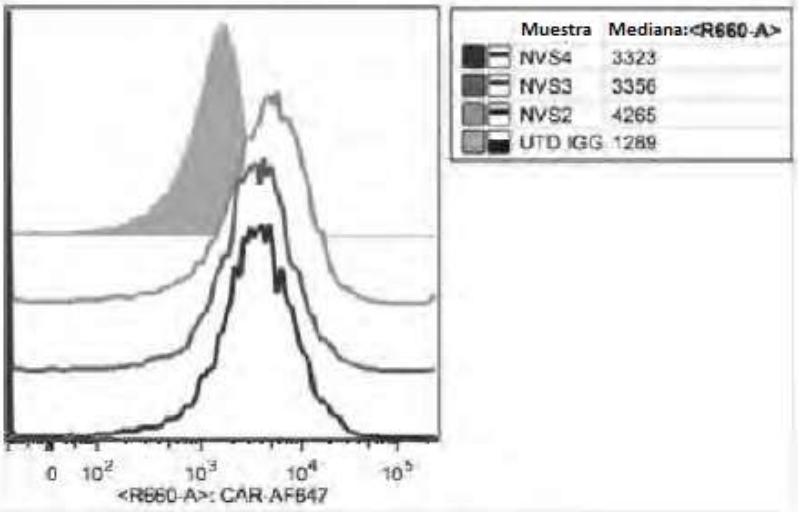


FIG. 45

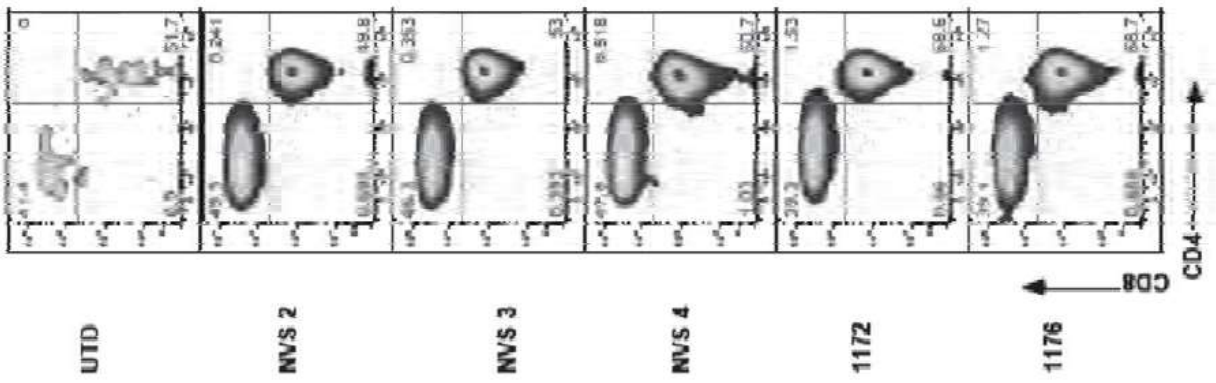


FIG. 46

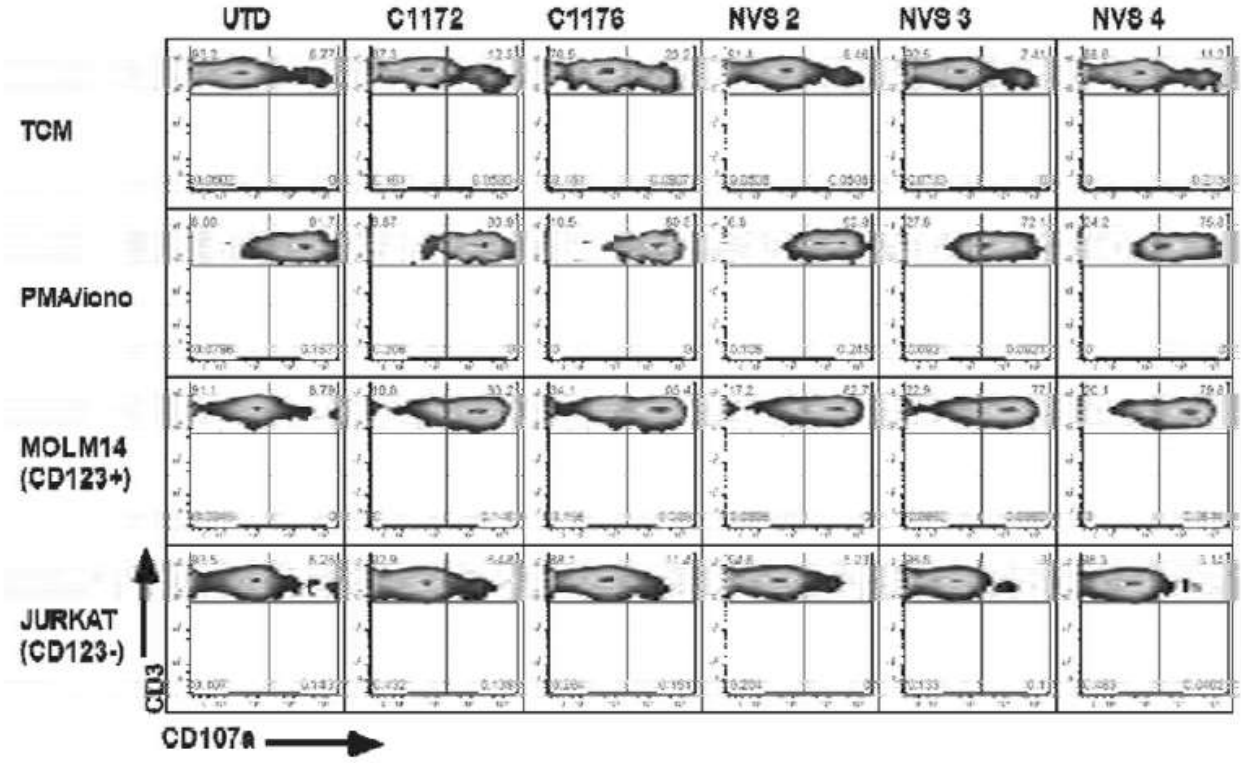

UTD
C1172
C1176
NVS 2
NVS 3
NVS 4
TCM
PMA/iono
MOLM14
(CD123+)
JURKAT
(CD123-)
CD3
CD107a

FIG. 47

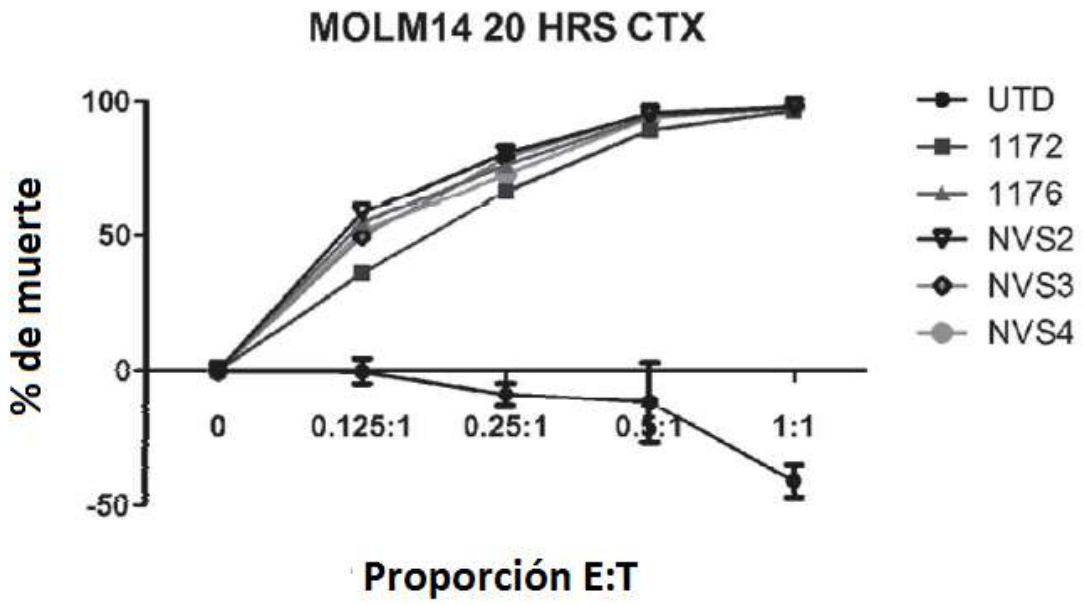
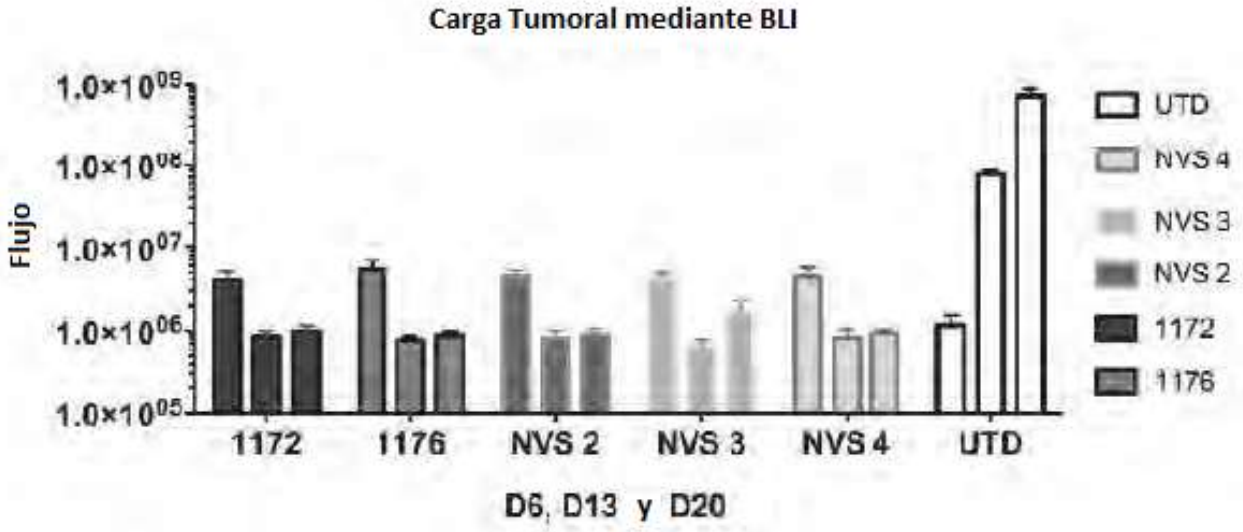

MOLM14 20 HRS CTX
% de muerte
100
50
0
-50
0
0.125:1
0.25:1
0.5:1
1:1
Proporción E:T
UTD
1172
1176
NVS2
NVS3
NVS4

FIG. 48


Carga Tumoral mediante BLI
Flujo
1.0×10^09
1.0×10^08
1.0×10^07
1.0×10^06
1.0×10^05
1172
1176
NVS 2
NVS 3
NVS 4
UTD
D6, D13 y D20
UTD
NVS 4
NVS 3
NVS 2
1172
1176

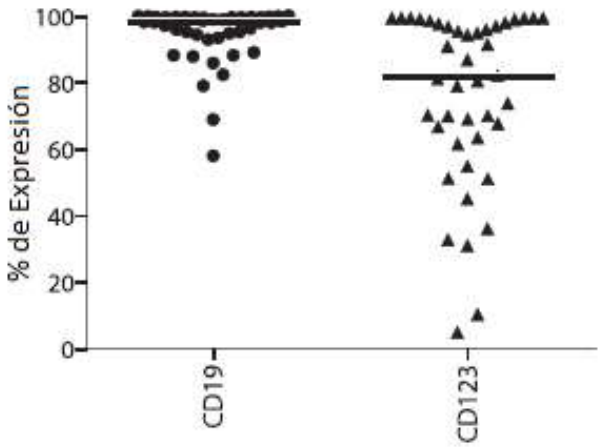


FIG. 49A

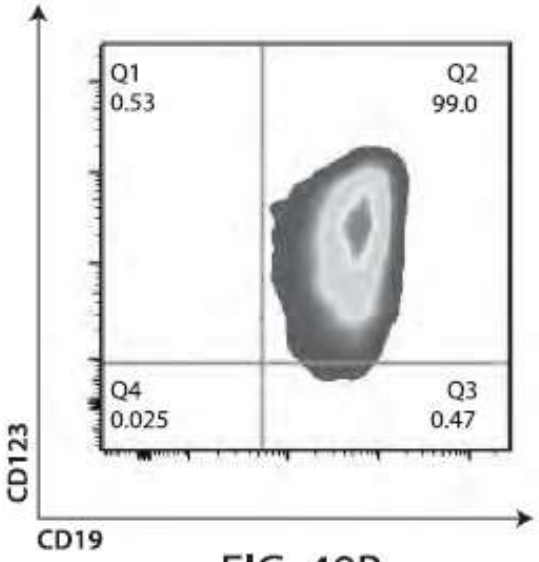


FIG. 49B

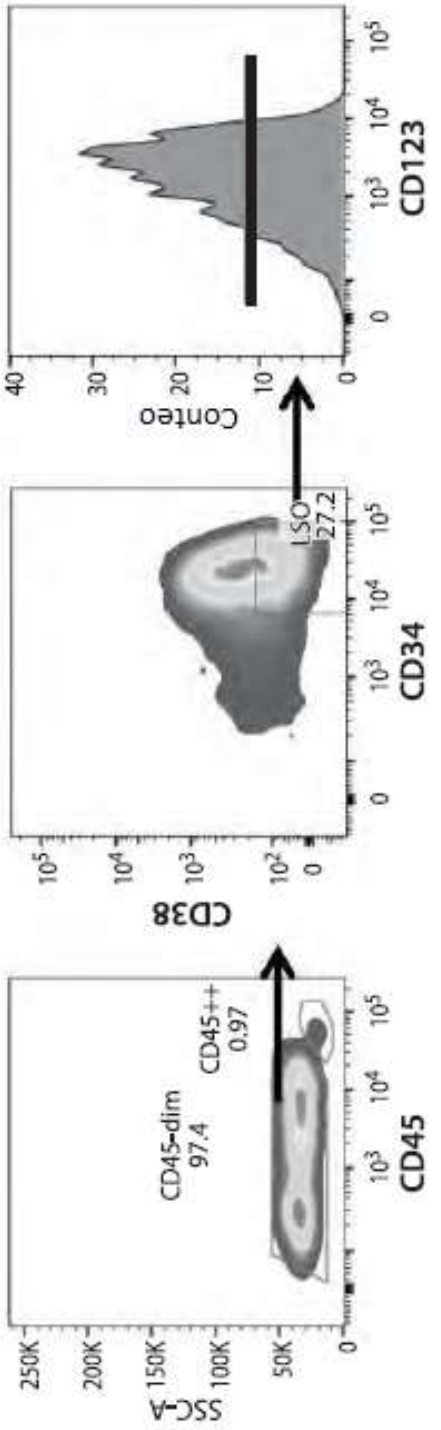

SSC-A
250K
200K
150K
100K
50K
0
CD45-dim
97.4
CD45++
0.97
10^3 10^4 10^5
CD45
CD38
10^5
10^4
10^3
10^2
0
LSO
27.2
10^3 10^4 10^5
CD34
Conteo
40
30
20
10
0
0 10^3 10^4 10^5
CD123

FIG. 49C

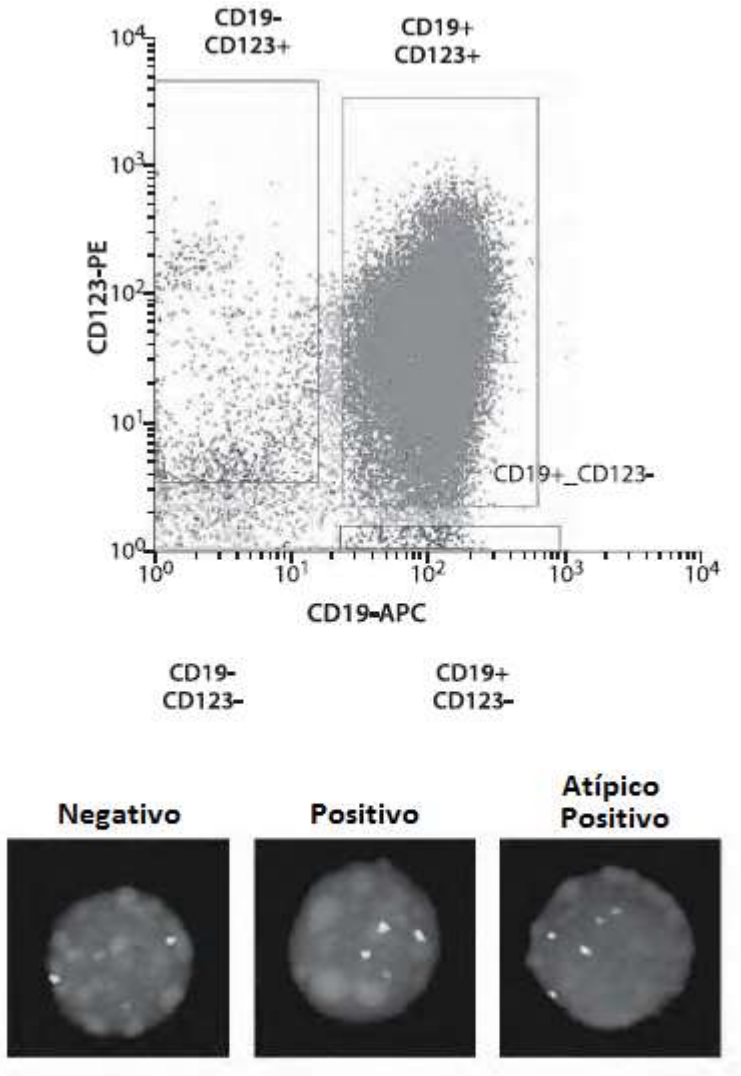

CD19-
CD123+
CD19+
CD123+
CD123-PE
CD19+_CD123-
CD19-APC
CD19-
CD123-
CD19+
CD123-
Negativo
Positivo
Atípico
Positivo

FIG. 49D

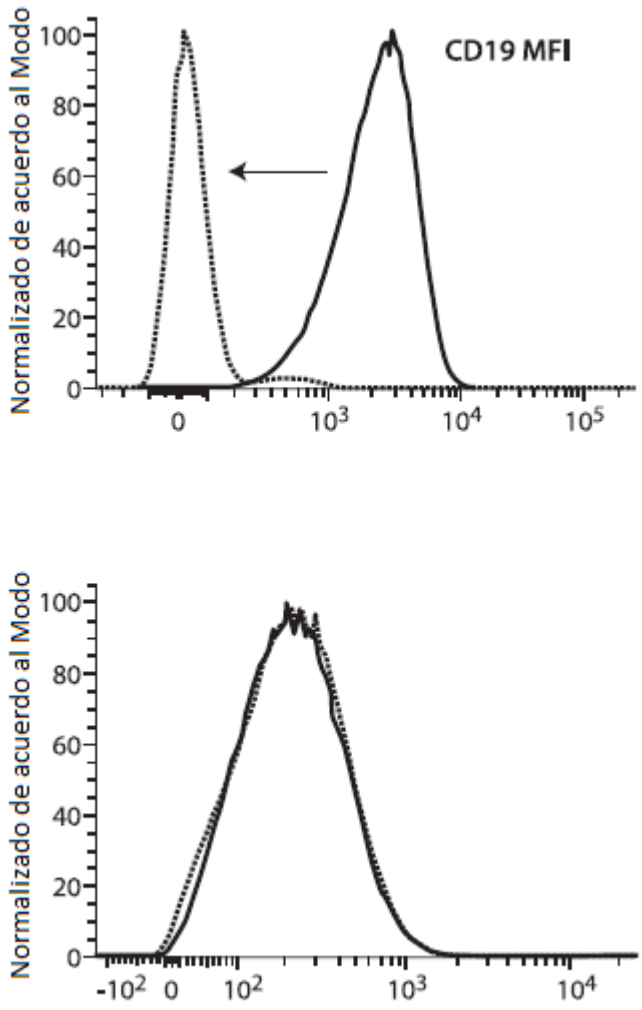

CD19 MFI
Normalizado de acuerdo al Modo
100
80
60
40
20
0
0
10^3
10^4
10^5
Normalizado de acuerdo al Modo
100
80
60
40
20
0
-10^2
0
10^2
10^3
10^4

FIG. 49E

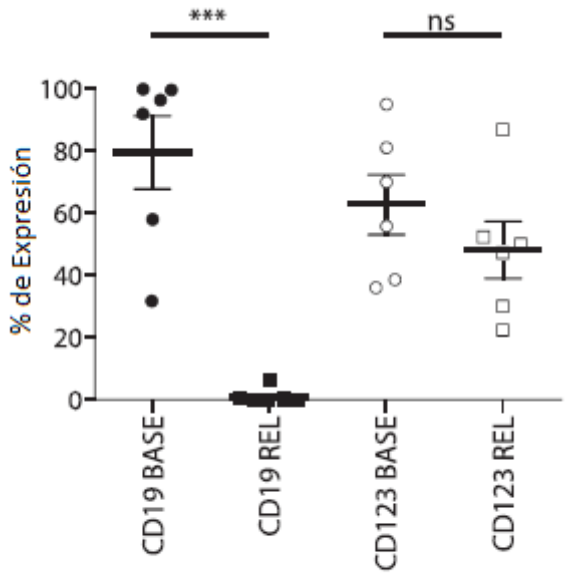

***
ns
100
80
60
40
20
0
% de Expresión
CD19 BASE
CD19 REL
CD123 BASE
CD123 REL

FIG. 49F

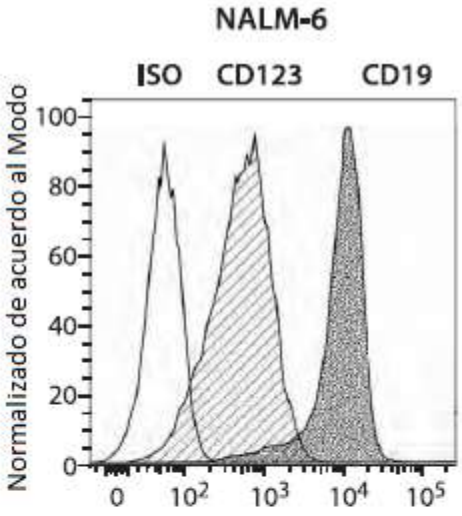


FIG. 50A

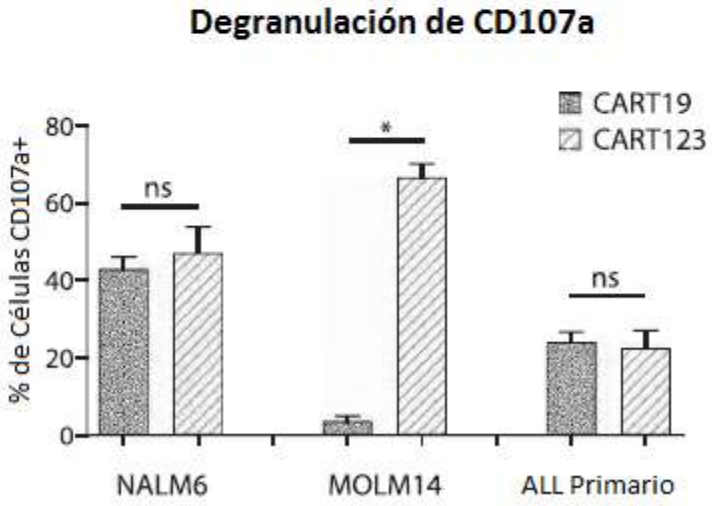


FIG. 50B

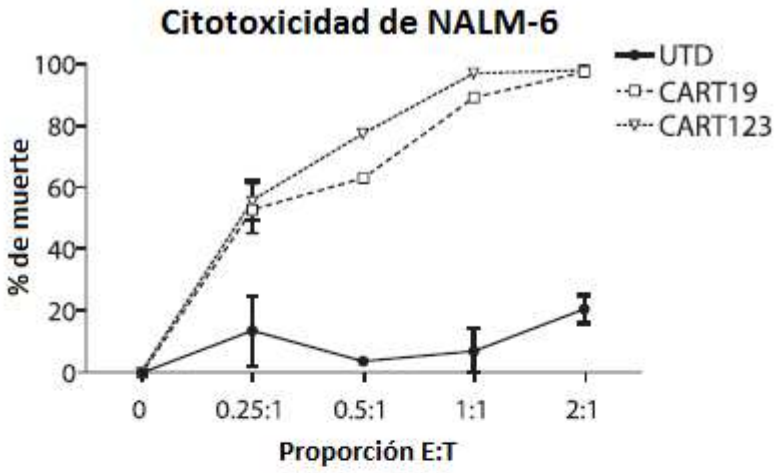


FIG. 50C

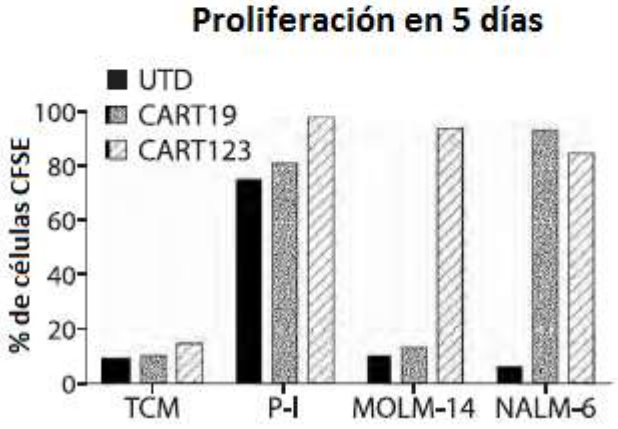


FIG. 50D

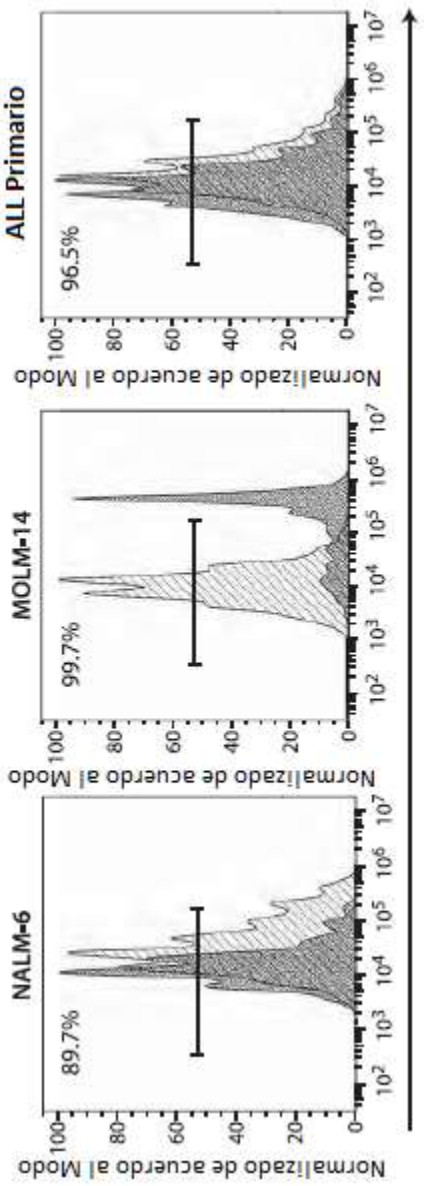

NALM-6
89.7%
MOLM-14
99.7%
ALL Primario
96.5%
Normalizado de acuerdo al Modo
CFSE

FIG. 50E

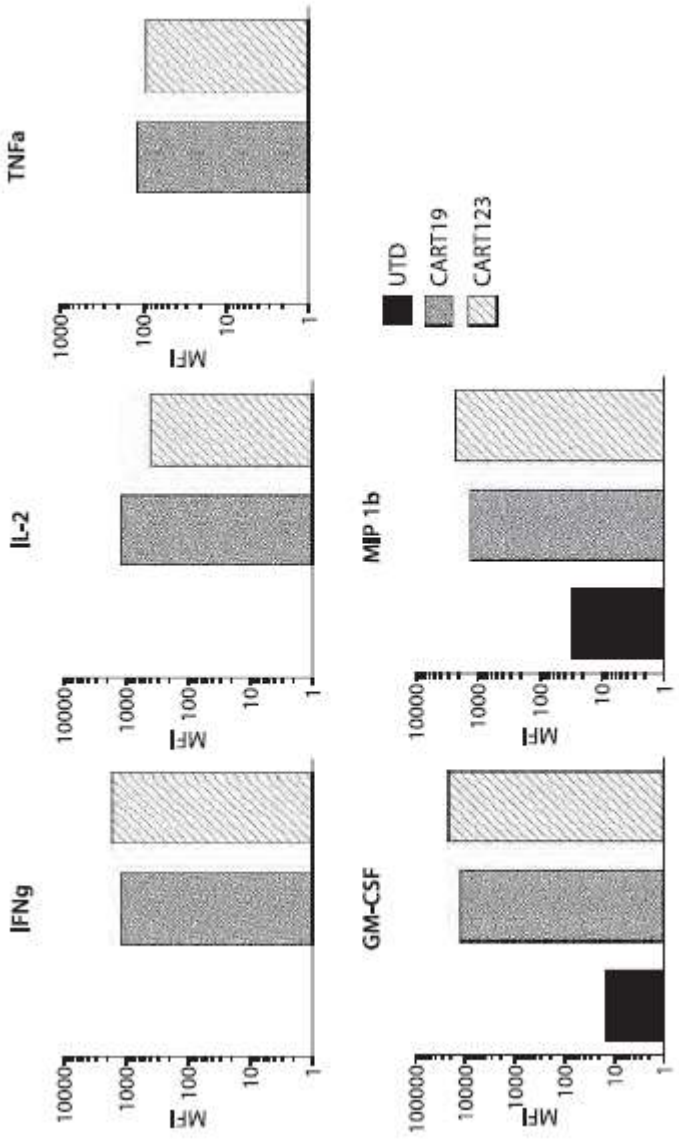


FIG. 50F

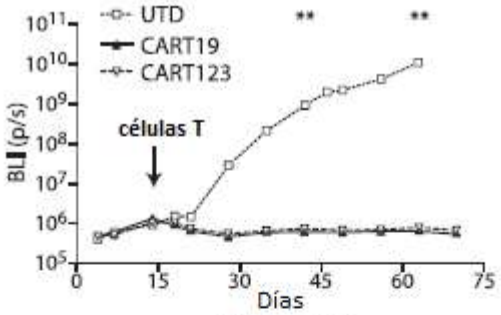


FIG. 51A

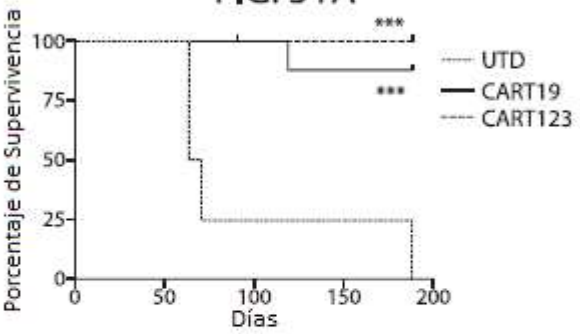


FIG. 51B

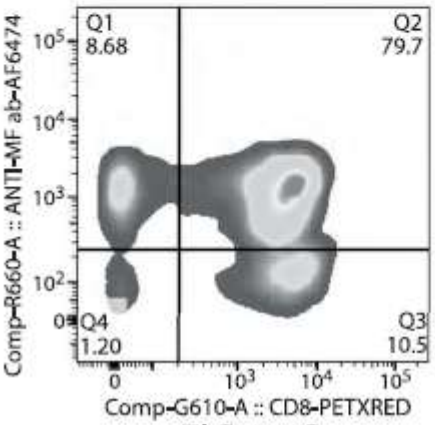


FIG. 51C

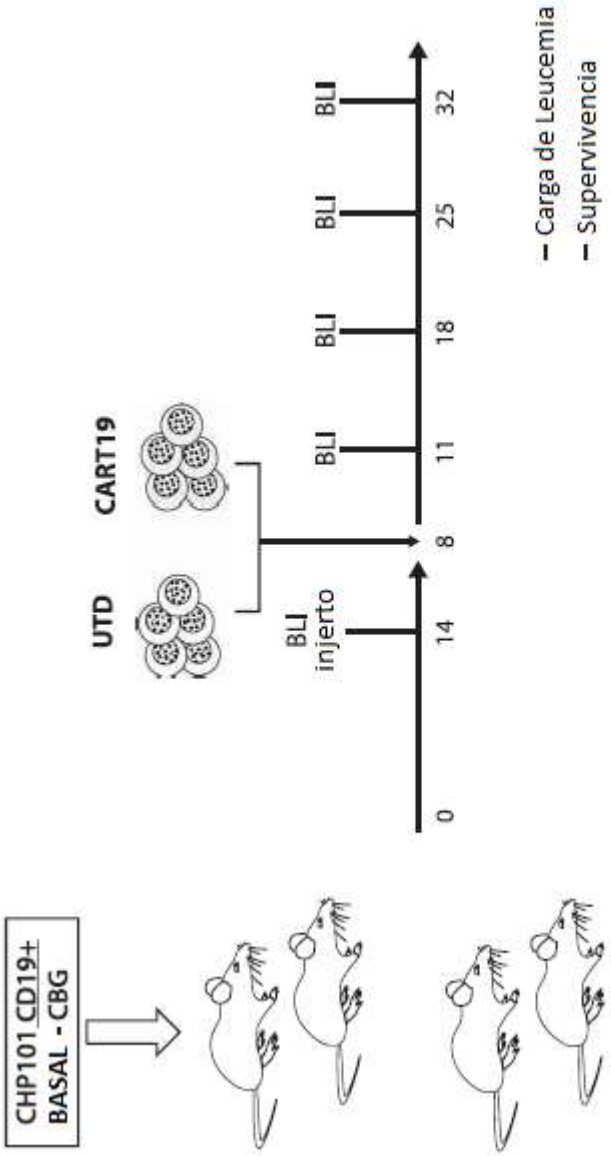

CHP101 CD19+
BASAL - CBG
UTD
CART19
BLI
injerto
0
14
8
11
18
25
32
BLI
BLI
BLI
BLI
Carga de Leucemia
Supervivencia
CHP101 CD19-
RECAÍDA - CBR

FIG. 52A

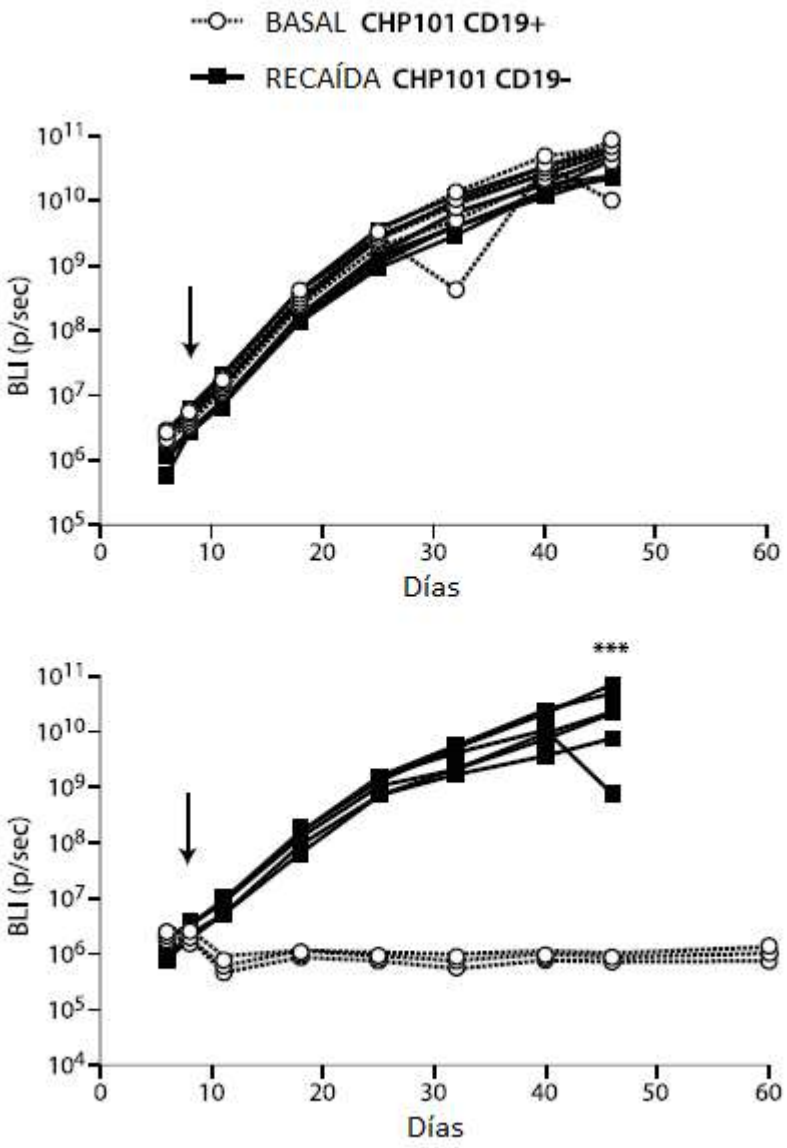


FIG. 52B

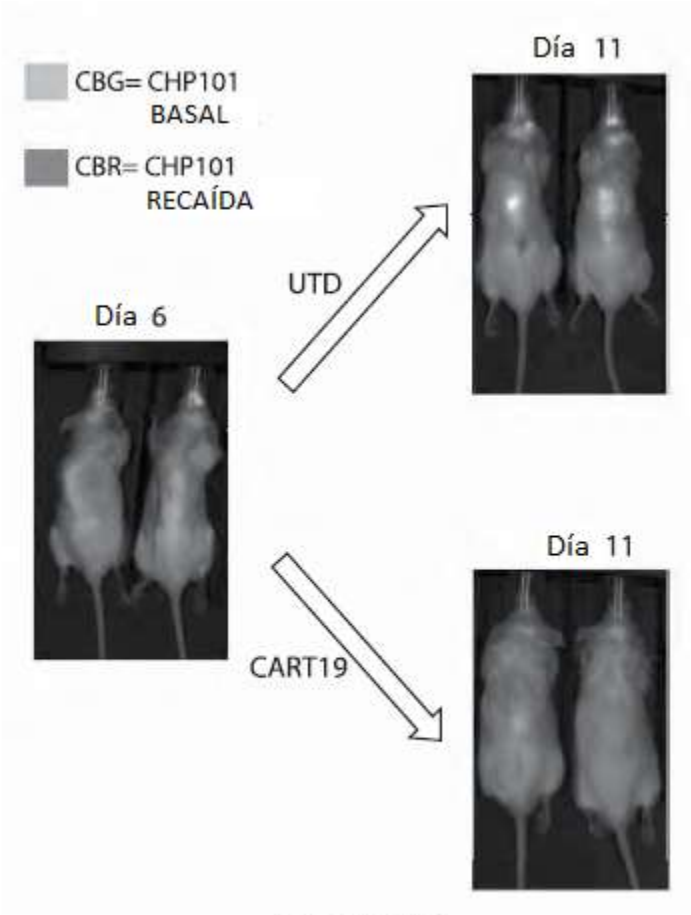

CBG= CHP101
BASAL
CBR= CHP101
RECAÍDA
Día 6
UTD
Día 11
CART19
Día 11

FIG. 52C

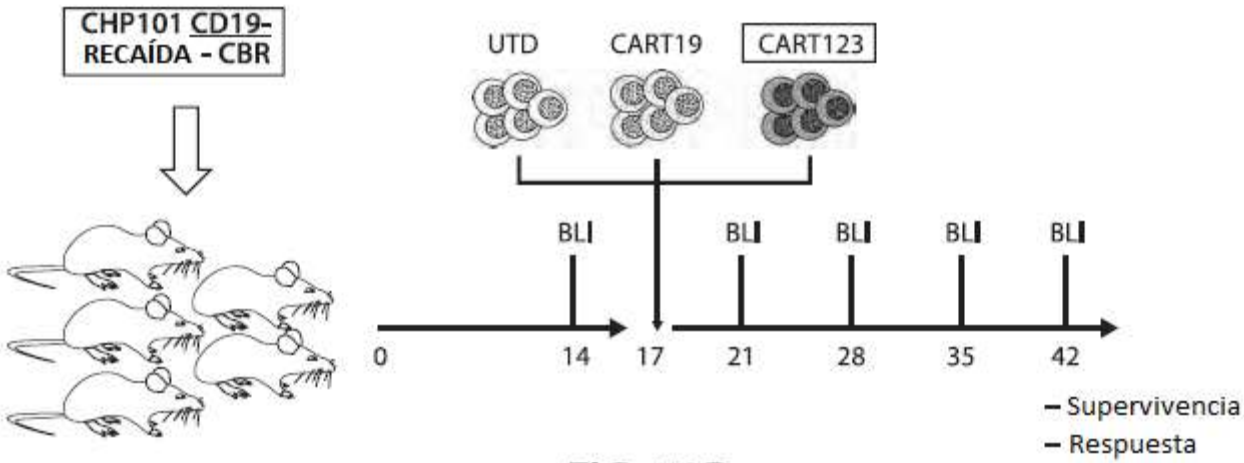

CHP101 CD19-
RECAÍDA - CBR
UTD
CART19
CART123
BLI
BLI
BLI
BLI
BLI
0
14
17
21
28
35
42
– Supervivencia
– Respuesta

FIG. 52D

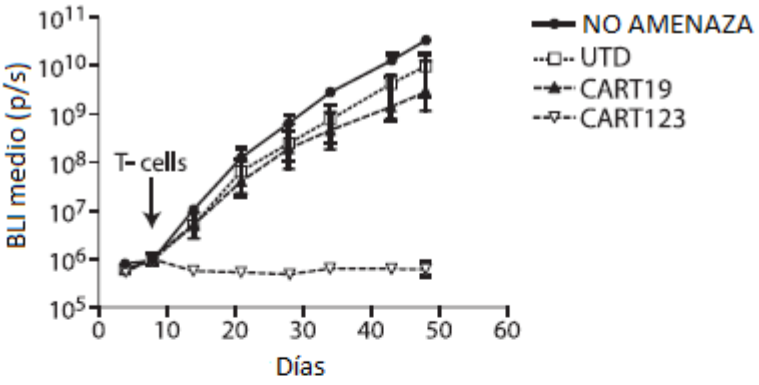


FIG. 52E

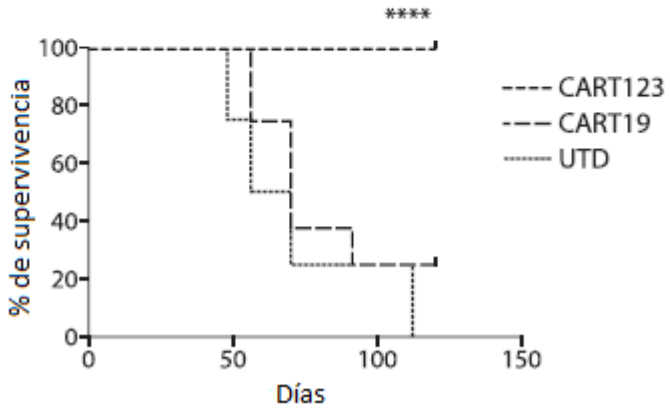


FIG. 52F

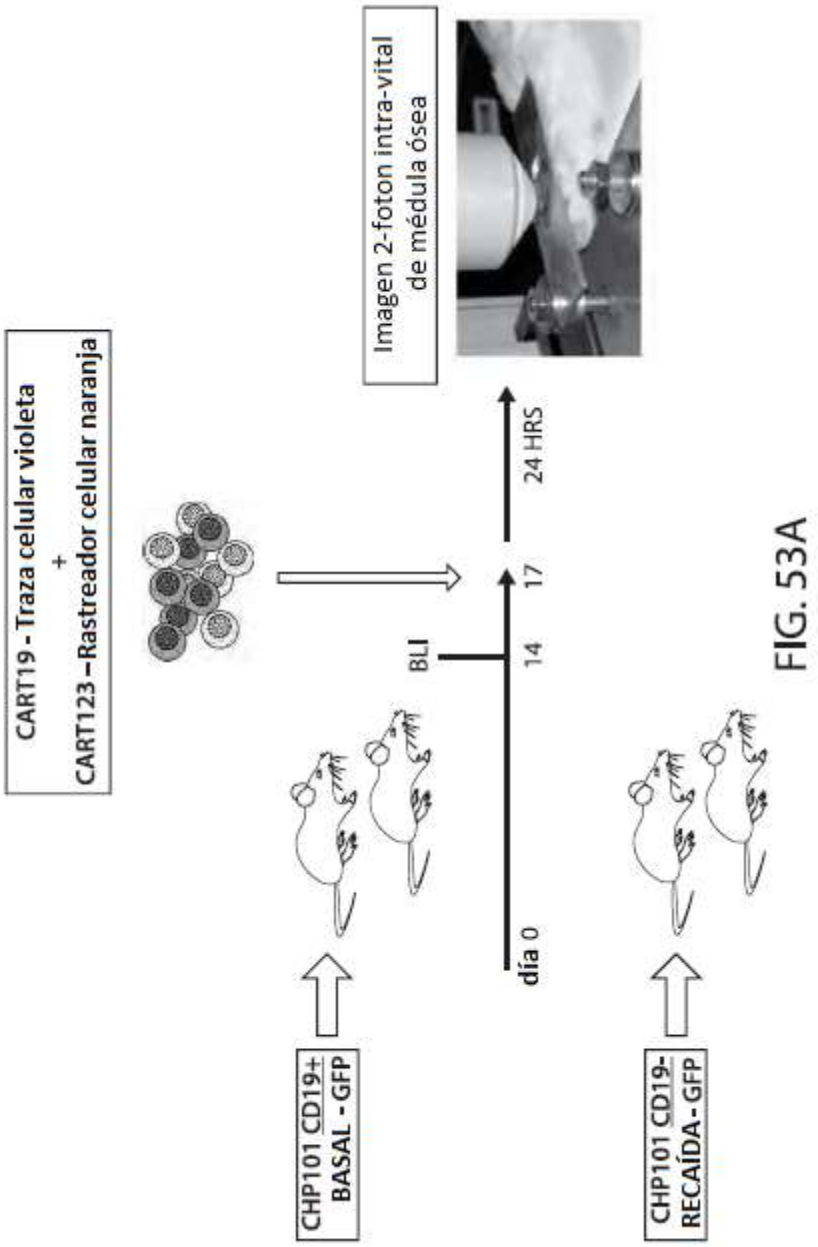

CART19 - Traza celular violeta
+
CART123 –Rastreador celular naranja
Imagen 2-foton intra-vital de médula ósea
CHP101 CD19+ BASAL - GFP
CHP101 CD19- RECAÍDA - GFP
día 0
BLI
14
17
24 HRS

FIG. 53A

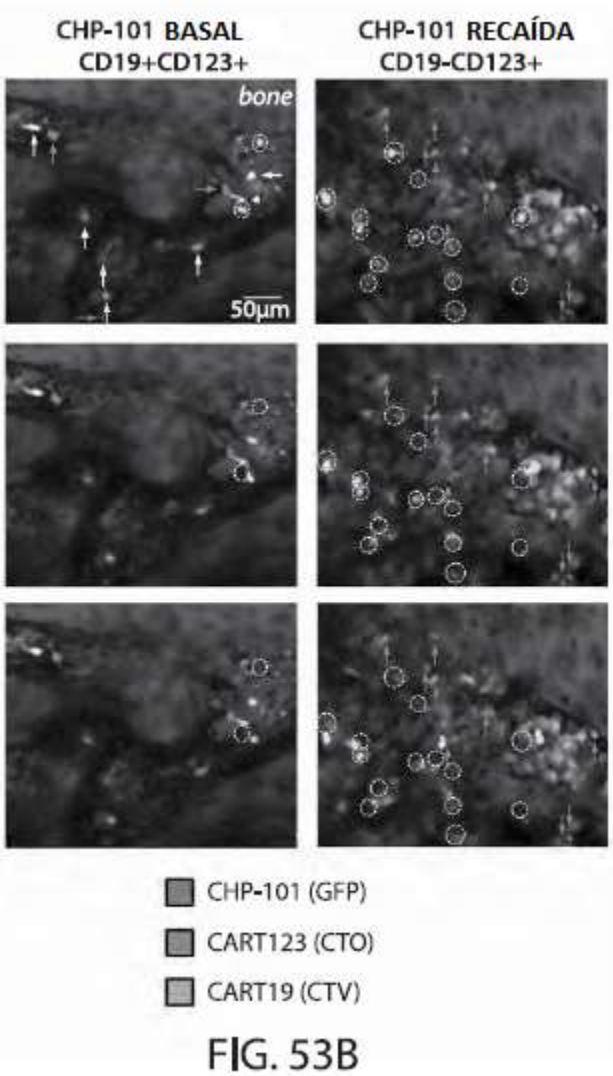

CHP-101 BASAL
CD19+CD123+
CHP-101 RECAÍDA
CD19-CD123+
bone
50µm
CHP-101 (GFP)
CART123 (CTO)
CART19 (CTV)

FIG. 53B

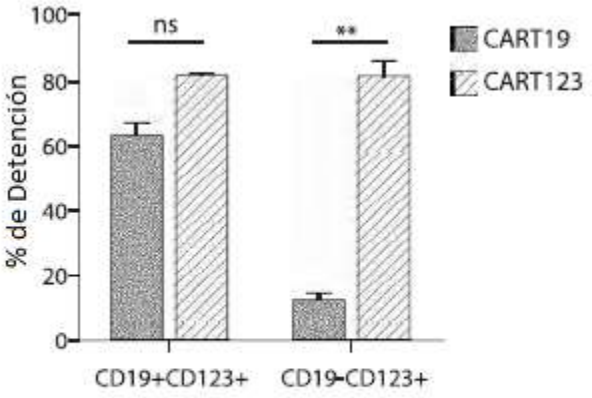

100
80
60
40
20
0
% de Detención
ns
**
CART19
CART123
CD19+CD123+
CD19-CD123+

FIG. 53C

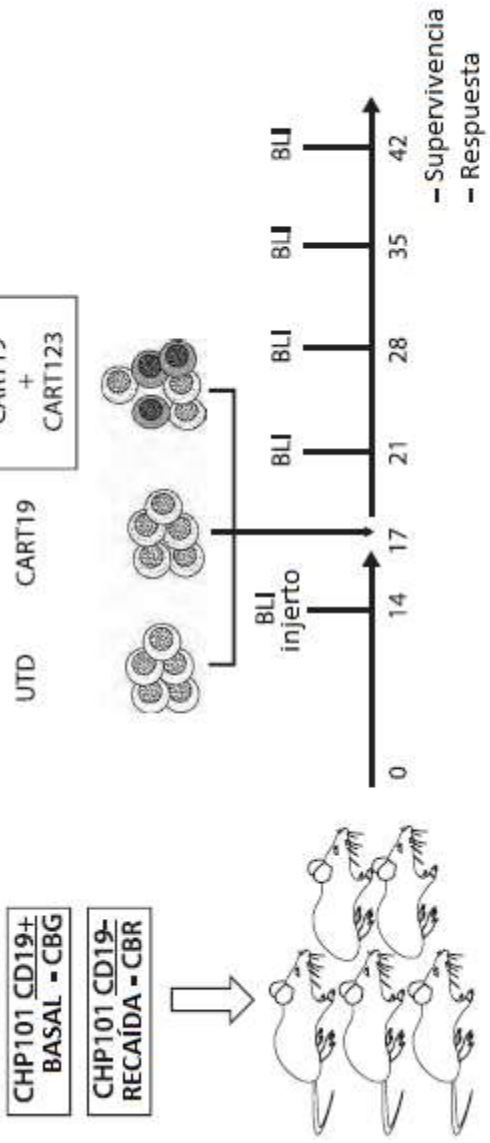

CHP101 CD19+
BASAL - CBG
CHP101 CD19-
RECAÍDA - CBR
UTD
CART19
CART19
+
CART123
BLI
injerto
BLI
BLI
BLI
BLI
BLI
0
14
17
21
28
35
42
- Supervivencia
- Respuesta

FIG. 54A

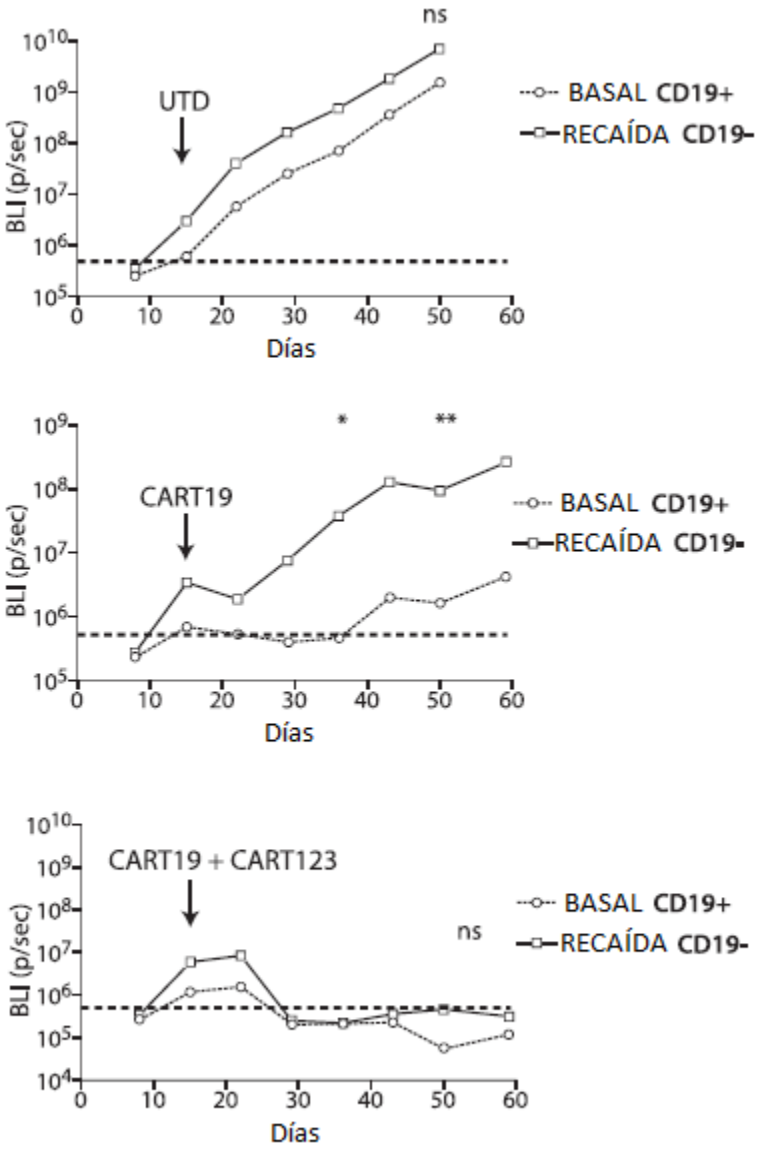

ns
UTD
BLI (p/sec)
Días
BASAL CD19+
RECAÍDA CD19-
*
**
CART19
CART19 + CART123

FIG. 54B

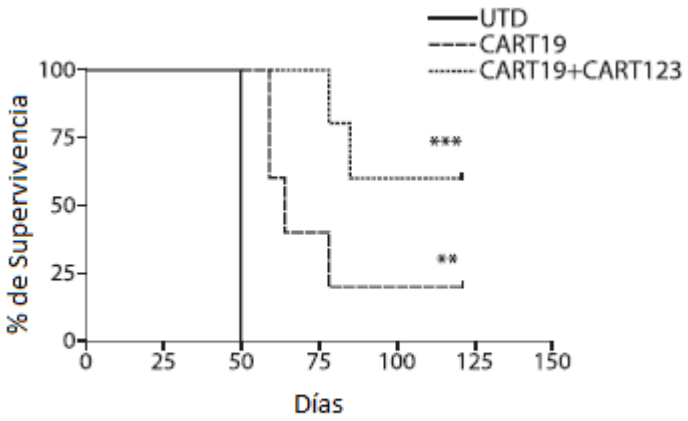

UTD
CART19
CART19+CART123
% de Supervivencia
100
75
50
25
0
***
**
0
25
50
75
100
125
150
Días

FIG. 54C

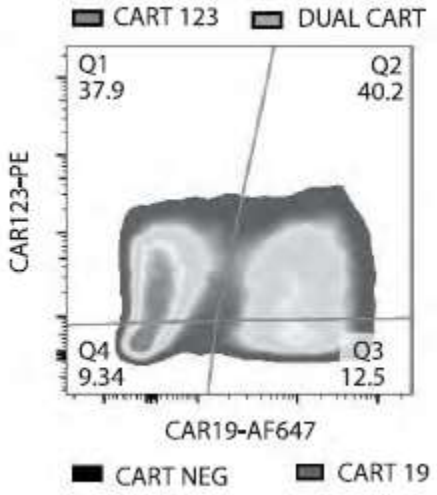


FIG. 55A

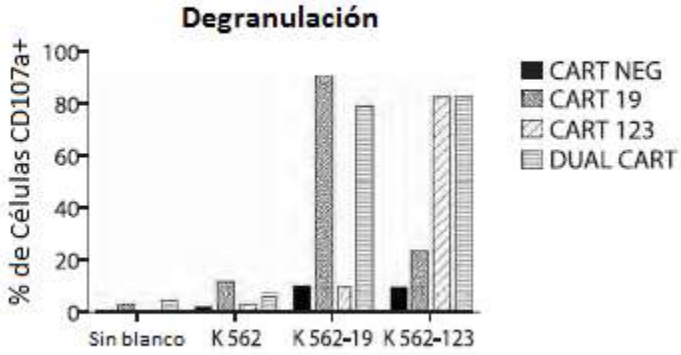


FIG. 55B

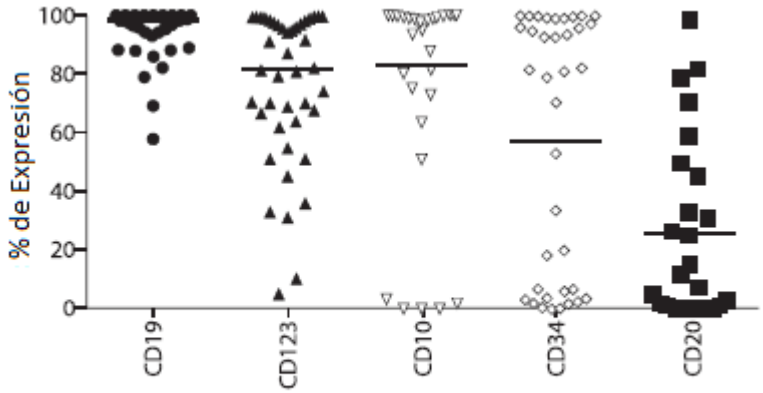
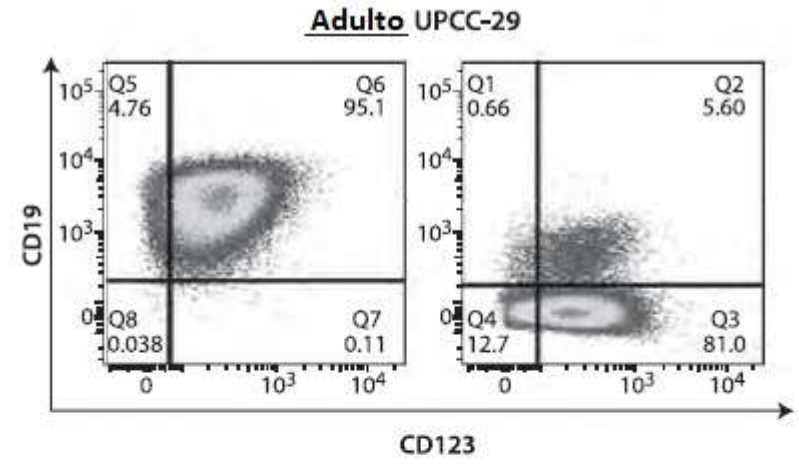


FIG. 56A


Adulto UPCC-29
CD19
CD123
Q5
4.76
Q6
95.1
Q8
0.038
Q7
0.11
Q1
0.66
Q2
5.60
Q4
12.7
Q3
81.0

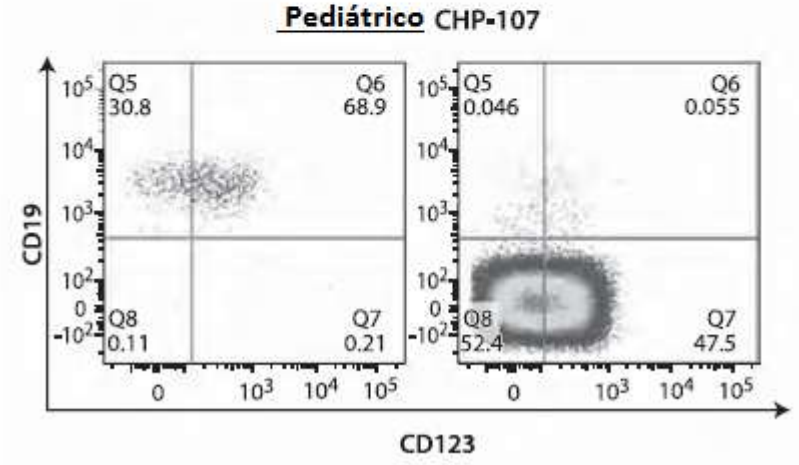

Pediátrico CHP-107
CD19
CD123
Q5
30.8
Q6
68.9
Q8
0.11
Q7
0.21
Q5
0.046
Q6
0.055
Q8
52.4
Q7
47.5

FIG. 56B

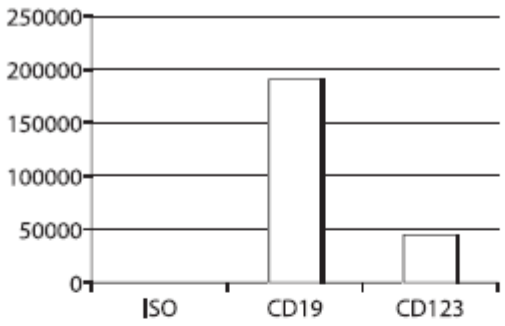


FIG. 57A

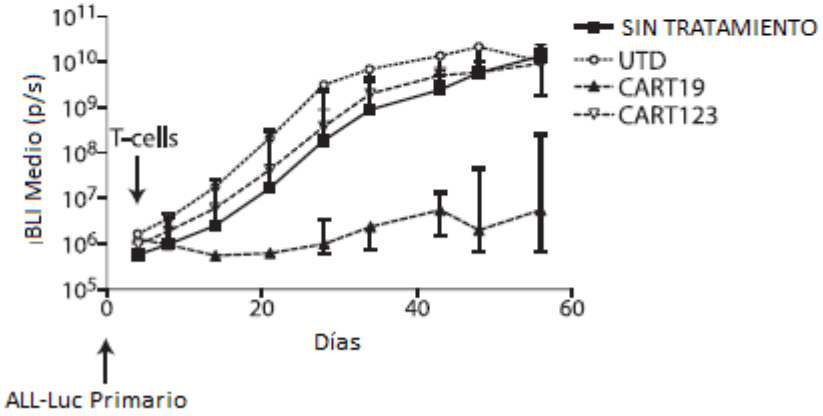


FIG. 57B

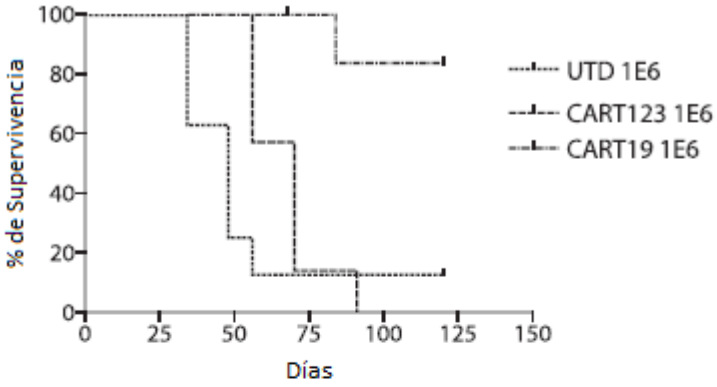


FIG. 57C

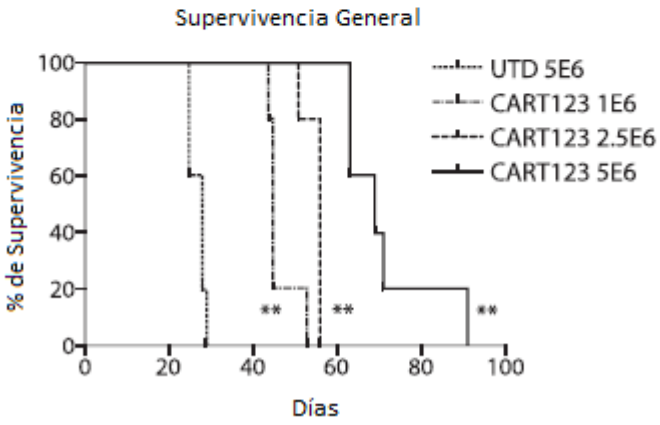


FIG. 57D

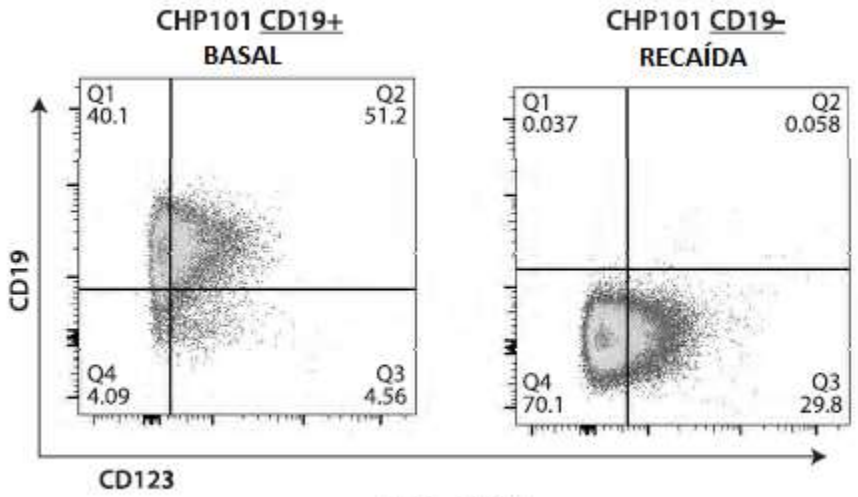

CHP101 CD19+
BASAL
Q1
40.1
Q2
51.2
Q4
4.09
Q3
4.56
CHP101 CD19-
RECAÍDA
Q1
0.037
Q2
0.058
Q4
70.1
Q3
29.8
CD19
CD123

FIG. 58A

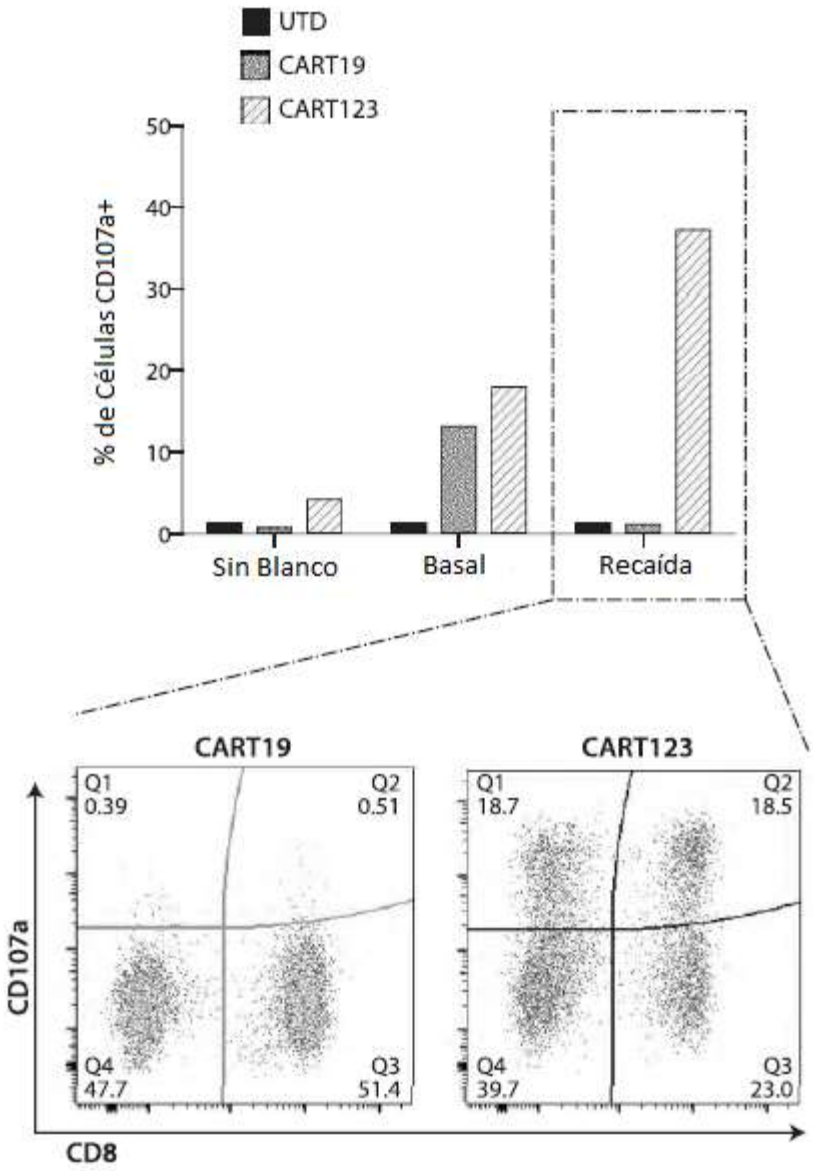

UTD
CART19
CART123
% de Células CD107a+
50
40
30
20
10
0
Sin Blanco
Basal
Recaída
CART19
CART123
Q1
0.39
Q2
0.51
Q4
47.7
Q3
51.4
Q1
18.7
Q2
18.5
Q4
39.7
Q3
23.0
CD107a
CD8

FIG. 58B

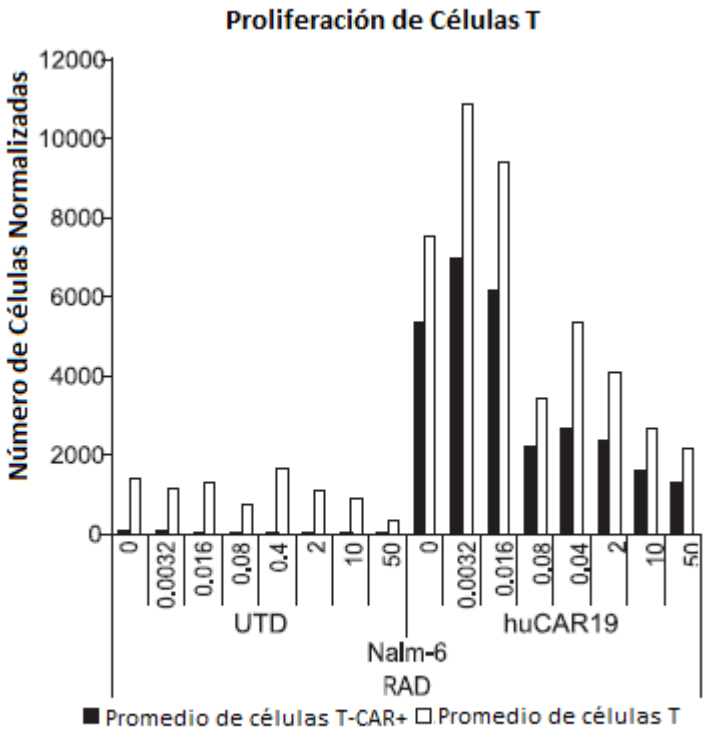

Proliferación de Células T
Número de Células Normalizadas
12000
10000
8000
6000
4000
2000
0
0
0,0032
0,016
0,08
0,4
2
10
50
0
0,0032
0,016
0,08
0,04
2
10
50
UTD
huCAR19
Nalm-6
RAD
Promedio de células T-CAR+
Promedio de células T

Fig.59

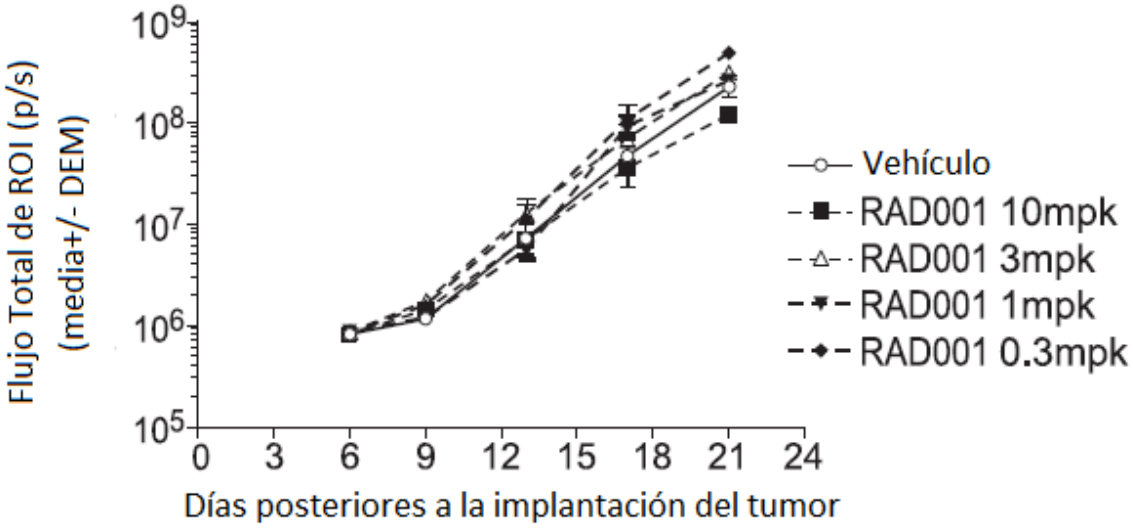

Flujo Total de ROI (p/s)
(media+/- DEM)
10^9
10^8
10^7
10^6
10^5
0
3
6
9
12
15
18
21
24
Días posteriores a la implantación del tumor
Vehículo
RAD001 10mpk
RAD001 3mpk
RAD001 1mpk
RAD001 0.3mpk

Fig. 60

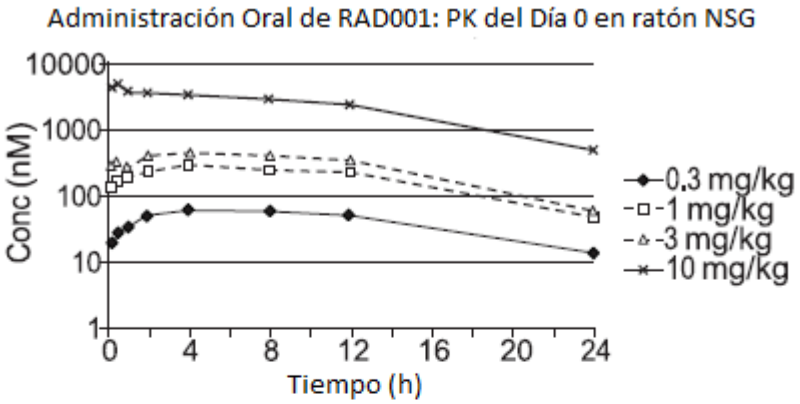


Fig. 61A

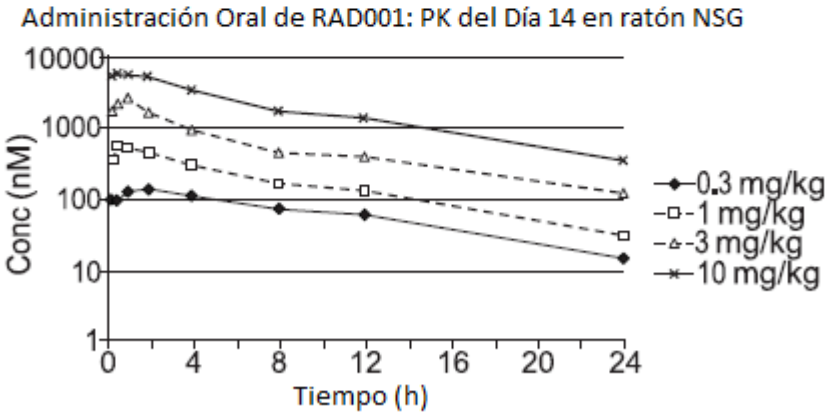


Fig. 61B

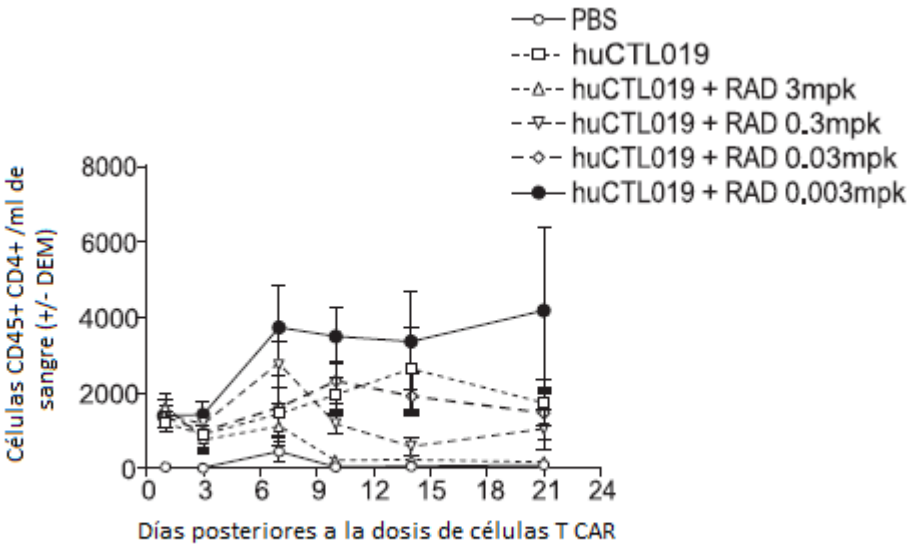


Fig. 62A

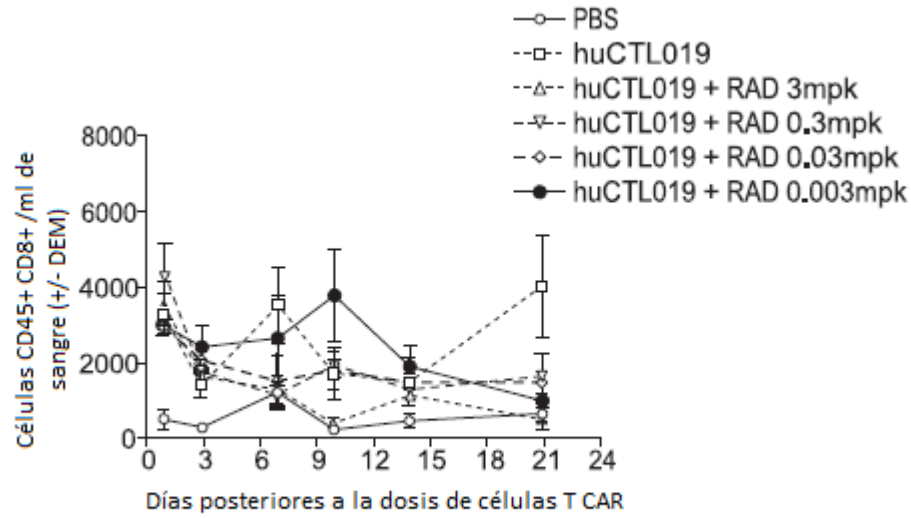


Fig. 62B

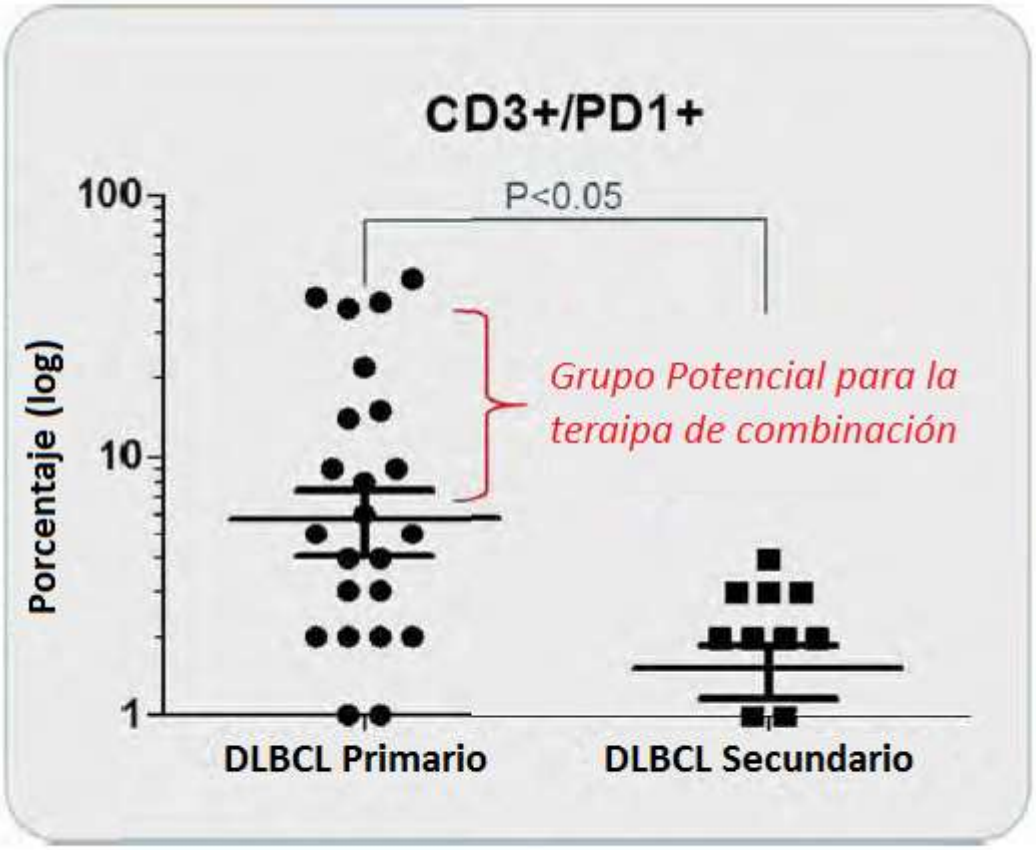

CD3+/PD1+
P<0.05
100
10
1
Porcentaje (log)
Grupo Potencial para la teraipa de combinación
DLBCL Primario
DLBCL Secundario

Fig. 63

Se expresa un amplio rango de CD19 en pacientes de DLBCL
El PD-L1 está asociado con células no tumorales en pacientes de DLBCL



Fig. 64

Fig. 65

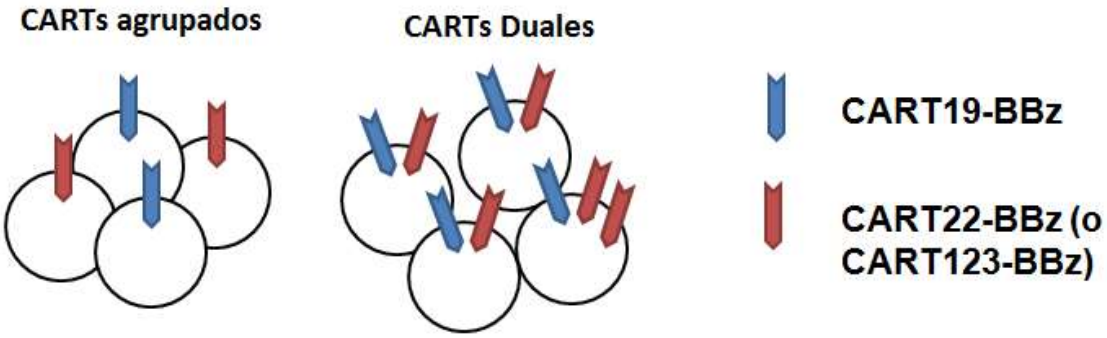

CARTs agrupados
CARTs Duales
CART19-BBz
CART22-BBz (o
CART123-BBz)

Figura 66

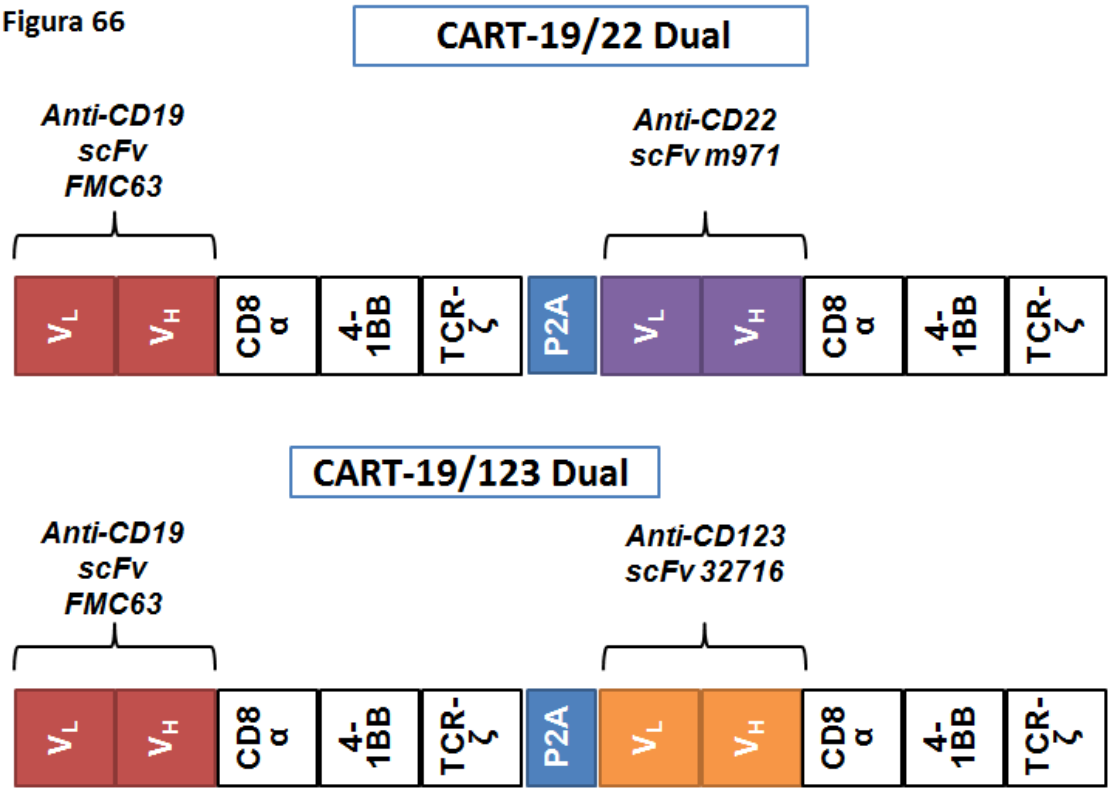

CART-19/22 Dual
Anti-CD19 scFv FMC63
Anti-CD22 scFv m971
VL
VH
CD8 α
4-1BB
TCR-ζ
P2A
VL
VH
CD8 α
4-1BB
TCR-ζ
CART-19/123 Dual
Anti-CD19 scFv FMC63
Anti-CD123 scFv 32716
VL
VH
CD8 α
4-1BB
TCR-ζ
P2A
VL
VH
CD8 α
4-1BB
TCR-ζ

Figura 67

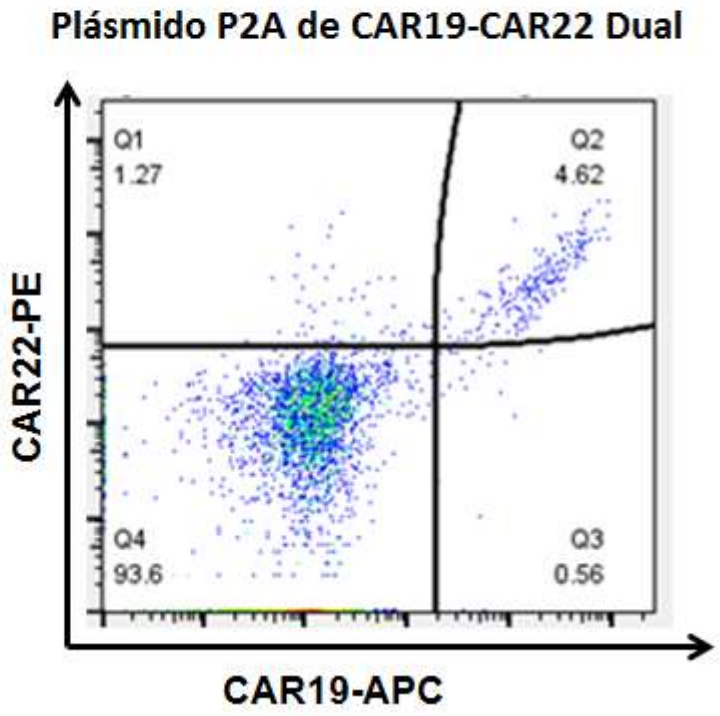

Plásmido P2A de CAR19-CAR22 Dual
Q1
1.27
Q2
4.62
Q4
93.6
Q3
0.56
CAR22-PE
CAR19-APC

Figura 68

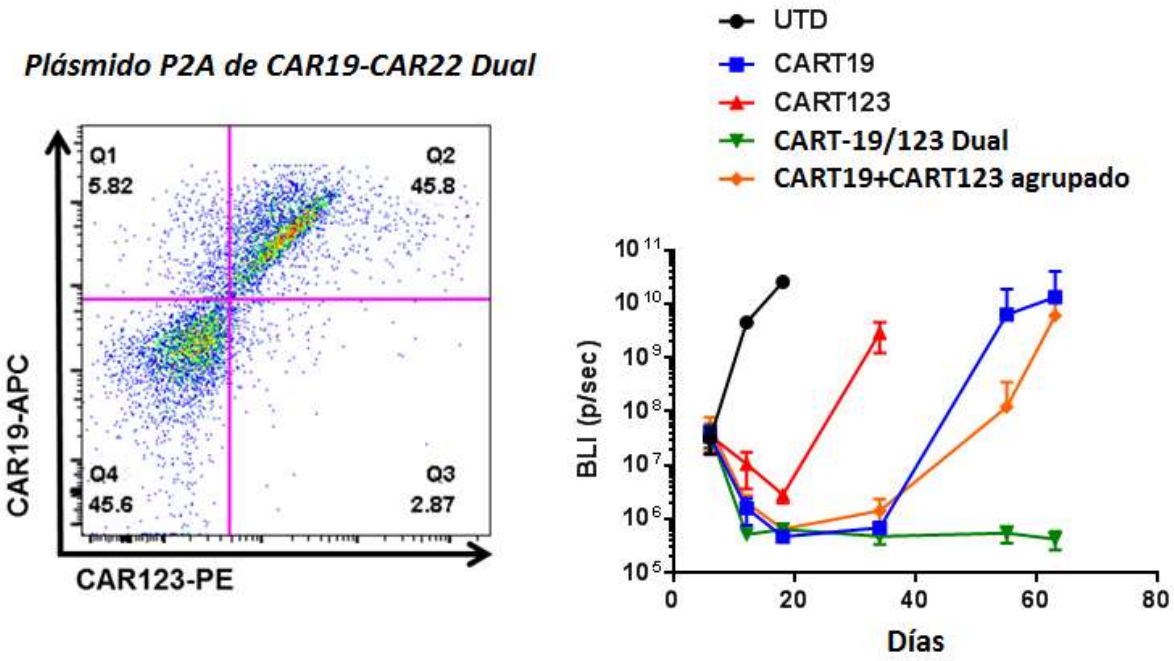
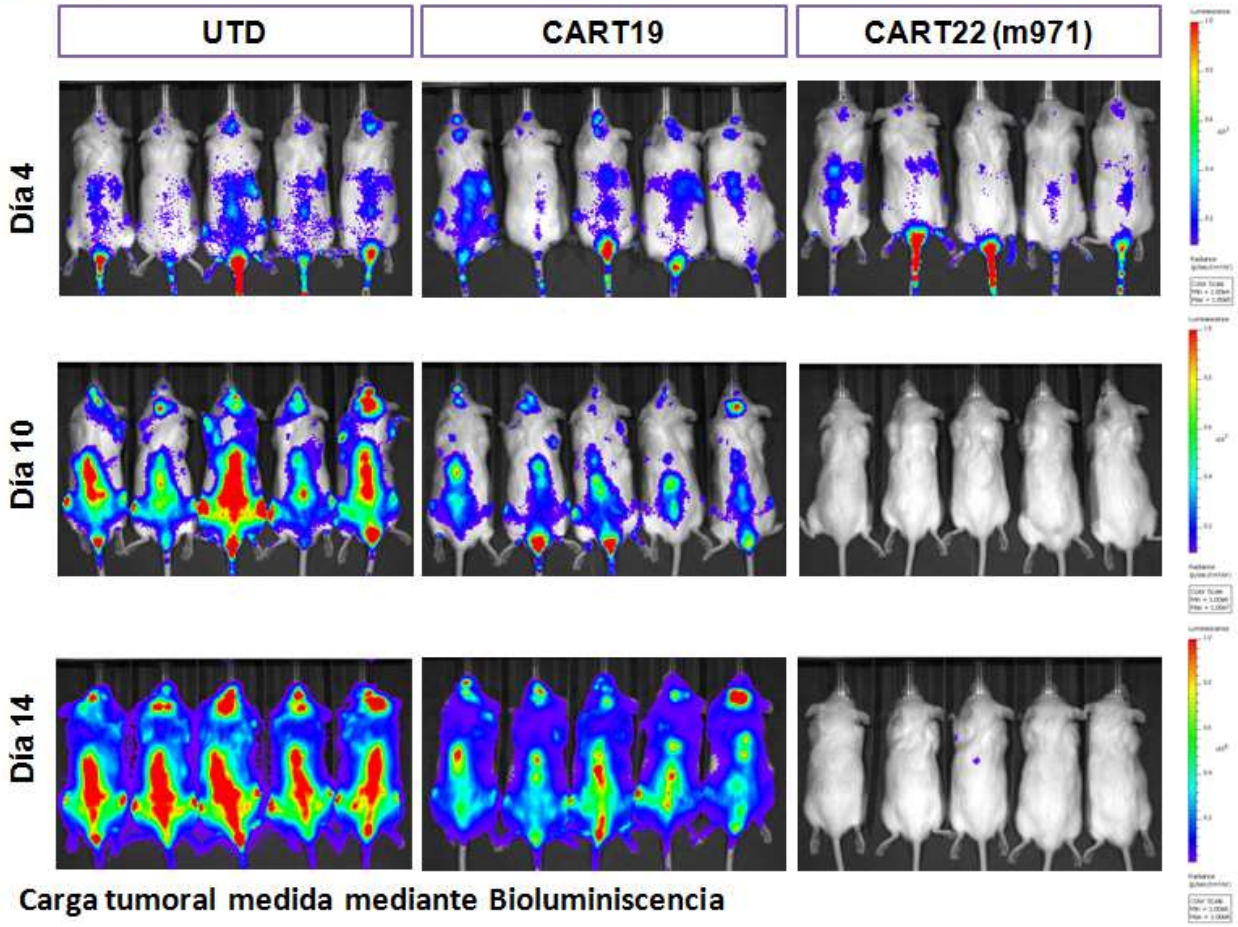

Plásmido P2A de CAR19-CAR22 Dual
Q1
5.82
Q2
45.8
Q4
45.6
Q3
2.87
CAR19-APC
CAR123-PE
UTD
CART19
CART123
CART-19/123 Dual
CART19+CART123 agrupado
BLI (p/sec)
Días
0
20
40
60
80

Figura 69



Carga tumoral medida mediante Bioluminiscencia

Figura 70

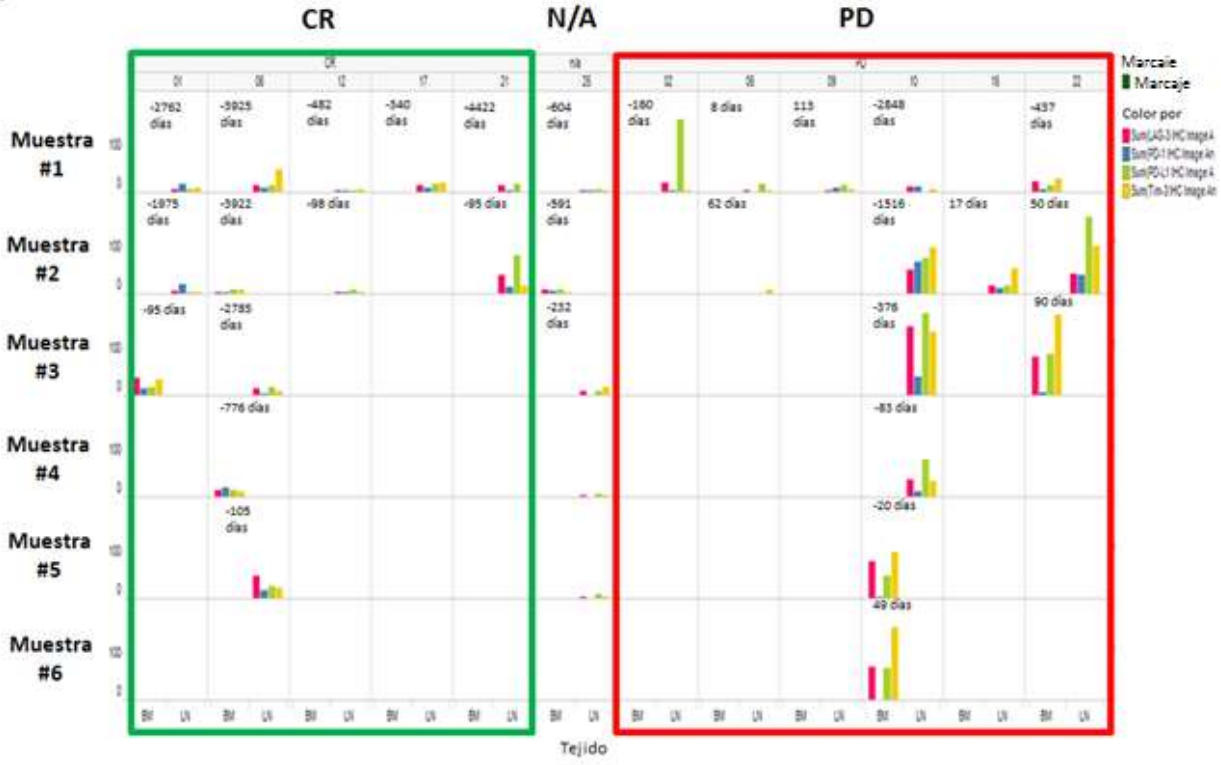

CR
N/A
PD
Muestra #1
Muestra #2
Muestra #3
Muestra #4
Muestra #5
Muestra #6
Tejido
Marcaje
Color por

Figura 71

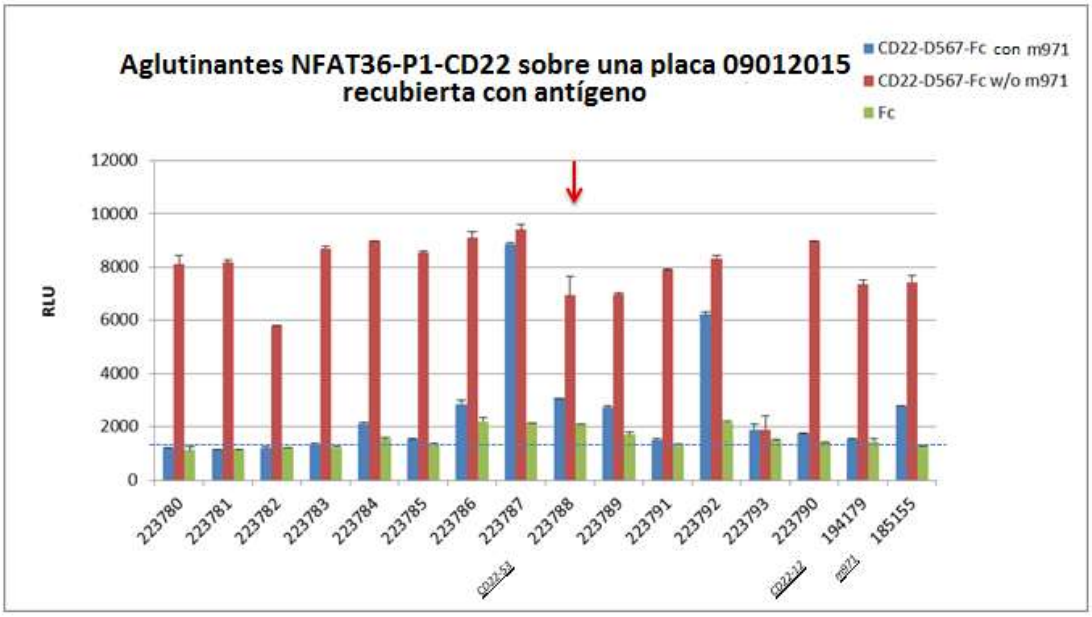

Aglutinantes NFAT36-P1-CD22 sobre una placa 09012015 recubierta con antígeno
CD22-D567-Fc con m971
CD22-D567-Fc w/o m971
Fc
RLU
12000
10000
8000
6000
4000
2000
0
223780
223781
223782
223783
223784
223785
223786
223787
223788
223789
223791
223792
223793
223790
194179
185155
CD22-S3
CD22-12
m971

Figura 72

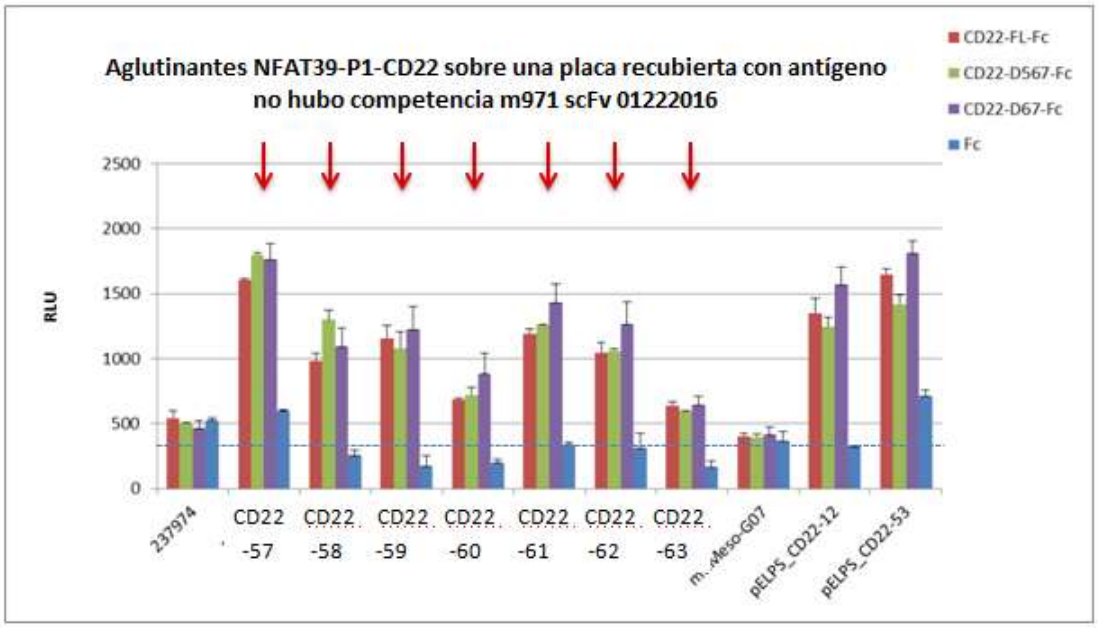

Aglutinantes NFAT39-P1-CD22 sobre una placa recubierta con antígeno
no hubo competencia m971 scFv 01222016
CD22-FL-Fc
CD22-D567-Fc
CD22-D67-Fc
Fc
RLU
2500
2000
1500
1000
500
0
237974
CD22 -57
CD22 -58
CD22 -59
CD22 -60
CD22 -61
CD22 -62
CD22 -63
m. Meso-G07
pELP5_CD22-12
pELP5_CD22-53

Figura 73

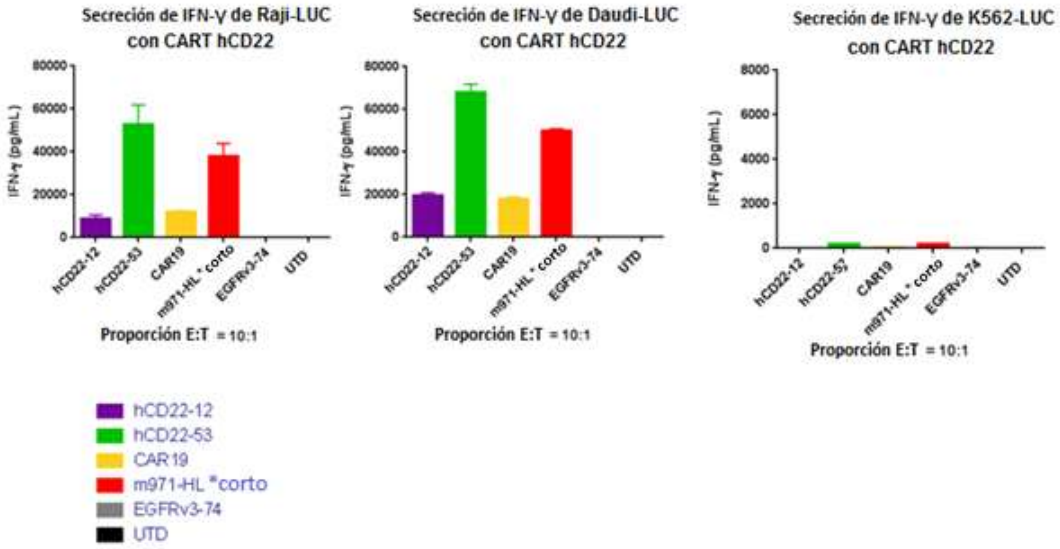

Secreción de IFN-γ de Raji-LUC
con CART hCD22
Secreción de IFN-γ de Daudi-LUC
con CART hCD22
Secreción de IFN-γ de K562-LUC
con CART hCD22
IFN-γ (pg/mL)
hCD22-12
hCD22-53
CAR19
m971-HL * corto
EGFRv3-74
UTD
Proporción E:T = 10:1

Figura 74

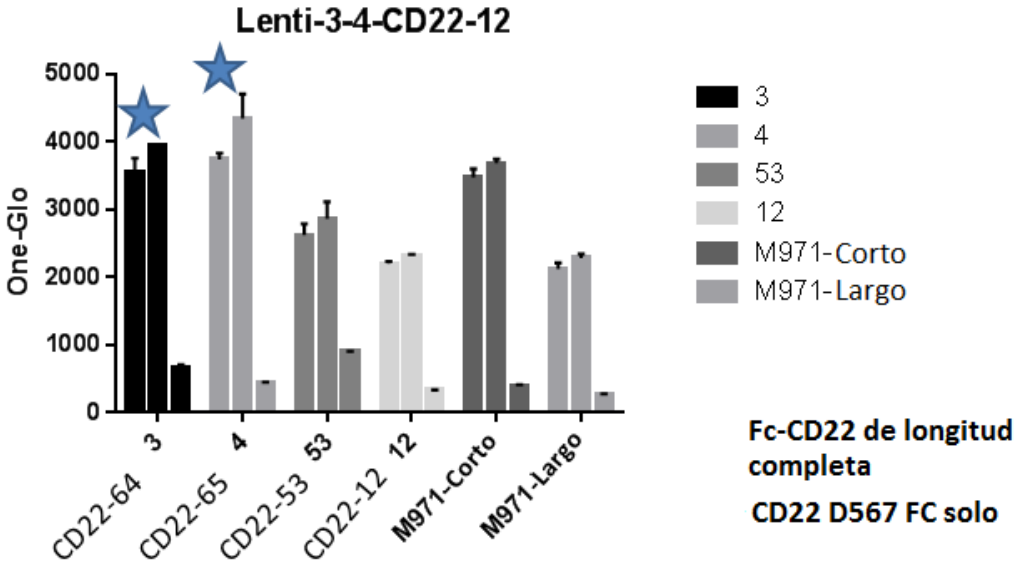
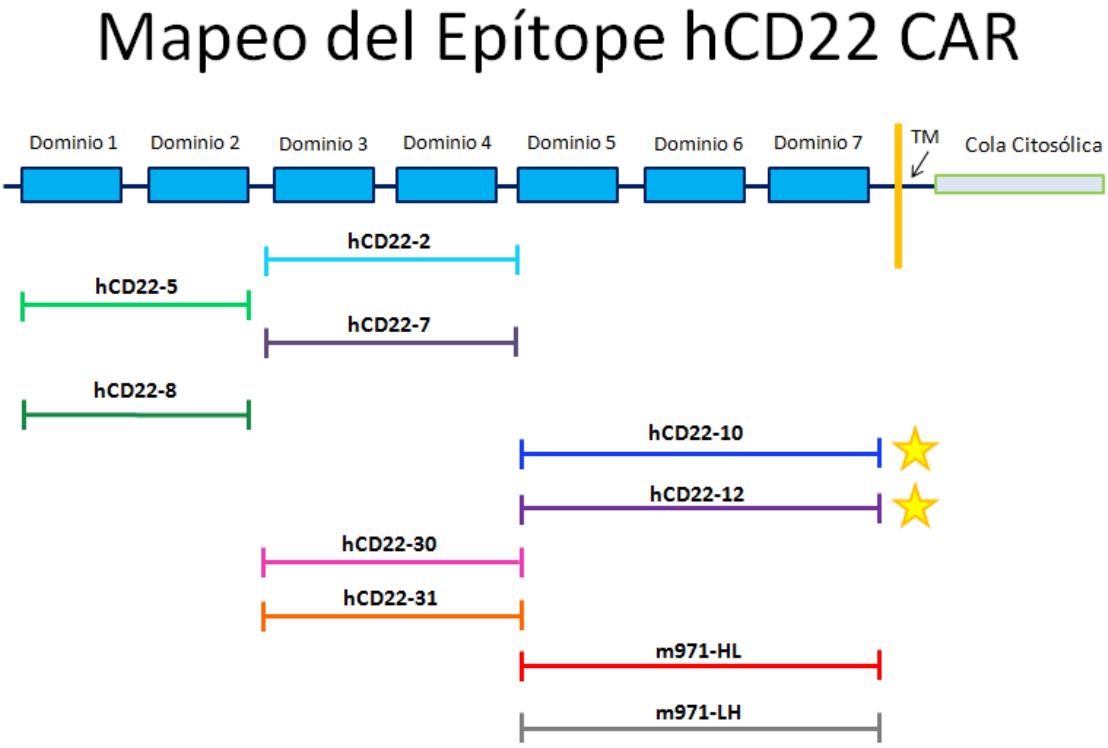

Lenti-3-4-CD22-12
One-Glo
5000
4000
3000
2000
1000
0
CD22-64
CD22-65
CD22-53
CD22-12
M971-Corto
M971-Largo
3
4
53
12
M971-Corto
M971-Largo
Fc-CD22 de longitud completa
CD22 D567 FC solo

Figura 75


Mapeo del Epítope hCD22 CAR
Dominio 1
Dominio 2
Dominio 3
Dominio 4
Dominio 5
Dominio 6
Dominio 7
TM
Cola Citosólica
hCD22-2
hCD22-5
hCD22-7
hCD22-8
hCD22-10
hCD22-12
hCD22-30
hCD22-31
m971-HL
m971-LH

SEQUENCE LISTING

<110> NOVARTIS AG
THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA

<120> CD20 THERAPIES, CD22 THERAPIES, AND COMBINATION THERAPIES WITH A CD19 CHIMERIC ANTIGEN RECEPTOR (CAR)- EXPRESSING CELL

<130> N2067-7072WO

<140> PCT/US2016/026655
<141> 2016-04-08

<150> 62/263,423
<151> 2015-12-04

<150> 62/207,255
<151> 2015-08-19

<150> 62/144,615
<151> 2015-04-08

<150> 62/144,497
<151> 2015-04-08

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<151> 2015-04-08

<160> 1529

<170> PatentIn version 3.5

<210> 1
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr

```
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Glu
        115                 120                 125

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
    130                 135                 140

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145                 150                 155                 160

Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser
                165                 170                 175

Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser
            180                 185                 190

Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr
        195                 200                 205

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
```

210 215 220

Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
225 230 235 240

Ser Ser

<210> 2
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 2
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
100 105 110

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Glu
        115                 120                 125

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
    130                 135                 140

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145                 150                 155                 160

Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser
                165                 170                 175

Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser
            180                 185                 190

Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr
        195                 200                 205

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
    210                 215                 220

Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
225                 230                 235                 240

Ser Ser
```

<210> 3
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 3

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Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                  10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr
            20                  25                  30

Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu
65                  70                  75                  80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Ala
    130                 135                 140

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
145                 150                 155                 160

Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175

Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly
            180                 185                 190
```

```
Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu
        195                 200                 205


Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln
    210                 215                 220


Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu
225                 230                 235                 240


Ile Lys
```

<210> 4
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 4

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Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr
            20                  25                  30


Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys
    50                  55                  60


Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu
65                  70                  75                  80
```

```
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Ala
    130                 135                 140

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
145                 150                 155                 160

Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175

Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly
            180                 185                 190

Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu
        195                 200                 205

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln
    210                 215                 220

Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu
225                 230                 235                 240

Ile Lys
```

<210> 5
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 5
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
100 105 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
115 120 125

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
130 135 140

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
145 150 155 160

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly

165 170 175

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
180 185 190

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
195 200 205

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
210 215 220

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
225 230 235 240

Thr Leu Val Thr Val Ser Ser
245

<210> 6
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

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Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

```
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
        115                 120                 125

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
    130                 135                 140

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
145                 150                 155                 160

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
                165                 170                 175

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser
            180                 185                 190

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
        195                 200                 205

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
    210                 215                 220

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
225                 230                 235                 240

Thr Leu Val Thr Val Ser Ser
                245
```

<210> 7
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 7

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Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                  10                  15


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr
            20                  25                  30


Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys
    50                  55                  60


Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu
65                  70                  75                  80


Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
    130                 135                 140
```

```
Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
145                 150                 155                 160


Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
                165                 170                 175


Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
            180                 185                 190


Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205


Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
    210                 215                 220


Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
225                 230                 235                 240


Gly Thr Lys Leu Glu Ile Lys
                245


<210> 8
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 8
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr
            20                  25                  30
```

```
Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu
65                  70                  75                  80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
    130                 135                 140

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
145                 150                 155                 160

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
                165                 170                 175

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
            180                 185                 190

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
    210                 215                 220
```

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
225 230 235 240

Gly Thr Lys Leu Glu Ile Lys
245

<210> 9
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

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Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
100 105 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln

115 120 125

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
130 135 140

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
145 150 155 160

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
165 170 175

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys Ser
180 185 190

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
195 200 205

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
210 215 220

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
225 230 235 240

Thr Leu Val Thr Val Ser Ser
245

<210> 10
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 10
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

```
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr
            20                  25                  30

Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu
65                  70                  75                  80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
    130                 135                 140

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
145                 150                 155                 160

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
                165                 170                 175

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
            180                 185                 190

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205
```

```
Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
    210                 215                 220

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
225                 230                 235                 240

Gly Thr Lys Leu Glu Ile Lys
                245
```

<210> 11
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 11

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1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95
```

```
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Glu
        115                 120                 125

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
    130                 135                 140

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145                 150                 155                 160

Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser
                165                 170                 175

Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys Ser Arg Val Thr Ile Ser
            180                 185                 190

Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr
        195                 200                 205

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
    210                 215                 220

Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
225                 230                 235                 240

Ser Ser
```

<210> 12
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 12

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                  10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr
            20                  25                  30

Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu
65                  70                  75                  80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Ala
    130                 135                 140

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
145                 150                 155                 160

Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175
```

Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly
180 185 190

Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu
195 200 205

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln
210 215 220

Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu
225 230 235 240

Ile Lys

<210> 13
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 13
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro
20

<210> 14
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 14
Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
1 5 10 15

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
20 25 30

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
35 40 45

<210> 15
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 15
Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
1 5 10 15

Ser Leu Val Ile Thr Leu Tyr Cys
20

<210> 16
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 16
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Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
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Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
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Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
85 90 95

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100 105 110

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<212> PRT
<213> Artificial Sequence

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<211> 10
<212> PRT
<213> Artificial Sequence

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<221> source
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<213> Artificial Sequence

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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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<210> 23
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<212> PRT
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<212> PRT
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<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

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<211> 11
<212> PRT
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His Thr Ser Arg Leu His Ser
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<223> /note="This sequence may encompass 50-5000 nucleotides"

<220>
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<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"
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<220>
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<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

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<223> /note="This sequence may encompass 50-5000 nucleotides"

<220>
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<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

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<210> 31
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

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Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
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His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

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Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270
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Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460
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Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
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<210> 32
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
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1               5                   10                  15


His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30


Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45


Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60


Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80


Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95


Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110
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Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300
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Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg
                485
```

<210> 33
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 33

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
        35                  40                  45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80

Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
```

```
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
        195                 200                 205

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
                245                 250                 255

Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
```

340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 34
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 34

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
        35                  40                  45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80

Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
            180                 185                 190
```

```
Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
        195                 200                 205

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
                245                 250                 255

Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380
```

```
Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400


Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415


Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430


Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445


Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485


<210> 35
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 35
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30
```

```
Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220
```

```
Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240


Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255


Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270


Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285


Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300


Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320


Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335


Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350


Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365


Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380


Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400


Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415
```

```
Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430


Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445


Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460


His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480


Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 36
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 36
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30


Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45


Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60
```

```
Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80


Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95


Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110


Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140


Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160


Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175


Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190


Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln
        195                 200                 205


Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220


Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240


Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255
```

```
Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445
```

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 37
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 37
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65 70 75 80

Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
85 90 95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala

```
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
                165                 170                 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
```

```
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
```

485 490

<210> 38
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 38
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65 70 75 80

Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
85 90 95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
100 105 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
130 135 140

```
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
                165                 170                 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335
```

```
Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 39
<211> 491
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 39

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175
```

```
Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365
```

```
Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380


Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400


Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415


Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430


Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445


Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460


His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480


Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 40
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 40
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15
```

```
His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn
        195                 200                 205
```

```
Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400
```

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 41
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 41
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys

50 55 60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65 70 75 80

Asn Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
85 90 95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
100 105 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
165 170 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
180 185 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
195 200 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
210 215 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225 230 235 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro

245 250 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro
260 265 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
275 280 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
290 295 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305 310 315 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
325 330 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
340 345 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
355 360 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu

435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 42
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 42
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

```
Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285
```

```
Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480
```

Gln Ala Leu Pro Pro Arg
485

<210> 43
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 43
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
1 5 10 15

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
20 25 30

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
35 40 45

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
50 55 60

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65 70 75 80

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
85 90 95

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
100 105 110

<210> 44
<211> 336
<212> DNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 44
agagtgaagt tcagcaggag cgcagacgcc cccgcgtacc agcagggcca gaaccagctc 60

tataacgagc tcaatctagg acgaagagag gagtacgatg ttttggacaa gagacgtggc 120

cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat 180

gaactgcaga aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc 240

cggaggggca aggggcacga tggcctttac cagggtctca gtacagccac caaggacacc 300

tacgacgccc ttcacatgca ggccctgccc cctcgc 336

<210> 45
<211> 230
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 45
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60

```
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80


Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95


Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110


Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125


Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
145                 150                 155                 160


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190


Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220


Leu Ser Leu Gly Lys Met
225                 230


<210> 46
<211> 690
<212> DNA
<213> Artificial Sequence
```

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 46
gagagcaagt acggccctcc ctgcccccct tgccctgccc ccgagttcct gggcggaccc 60

agcgtgttcc tgttcccccc caagcccaag gacaccctga tgatcagccg gacccccgag 120

gtgacctgtg tggtggtgga cgtgtcccag gaggaccccg aggtccagtt caactggtac 180

gtggacggcg tggaggtgca caacgccaag accaagcccc gggaggagca gttcaatagc 240

acctaccggg tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaggaa 300

tacaagtgta aggtgtccaa caagggcctg cccagcagca tcgagaaaac catcagcaag 360

gccaagggcc agcctcggga gccccaggtg tacaccctgc cccctagcca agaggagatg 420

accaagaacc aggtgtccct gacctgcctg gtgaagggct tctaccccag cgacatcgcc 480

gtggagtggg agagcaacgg ccagcccgag aacaactaca agaccacccc ccctgtgctg 540

gacagcgacg gcagcttctt cctgtacagc cggctgaccg tggacaagag ccggtggcag 600

gagggcaacg tctttagctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag 660

aagagcctga gcctgtccct gggcaagatg 690

<210> 47
<211> 282
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 47
Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala
1 5 10 15

Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala

```
            20                  25                  30

Thr Thr Arg Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys
        35                  40                  45

Glu Lys Glu Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro Glu Cys Pro
    50                  55                  60

Ser His Thr Gln Pro Leu Gly Val Tyr Leu Leu Thr Pro Ala Val Gln
65                  70                  75                  80

Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe Val Val Gly
                85                  90                  95

Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala Gly Lys Val
            100                 105                 110

Pro Thr Gly Gly Val Glu Glu Gly Leu Leu Glu Arg His Ser Asn Gly
        115                 120                 125

Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser Leu Trp Asn
    130                 135                 140

Ala Gly Thr Ser Val Thr Cys Thr Leu Asn His Pro Ser Leu Pro Pro
145                 150                 155                 160

Gln Arg Leu Met Ala Leu Arg Glu Pro Ala Ala Gln Ala Pro Val Lys
                165                 170                 175

Leu Ser Leu Asn Leu Leu Ala Ser Ser Asp Pro Pro Glu Ala Ala Ser
            180                 185                 190

Trp Leu Leu Cys Glu Val Ser Gly Phe Ser Pro Pro Asn Ile Leu Leu
        195                 200                 205

Met Trp Leu Glu Asp Gln Arg Glu Val Asn Thr Ser Gly Phe Ala Pro
```

210 215 220

Ala Arg Pro Pro Pro Gln Pro Gly Ser Thr Thr Phe Trp Ala Trp Ser
225 230 235 240

Val Leu Arg Val Pro Ala Pro Pro Ser Pro Gln Pro Ala Thr Tyr Thr
245 250 255

Cys Val Val Ser His Glu Asp Ser Arg Thr Leu Leu Asn Ala Ser Arg
260 265 270

Ser Leu Glu Val Ser Tyr Val Thr Asp His
275 280

<210> 48
<211> 847
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 48
aggtggcccg aaagtcccaa ggcccaggca tctagtgttc ctactgcaca gccccaggca 60

gaaggcagcc tagccaaagc tactactgca cctgccacta cgcgcaatac tggccgtggc 120

ggggaggaga agaaaaagga gaaagagaaa gaagaacagg aagagaggga gaccaagacc 180

cctgaatgtc catcccatac ccagccgctg ggcgtctatc tcttgactcc cgcagtacag 240

gacttgtggc ttagagataa ggccaccttt acatgtttcg tcgtgggctc tgacctgaag 300

gatgcccatt tgacttggga ggttgccgga aaggtaccca ggggggggt tgaggaaggg 360

ttgctggagc gccattccaa tggctctcag agccagcact caagactcac ccttccgaga 420

tccctgtgga acgccgggac ctctgtcaca tgtactctaa atcatcctag cctgccccca 480

cagcgtctga tggcccttag agagccagcc gcccaggcac cagttaagct tagcctgaat 540

ctgctcgcca gtagtgatcc cccagaggcc gccagctggc tcttatgcga agtgtccggc 600

tttagcccgc ccaacatctt gctcatgtgg ctggaggacc agcgagaagt gaacaccagc 660

ggcttcgctc cagcccggcc cccaccccag ccgggttcta ccacattctg ggcctggagt 720

gtcttaaggg tcccagcacc acctagcccc cagccagcca catacacctg tgttgtgtcc 780

catgaagata gcaggaccct gctaaatgct tctaggagtc tggaggtttc ctacgtgact 840

gaccatt 847

<210> 49
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 49
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> 50
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 50
ggtggcggag gttctggagg tggaggttcc 30

<210> 51
<211> 48
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 51
Gln Arg Arg Lys Tyr Arg Ser Asn Lys Gly Glu Ser Pro Val Glu Pro
1 5 10 15

Ala Glu Pro Cys Arg Tyr Ser Cys Pro Arg Glu Glu Glu Gly Ser Thr
20 25 30

Ile Pro Ile Gln Glu Asp Tyr Arg Lys Pro Glu Pro Ala Cys Ser Pro
35 40 45

<210> 52
<211> 123
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 52
aggagtaaga ggagcaggct cctgcacagt gactacatga acatgactcc ccgccgcccc 60

gggcccaccc gcaagcatta ccagccctat gccccaccac gcgacttcgc agcctatcgc 120

tcc 123

<210> 53
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>
<221> MISC_FEATURE

<222> (1)..(30)
<223> /note="This sequence may encompass 1-6 'Gly-Gly-Gly-Gly-Ser' repeating units"

<220>
<221> source
<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 53
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25 30

<210> 54
<211> 63
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 54
atggccctgc ctgtgacagc cctgctgctg cctctggctc tgctgctgca tgccgctaga 60

ccc 63

<210> 55
<211> 135
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 55
accacgacgc cagcgccgcg accaccaaca ccggcgccca ccatcgcgtc gcagcccctg 60

tccctgcgcc cagaggcgtg ccggccagcg gcgggggcg cagtgcacac gagggggctg 120

gacttcgcct gtgat 135

<210> 56
<211> 72
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 56
atctacatct gggcgccctt ggccgggact tgtggggtcc ttctcctgtc actggttatc 60

acccttact gc 72

<210> 57
<211> 5000
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (1)..(5000)
<223> /note="This sequence may encompass 100-5000 nucleotides"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 57
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 180

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 240

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 300

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 360

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 420

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 600

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 660

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 720

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 840

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 900

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 960

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1020

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1080

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1140

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1200

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1260

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1320

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1560

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1680

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1860

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1920

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1980

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2040

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 4380

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 4440

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 4500

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 4740

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 4800

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 4860

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 4920

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 4980

aaaaaaaaaa aaaaaaaaaa 5000

<210> 58
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 58
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu
20 25 30

Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr
50 55 60

Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val Pro
65 70 75 80

```
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile
                85                  90                  95

Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205

Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220

Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Ser Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270
```

```
Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460
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Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485


<210> 59
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 59
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1               5                   10                  15


Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
            20                  25                  30


Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45


Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65                  70                  75                  80


Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Gly Gly Gly Ser
            100                 105                 110
```

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Lys Leu Gln Glu
        115                 120                 125


Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser Val Thr Cys
    130                 135                 140


Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145                 150                 155                 160


Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Gly Ser
                165                 170                 175


Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu Thr Ile Ile
            180                 185                 190


Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn Ser Leu Gln
        195                 200                 205


Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
    210                 215                 220


Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val
225                 230                 235                 240


Ser Ser
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<210> 60
<211> 126
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 60

aaacggggca gaaagaaact cctgtatata ttcaaacaac catttatgag accagtacaa 60

actactcaag aggaagatgg ctgtagctgc cgatttccag aagaagaaga aggaggatgt 120

gaactg 126

<210> 61
<211> 813
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 61
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaaattg tgatgaccca gtcacccgcc actcttagcc tttcacccgg tgagcgcgca 120

accctgtctt gcagagcctc ccaagacatc tcaaaatacc ttaattggta tcaacagaag 180

cccggacagg ctcctcgcct tctgatctac cacaccagcc ggctccattc tggaatccct 240

gccaggttca gcggtagcgg atctgggacc gactacaccc tcactatcag ctcactgcag 300

ccagaggact tcgctgtcta tttctgtcag caagggaaca ccctgcccta cacctttgga 360

cagggcacca agctcgagat taaaggtgga ggtggcagcg gaggaggtgg gtccggcggt 420

ggaggaagcc aggtccaact ccaagaaagc ggaccgggtc ttgtgaagcc atcagaaact 480

ctttcactga cttgtactgt gagcggagtg tctctccccg attacggggt gtcttggatc 540

agacagccac cggggaaggg tctggaatgg attggagtga tttggggctc tgagactact 600

tactactctt catccctcaa gtcacgcgtc accatctcaa aggacaactc taagaatcag 660

gtgtcactga aactgtcatc tgtgaccgca gccgacaccg ccgtgtacta ttgcgctaag 720

cattactatt atggcgggag ctacgcaatg gattactggg gacagggtac tctggtcacc 780

gtgtccagcc accaccatca tcaccatcac cat 813

<210> 62

<211> 813
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 62
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaaattg tgatgaccca gtcacccgcc actcttagcc tttcacccgg tgagcgcgca 120

accctgtctt gcagagcctc ccaagacatc tcaaaatacc ttaattggta tcaacagaag 180

cccggacagg ctcctcgcct tctgatctac cacaccagcc ggctccattc tggaatccct 240

gccaggttca gcggtagcgg atctgggacc gactacaccc tcactatcag ctcactgcag 300

ccagaggact tcgctgtcta tttctgtcag caagggaaca ccctgcccta caccttgga 360

cagggcacca agctcgagat taaaggtgga ggtggcagcg gaggaggtgg gtccggcggt 420

ggaggaagcc aggtccaact ccaagaaagc ggaccgggtc ttgtgaagcc atcagaaact 480

ctttcactga cttgtactgt gagcggagtg tctctccccg attacggggt gtcttggatc 540

agacagccac cggggaaggg tctggaatgg attggagtga tttggggctc tgagactact 600

tactaccaat catccctcaa gtcacgcgtc accatctcaa aggacaactc taagaatcag 660

gtgtcactga aactgtcatc tgtgaccgca gccgacaccg ccgtgtacta ttgcgctaag 720

cattactatt atggcgggag ctacgcaatg gattactggg gacagggtac tctggtcacc 780

gtgtccagcc accaccatca tcaccatcac cat 813

<210> 63
<211> 813
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 63
atggctctgc ccgtgaccgc actcctcctg ccactggctc tgctgcttca cgccgctcgc 60

ccacaagtcc agcttcaaga atcagggcct ggtctggtga agccatctga gactctgtcc 120

ctcacttgca ccgtgagcgg agtgtccctc ccagactacg gagtgagctg gattagacag 180

cctcccggaa agggactgga gtggatcgga gtgatttggg gtagcgaaac cacttactat 240

tcatcttccc tgaagtcacg ggtcaccatt tcaaaggata actcaaagaa tcaagtgagc 300

ctcaagctct catcagtcac cgccgctgac accgccgtgt attactgtgc caagcattac 360

tactatggag ggtcctacgc catggactac tggggccagg gaactctggt cactgtgtca 420

tctggtggag gaggtagcgg aggaggcggg agcggtggag gtggctccga aatcgtgatg 480

acccagagcc ctgcaaccct gtccctttct cccggggaac gggctaccct ttcttgtcgg 540

gcatcacaag atatctcaaa atacctcaat tggtatcaac agaagccggg acaggcccct 600

aggcttctta tctaccacac ctctcgcctg catagcggga ttcccgcacg ctttagcggg 660

tctggaagcg ggaccgacta cactctgacc atctcatctc tccagcccga ggacttcgcc 720

gtctacttct gccagcaggg taacaccctg ccgtacacct tcggccaggg caccaagctt 780

gagatcaaac atcaccacca tcatcaccat cac 813

<210> 64
<211> 813
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 64
atggctctgc ccgtgaccgc actcctcctg ccactggctc tgctgcttca cgccgctcgc 60

ccacaagtcc agcttcaaga atcagggcct ggtctggtga agccatctga gactctgtcc 120

ctcacttgca ccgtgagcgg agtgtccctc ccagactacg gagtgagctg gattagacag 180

cctcccggaa agggactgga gtggatcgga gtgatttggg gtagcgaaac cacttactat 240

caatcttccc tgaagtcacg ggtcaccatt tcaaaggata actcaaagaa tcaagtgagc 300

ctcaagctct catcagtcac cgccgctgac accgccgtgt attactgtgc caagcattac 360

tactatggag ggtcctacgc catggactac tggggccagg gaactctggt cactgtgtca 420

tctggtggag gaggtagcgg aggaggcggg agcggtggag gtggctccga aatcgtgatg 480

acccagagcc ctgcaaccct gtccctttct cccggggaac gggctaccct ttcttgtcgg 540

gcatcacaag atatctcaaa atacctcaat tggtatcaac agaagccggg acaggccct 600

aggcttctta tctaccacac ctctcgcctg catagcggga ttcccgcacg ctttagcggg 660

tctggaagcg ggaccgacta cactctgacc atctcatctc tccagcccga ggacttcgcc 720

gtctacttct gccagcaggg taacaccctg ccgtacacct tcggccaggg caccaagctt 780

gagatcaaac atcaccacca tcatcaccat cac 813

<210> 65
<211> 828
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 65
atggccctcc cagtgaccgc tctgctgctg cctctcgcac ttcttctcca tgccgctcgg 60

cctgagatcg tcatgaccca aagccccgct accctgtccc tgtcacccgg cgagagggca 120

acccttttcat gcagggccag ccaggacatt tctaagtacc tcaactggta tcagcagaag 180

ccagggcagg ctcctcgcct gctgatctac cacaccagcc gcctccacag cggtatcccc 240

gccagatttt ccgggagcgg gtctggaacc gactacaccc tcaccatctc ttctctgcag 300

cccgaggatt tcgccgtcta tttctgccag caggggaata ctctgccgta caccttcggt 360

caaggtacca agctggaaat caagggaggc ggaggatcag gcggtggcgg aagcggagga 420

ggtggctccg gaggaggagg ttcccaagtg cagcttcaag aatcaggacc cggacttgtg 480

aagccatcag aaaccctctc cctgacttgt accgtgtccg gtgtgagcct ccccgactac 540

ggagtctctt ggattcgcca gcctccgggg aagggtcttg aatggattgg ggtgatttgg 600

ggatcagaga ctacttacta ctcttcatca cttaagtcac gggtcaccat cagcaaagat 660

aatagcaaga accaagtgtc acttaagctg tcatctgtga ccgccgctga caccgccgtg 720

tactattgtg ccaaacatta ctattacgga gggtcttatg ctatggacta ctggggacag 780

gggaccctgg tgactgtctc tagccatcac catcaccacc atcatcac 828

<210> 66
<211> 828
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 66
atggccctcc cagtgaccgc tctgctgctg cctctcgcac ttcttctcca tgccgctcgg 60

cctgagatcg tcatgaccca aagccccgct accctgtccc tgtcacccgg cgagagggca 120

acccttttcat gcagggccag ccaggacatt tctaagtacc tcaactggta tcagcagaag 180

ccagggcagg ctcctcgcct gctgatctac cacaccagcc gcctccacag cggtatcccc 240

gccagatttt ccgggagcgg gtctggaacc gactacaccc tcaccatctc ttctctgcag 300

cccgaggatt tcgccgtcta tttctgccag caggggaata ctctgccgta caccttcggt 360

caaggtacca agctggaaat caagggaggc ggaggatcag gcggtggcgg aagcggagga 420

ggtggctccg gaggaggagg ttcccaagtg cagcttcaag aatcaggacc cggacttgtg 480

aagccatcag aaaccctctc cctgacttgt accgtgtccg gtgtgagcct ccccgactac 540

ggagtctctt ggattcgcca gcctccgggg aagggtcttg aatggattgg ggtgatttgg 600

ggatcagaga ctacttacta ccagtcatca cttaagtcac gggtcaccat cagcaaagat 660

aatagcaaga accaagtgtc acttaagctg tcatctgtga ccgccgctga caccgccgtg 720

tactattgtg ccaaacatta ctattacgga gggtcttatg ctatggacta ctggggacag 780

gggaccctgg tgactgtctc tagccatcac catcaccacc atcatcac 828

<210> 67
<211> 828
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 67
atggcactgc ctgtcactgc cctcctgctg cctctggccc tccttctgca tgccgccagg 60

ccccaagtcc agctgcaaga gtcaggaccc ggactggtga agccgtctga gactctctca 120

ctgacttgta ccgtcagcgg cgtgtccctc cccgactacg gagtgtcatg gatccgccaa 180

cctcccggga aagggcttga atggattggt gtcatctggg gttctgaaac cacctactac 240

tcatcttccc tgaagtccag ggtgaccatc agcaaggata attccaagaa ccaggtcagc 300

cttaagctgt catctgtgac cgctgctgac accgccgtgt attactgcgc caagcactac 360

tattacggag gaagctacgc tatggactat tggggacagg gcactctcgt gactgtgagc 420

agcggcggtg gagggtctgg aggtggagga tccggtggtg gtgggtcagg cggaggaggg 480

agcgagattg tgatgactca gtcaccagcc acccтttctc tttcacccgg cgagagagca 540

accctgagct gtagagccag ccaggacatt tctaagtacc tcaactggta tcagcaaaaa 600

ccggggcagg cccctcgcct cctgatctac catacctcac gccttcactc tggtatcccc 660

gctcggttta gcggatcagg atctggtacc gactacactc tgaccatttc agcctgcag 720

ccagaagatt tcgcagtgta tttctgccag cagggcaata cccttcctta caccttcggt 780

cagggaacca agctcgaaat caagcaccat caccatcatc accaccat 828

<210> 68

<211> 828
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 68
atggcactgc ctgtcactgc cctcctgctg cctctggccc tccttctgca tgccgccagg 60

ccccaagtcc agctgcaaga gtcaggaccc ggactggtga agccgtctga gactctctca 120

ctgacttgta ccgtcagcgg cgtgtccctc cccgactacg gagtgtcatg gatccgccaa 180

cctcccggga aagggcttga atggattggt gtcatctggg gttctgaaac cacctactac 240

cagtcttccc tgaagtccag ggtgaccatc agcaaggata attccaagaa ccaggtcagc 300

cttaagctgt catctgtgac cgctgctgac accgccgtgt attactgcgc caagcactac 360

tattacggag gaagctacgc tatggactat tggggacagg gcactctcgt gactgtgagc 420

agcggcggtg gagggtctgg aggtggagga tccggtggtg gtgggtcagg cggaggaggg 480

agcgagattg tgatgactca gtcaccagcc acccttctc tttcacccgg cgagagagca 540

accctgagct gtagagccag ccaggacatt tctaagtacc tcaactggta tcagcaaaaa 600

ccggggcagg cccctcgcct cctgatctac catacctcac gccttcactc tggtatcccc 660

gctcggttta gcggatcagg atctggtacc gactacactc tgaccatttc cagcctgcag 720

ccagaagatt tcgcagtgta tttctgccag cagggcaata cccttcctta caccttcggt 780

cagggaacca agctcgaaat caagcaccat caccatcatc atcaccac 828

<210> 69
<211> 828
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 69
atggccctcc cagtgaccgc tctgctgctg cctctcgcac ttcttctcca tgccgctcgg 60

cctgagatcg tcatgaccca aagccccgct accctgtccc tgtcacccgg cgagagggca 120

acccтttcat gcagggccag ccaggacatt tctaagtacc tcaactggta tcagcagaag 180

ccagggcagg ctcctcgcct gctgatctac cacaccagcc gcctccacag cggtatcccc 240

gccagatttt ccgggagcgg gtctggaacc gactacaccc tcaccatctc ttctctgcag 300

cccgaggatt tcgccgtcta tttctgccag caggggaata ctctgccgta caccttcggt 360

caaggtacca agctggaaat caagggaggc ggaggatcag gcggtggcgg aagcggagga 420

ggtggctccg gaggaggagg ttcccaagtg cagcttcaag aatcaggacc cggacttgtg 480

aagccatcag aaaccctctc cctgacttgt accgtgtccg gtgtgagcct ccccgactac 540

ggagtctctt ggattcgcca gcctccgggg aagggtcttg aatggattgg ggtgatttgg 600

ggatcagaga ctacttacta caattcatca cttaagtcac gggtcaccat cagcaaagat 660

aatagcaaga accaagtgtc acttaagctg tcatctgtga ccgccgctga caccgccgtg 720

tactattgtg ccaaacatta ctattacgga gggtcttatg ctatggacta ctggggacag 780

gggaccctgg tgactgtctc tagccatcac catcaccacc atcatcac 828

<210> 70
<211> 828
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 70
atggcactgc ctgtcactgc cctcctgctg cctctggccc tccttctgca tgccgccagg 60

ccccaagtcc agctgcaaga gtcaggaccc ggactggtga agccgtctga gactctctca 120

ctgacttgta ccgtcagcgg cgtgtccctc cccgactacg gagtgtcatg gatccgccaa 180

cctcccggga aagggcttga atggattggt gtcatctggg gttctgaaac cacctactac 240

aactcttccc tgaagtccag ggtgaccatc agcaaggata attccaagaa ccaggtcagc 300

cttaagctgt catctgtgac cgctgctgac accgccgtgt attactgcgc caagcactac 360

tattacggag gaagctacgc tatggactat tggggacagg gcactctcgt gactgtgagc 420

agcggcggtg gagggtctgg aggtggagga tccggtggtg gtgggtcagg cggaggaggg 480

agcgagattg tgatgactca gtcaccagcc acccttctc tttcacccgg cgagagagca 540

accctgagct gtagagccag ccaggacatt tctaagtacc tcaactggta tcagcaaaaa 600

ccggggcagg cccctcgcct cctgatctac catacctcac gccttcactc tggtatcccc 660

gctcggttta gcggatcagg atctggtacc gactacactc tgaccatttc cagcctgcag 720

ccagaagatt tcgcagtgta tttctgccag cagggcaata cccttcctta caccttcggt 780

cagggaacca agctcgaaat caagcaccat caccatcatc accaccat 828

<210> 71
<211> 813
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 71
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaaattg tgatgaccca gtcacccgcc actcttagcc tttcacccgg tgagcgcgca 120

accctgtctt gcagagcctc ccaagacatc tcaaaatacc ttaattggta tcaacagaag 180

cccggacagg ctcctcgcct tctgatctac cacaccagcc ggctccattc tggaatccct 240

gccaggttca gcggtagcgg atctgggacc gactacaccc tcactatcag ctcactgcag 300

ccagaggact tcgctgtcta tttctgtcag caagggaaca ccctgcccta caccttgga 360

cagggcacca agctcgagat taaaggtgga ggtggcagcg gaggaggtgg gtccggcggt 420

ggaggaagcc aggtccaact ccaagaaagc ggaccgggtc ttgtgaagcc atcagaaact 480

ctttcactga cttgtactgt gagcggagtg tctctccccg attacggggt gtcttggatc 540

agacagccac cggggaaggg tctggaatgg attggagtga tttggggctc tgagactact 600

tactacaatt catccctcaa gtcacgcgtc accatctcaa aggacaactc taagaatcag 660

gtgtcactga aactgtcatc tgtgaccgca gccgacaccg ccgtgtacta ttgcgctaag 720

cattactatt atggcgggag ctacgcaatg gattactggg gacagggtac tctggtcacc 780

gtgtccagcc accaccatca tcaccatcac cat 813

<210> 72
<211> 813
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 72
atggctctgc ccgtgaccgc actcctcctg ccactggctc tgctgcttca cgccgctcgc 60

ccacaagtcc agcttcaaga atcagggcct ggtctggtga agccatctga gactctgtcc 120

ctcacttgca ccgtgagcgg agtgtccctc ccagactacg gagtgagctg gattagacag 180

cctcccggaa agggactgga gtggatcgga gtgatttggg gtagcgaaac cacttactat 240

aactcttccc tgaagtcacg ggtcaccatt tcaaaggata actcaaagaa tcaagtgagc 300

ctcaagctct catcagtcac cgccgctgac accgccgtgt attactgtgc caagcattac 360

tactatggag ggtcctacgc catggactac tggggccagg gaactctggt cactgtgtca 420

tctggtggag gaggtagcgg aggaggcggg agcggtggag gtggctccga aatcgtgatg 480

acccagagcc ctgcaaccct gtccctttct cccggggaac gggctaccct ttcttgtcgg 540

gcatcacaag atatctcaaa atacctcaat tggtatcaac agaagccggg acaggccct 600

aggcttctta tctaccacac ctctcgcctg catagcggga ttcccgcacg ctttagcggg 660

tctggaagcg ggaccgacta cactctgacc atctcatctc tccagcccga ggacttcgcc 720

gtctacttct gccagcaggg taacaccctg ccgtacacct tcggccaggg caccaagctt 780

gagatcaaac atcaccacca tcatcaccat cac 813

<210> 73
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 73
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
35 40 45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
100 105 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

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Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser Ser Ser Leu Lys Ser
        195                 200                 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Leu Val Thr Val Ser Ser His His His His His His His His
            260                 265                 270
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<210> 74
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 74

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Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
    130                 135                 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145                 150                 155                 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
            180                 185                 190
```

```
Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser
        195                 200                 205


Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
    210                 215                 220


Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225                 230                 235                 240


His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255


Thr Leu Val Thr Val Ser Ser His His His His His His His His
            260                 265                 270


<210> 75
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 75
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30


Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
        35                  40                  45


Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60
```

```
Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80


Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95


Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110


Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125


Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
145                 150                 155                 160


Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175


Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
            180                 185                 190


Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
        195                 200                 205


Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220


Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240


Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
                245                 250                 255
```

Gly Thr Lys Leu Glu Ile Lys His His His His His His His His
260 265 270

<210> 76
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 76
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65 70 75 80

Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
85 90 95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
100 105 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly

130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
145 150 155 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
165 170 175

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
180 185 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
195 200 205

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225 230 235 240

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
245 250 255

Gly Thr Lys Leu Glu Ile Lys His His His His His His His His
260 265 270

<210> 77
<211> 276
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 77
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Ser
        195                 200                 205
```

```
Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220

Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240

Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser His His His His
            260                 265                 270

His His His His
        275
```

<210> 78
<211> 276
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 78

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60
```

```
Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80


Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95


Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110


Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140


Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160


Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175


Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190


Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Gln
        195                 200                 205


Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220


Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240


Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255
```

```
Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser His His His His
            260                 265                 270


His His His His
        275


<210> 79
<211> 276
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 79
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30


Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
        35                  40                  45


Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60


Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80


Ser Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95


Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110
```

```
Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
                165                 170                 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys His His His His
            260                 265                 270

His His His His
        275
```

<210> 80
<211> 276
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 80
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
35 40 45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
50 55 60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65 70 75 80

Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
85 90 95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
100 105 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro

165 170 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
180 185 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
195 200 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
210 215 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225 230 235 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
245 250 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys His His His His
260 265 270

His His His His
275

<210> 81
<211> 276
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 81
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu
20 25 30

```
Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
145                 150                 155                 160

Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser
                165                 170                 175

Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn
        195                 200                 205

Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn
    210                 215                 220
```

```
Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
225                 230                 235                 240


Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp
                245                 250                 255


Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser His His His His
            260                 265                 270


His His His His
        275


<210> 82
<211> 276
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 82
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30


Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
        35                  40                  45


Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60


Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80
```

```
Asn Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro
                165                 170                 175

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys
            180                 185                 190

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        195                 200                 205

Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser
    210                 215                 220

Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln
225                 230                 235                 240

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro
                245                 250                 255

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys His His His His
            260                 265                 270
```

His His His His
        275

<210> 83
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 83
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1   5   10   15

His Ala Ala Arg Pro Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu
            20   25   30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
        35   40   45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50   55   60

Pro Arg Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro
65   70   75   80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
                85   90   95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly
            100   105   110

Asn Thr Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115   120   125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
130 135 140

Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr
145 150 155 160

Leu Ser Leu Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
165 170 175

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
180 185 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ser Leu Lys Ser
195 200 205

Arg Val Thr Ile Ser Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys
210 215 220

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys
225 230 235 240

His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Leu Val Thr Val Ser Ser His His His His His His His His
260 265 270

<210> 84
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 84
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu

```
1               5                   10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Val
        35                  40                  45

Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr
65                  70                  75                  80

Asn Ser Ser Leu Lys Ser Arg Val Thr Ile Ser Lys Asp Asn Ser Lys
                85                  90                  95

Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met
        115                 120                 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr Leu Asn Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr His Thr Ser
```

195 200 205

Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225 230 235 240

Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
245 250 255

Gly Thr Lys Leu Glu Ile Lys His His His His His His His His
260 265 270

<210> 85
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 85
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaaattg tgatgaccca gtcacccgcc actcttagcc tttcacccgg tgagcgcgca 120

accctgtctt gcagagcctc ccaagacatc tcaaaatacc ttaattggta tcaacagaag 180

cccggacagg ctcctcgcct tctgatctac cacaccagcc ggctccattc tggaatccct 240

gccaggttca gcggtagcgg atctgggacc gactacaccc tcactatcag ctcactgcag 300

ccagaggact tcgctgtcta tttctgtcag caagggaaca ccctgcccta cacctttgga 360

cagggcacca agctcgagat taaaggtgga ggtggcagcg gaggaggtgg gtccggcggt 420

ggaggaagcc aggtccaact ccaagaaagc ggaccgggtc ttgtgaagcc atcagaaact 480

ctttcactga cttgtactgt gagcggagtg tctctccccg attacggggt gtcttggatc 540

agacagccac cggggaaggg tctggaatgg attggagtga tttggggctc tgagactact 600

tactactctt catccctcaa gtcacgcgtc accatctcaa aggacaactc taagaatcag 660

gtgtcactga aactgtcatc tgtgaccgca gccgacaccg ccgtgtacta ttgcgctaag 720

cattactatt atggcgggag ctacgcaatg gattactggg gacagggtac tctggtcacc 780

gtgtccagca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 86
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 86
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaaattg tgatgaccca gtcacccgcc actcttagcc tttcacccgg tgagcgcgca 120

accctgtctt gcagagcctc ccaagacatc tcaaaatacc ttaattggta tcaacagaag 180

cccggacagg ctcctcgcct tctgatctac cacaccagcc ggctccattc tggaatccct 240

gccaggttca gcggtagcgg atctgggacc gactacaccc tcactatcag ctcactgcag 300

ccagaggact tcgctgtcta tttctgtcag caagggaaca ccctgcccta cacctttgga 360

cagggcacca agctcgagat taaaggtgga ggtggcagcg gaggaggtgg gtccggcggt 420

ggaggaagcc aggtccaact ccaagaaagc ggaccgggtc ttgtgaagcc atcagaaact 480

ctttcactga cttgtactgt gagcggagtg tctctccccg attacggggt gtcttggatc 540

agacagccac cggggaaggg tctggaatgg attggagtga tttggggctc tgagactact 600

tactaccaat catccctcaa gtcacgcgtc accatctcaa aggacaactc taagaatcag 660

gtgtcactga aactgtcatc tgtgaccgca gccgacaccg ccgtgtacta ttgcgctaag 720

cattactatt atggcgggag ctacgcaatg gattactggg gacagggtac tctggtcacc 780

gtgtccagca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 87

<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 87
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ctcacttgca ccgtgagcgg agtgtccctc ccagactacg gagtgagctg gattagacag 180

cctcccggaa agggactgga gtggatcgga gtgatttggg gtagcgaaac cacttactat 240

tcatcttccc tgaagtcacg ggtcaccatt tcaaaggata actcaaagaa tcaagtgagc 300

ctcaagctct catcagtcac cgccgctgac accgccgtgt attactgtgc caagcattac 360

tactatggag ggtcctacgc catggactac tggggccagg gaactctggt cactgtgtca 420

tctggtggag gaggtagcgg aggaggcggg agcggtggag gtggctccga aatcgtgatg 480

acccagagcc ctgcaaccct gtccctttct cccggggaac gggctaccct ttcttgtcgg 540

gcatcacaag atatctcaaa atacctcaat tggtatcaac agaagccggg acaggcccct 600

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ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

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<210> 88
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

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ctcacttgca ccgtgagcgg agtgtccctc ccagactacg gagtgagctg gattagacag 180

cctcccggaa agggactgga gtggatcgga gtgatttggg gtagcgaaac cacttactat 240

caatcttccc tgaagtcacg ggtcaccatt tcaaaggata actcaaagaa tcaagtgagc 300

ctcaagctct catcagtcac cgccgctgac accgccgtgt attactgtgc caagcattac 360

tactatggag ggtcctacgc catggactac tggggccagg gaactctggt cactgtgtca 420

tctggtggag gaggtagcgg aggaggcggg agcggtggag gtggctccga aatcgtgatg 480

acccagagcc ctgcaaccct gtccctttct cccggggaac gggctaccct ttcttgtcgg 540

gcatcacaag atatctcaaa atacctcaat tggtatcaac agaagccggg acaggccct 600

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cagccgcttt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

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tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

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ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

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caggccctgc cgcctcgg 1458

<210> 89
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

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accctgtctt gcagagcctc ccaagacatc tcaaaatacc ttaattggta tcaacagaag 180

cccggacagg ctcctcgcct tctgatctac cacaccagcc ggctccattc tggaatccct 240

gccaggttca gcggtagcgg atctgggacc gactacaccc tcactatcag ctcactgcag 300

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cagggcacca agctcgagat taaaggtgga ggtggcagcg gaggaggtgg gtccggcggt 420

ggaggaagcg gcggaggcgg gagccaggtc caactccaag aaagcggacc gggtcttgtg 480

aagccatcag aaactctttc actgacttgt actgtgagcg gagtgtctct ccccgattac 540

ggggtgtctt ggatcagaca gccaccgggg aagggtctgg aatggattgg agtgatttgg 600

ggctctgaga ctacttacta ctcttcatcc ctcaagtcac gcgtcaccat ctcaaaggac 660

aactctaaga atcaggtgtc actgaaactg tcatctgtga ccgcagccga caccgccgtg 720

tactattgcg ctaagcatta ctattatggc gggagctacg caatggatta ctggggacag 780

ggtactctgg tcaccgtgtc cagcaccact accccagcac cgaggccacc caccccggct 840

cctaccatcg cctcccagcc tctgtccctg cgtccggagg catgtagacc cgcagctggt 900

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gctggtactt gcggggtcct gctgctttca ctcgtgatca ctctttactg taagcgcggt 1020

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gtgaaattca gccgcagcgc agatgctcca gcctacaagc aggggcagaa ccagctctac 1200

aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

gacccagaaa tgggcgggaa gccgcgcaga aagaatcccc aagagggcct gtacaacgag 1320

ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 90
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 90

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accctgtctt gcagagcctc ccaagacatc tcaaaatacc ttaattggta tcaacagaag 180

cccggacagg ctcctcgcct tctgatctac cacaccagcc ggctccattc tggaatccct 240

gccaggttca gcggtagcgg atctgggacc gactacaccc tcactatcag ctcactgcag 300

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cagggcacca agctcgagat taaaggtgga ggtggcagcg gaggaggtgg gtccggcggt 420

ggaggaagcg gaggcggagg gagccaggtc caactccaag aaagcggacc gggtcttgtg 480

aagccatcag aaactctttc actgacttgt actgtgagcg gagtgtctct ccccgattac 540

ggggtgtctt ggatcagaca gccaccgggg aagggtctgg aatggattgg agtgatttgg 600

ggctctgaga ctacttacta ccaatcatcc ctcaagtcac gcgtcaccat ctcaaaggac 660

aactctaaga atcaggtgtc actgaaactg tcatctgtga ccgcagccga caccgccgtg 720

tactattgcg ctaagcatta ctattatggc gggagctacg caatggatta ctggggacag 780

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cggaagaagc tgctgtacat ctttaagcaa cccttcatga ggcctgtgca gactactcaa 1080

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aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

gacccagaaa tgggcgggaa gccgcgcaga aagaatcccc aagagggcct gtacaacgag 1320

ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 91
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 91
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ctcacttgca ccgtgagcgg agtgtccctc ccagactacg gagtgagctg gattagacag 180

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agcgaaatcg tgatgaccca gagccctgca accctgtccc tttctcccgg ggaacgggct 540

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cccgaggact tcgccgtcta cttctgccag cagggtaaca ccctgccgta caccttcggc 780

cagggcacca agcttgagat caaaaccact actcccgctc caaggccacc cacccctgcc 840

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cggaagaagc tgctgtacat ctttaagcaa cccttcatga ggcctgtgca gactactcaa 1080

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aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

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ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

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<210> 92
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

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ccgggacagg cccctaggct tcttatctac cacacctctc gcctgcatag cgggattccc 660

gcacgcttta gcgggtctgg aagcgggacc gactacactc tgaccatctc atctctccag 720

cccgaggact tcgccgtcta cttctgccag cagggtaaca ccctgccgta caccttcggc 780

cagggcacca agcttgagat caaaaccact actcccgctc caaggccacc caccctgcc 840

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agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 93
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 93
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accctgtctt gcagagcctc ccaagacatc tcaaaatacc ttaattggta tcaacagaag 180

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ggctctgaga ctacttacta caactcatcc ctcaagtcac gcgtcaccat ctcaaaggac 660

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aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

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<210> 94
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

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aagccatcag aaactctttc actgacttgt actgtgagcg gagtgtctct ccccgattac 540

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ggctctgaga ctacttacta caactcatcc ctcaagtcac gcgtcaccat ctcaaaggac 660

aactctaaga atcaggtgtc actgaaactg tcatctgtga ccgcagccga caccgccgtg 720

tactattgcg ctaagcatta ctattatggc gggagctacg caatggatta ctggggacag 780

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ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 95
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

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gcacgcttta gcgggtctgg aagcgggacc gactacactc tgaccatctc atctctccag 720

cccgaggact tcgccgtcta cttctgccag cagggtaaca ccctgccgta caccttcggc 780

cagggcacca agcttgagat caaaaccact actcccgctc caaggccacc cacccctgcc 840

ccgaccatcg cctctcagcc gctttccctg cgtccggagg catgtagacc cgcagctggt 900

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cggaagaagc tgctgtacat ctttaagcaa cccttcatga ggcctgtgca gactactcaa 1080

gaggaggacg gctgttcatg ccggttccca gaggaggagg aaggcggctg cgaactgcgc 1140

gtgaaattca gccgcagcgc agatgctcca gcctacaagc aggggcagaa ccagctctac 1200

aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

gacccagaaa tgggcgggaa gccgcgcaga aagaatcccc aagagggcct gtacaacgag 1320

ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 96
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 96
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaaattg tgatgaccca gtcacccgcc actcttagcc tttcacccgg tgagcgcgca 120

accctgtctt gcagagcctc ccaagacatc tcaaaatacc ttaattggta tcaacagaag 180

cccggacagg ctcctcgcct tctgatctac cacaccagcc ggctccattc tggaatccct 240

gccaggttca gcggtagcgg atctgggacc gactacaccc tcactatcag ctcactgcag 300

ccagaggact tcgctgtcta tttctgtcag caagggaaca ccctgcccta caccttgga 360

cagggcacca agctcgagat taaaggtgga ggtggcagcg gaggaggtgg gtccggcggt 420

ggaggaagcc aggtccaact ccaagaaagc ggaccgggtc ttgtgaagcc atcagaaact 480

ctttcactga cttgtactgt gagcggagtg tctctccccg attacggggt gtcttggatc 540

agacagccac cggggaaggg tctggaatgg attggagtga tttggggctc tgagactact 600

tactacaact catccctcaa gtcacgcgtc accatctcaa aggacaactc taagaatcag 660

gtgtcactga aactgtcatc tgtgaccgca gccgacaccg ccgtgtacta ttgcgctaag 720

cattactatt atggcgggag ctacgcaatg gattactggg gacagggtac tctggtcacc 780

gtgtccagca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 97
<211> 813
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 97
atggccctgc ccgtcaccgc tctgctgctg ccccttgctc tgcttcttca tgcagcaagg 60

ccggacatcc agatgaccca aaccacctca tccctctctg cctctcttgg agacagggtg 120

accatttctt gtcgcgccag ccaggacatc agcaagtatc tgaactggta tcagcagaag 180

ccggacggaa ccgtgaagct cctgatctac catacctctc gcctgcatag cggcgtgccc 240

tcacgcttct ctggaagcgg atcaggaacc gattattctc tcactatttc aaatcttgag 300

caggaagata ttgccaccta tttctgccag cagggtaata ccctgcccta caccttcgga 360

ggagggacca agctcgaaat caccggtgga ggaggcagcg gcggtggagg gtctggtgga 420

ggtggttctg aggtgaagct gcaagaatca ggccctggac ttgtggcccc ttcacagtcc 480

ctgagcgtga cttgcaccgt gtccggagtc tccctgcccg actacggagt gtcatggatc 540

agacaacctc cacggaaagg actggaatgg ctcggtgtca tctggggtag cgaaactact 600

tactacaatt cagccctcaa aagcaggctg actattatca aggacaacag caagtcccaa 660

gtctttctta agatgaactc actccagact gacgacaccg caatctacta ttgtgctaag 720

cactactact acggaggatc ctacgctatg gattactggg gacaaggtac ttccgtcact 780

gtctcttcac accatcatca ccatcaccat cac 813

<210> 98
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 98
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu
            20                  25                  30

Ser Ala Ser Leu Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln
        35                  40                  45

Asp Ile Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr
    50                  55                  60

Val Lys Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val Pro
65                  70                  75                  80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile
                85                  90                  95

Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly
            100                 105                 110

Asn Thr Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
    130                 135                 140

Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser
145                 150                 155                 160

Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly
                165                 170                 175

Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly
            180                 185                 190

Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser
        195                 200                 205
```

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Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys
    210                 215                 220


Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys
225                 230                 235                 240


His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly
                245                 250                 255


Thr Ser Val Thr Val Ser Ser His His His His His His His His
            260                 265                 270


<210> 99
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"

<400> 99
atggccttac cagtgaccgc cttgctcctg ccgctggcct tgctgctcca cgccgccagg       60

ccggacatcc agatgacaca gactacatcc tccctgtctg cctctctggg agacagagtc      120

accatcagtt gcagggcaag tcaggacatt agtaaatatt taaattggta tcagcagaaa      180

ccagatggaa ctgttaaact cctgatctac catacatcaa gattacactc aggagtccca      240

tcaaggttca gtggcagtgg gtctggaaca gattattctc tcaccattag caacctggag      300

caagaagata ttgccactta cttttgccaa cagggtaata cgcttccgta cacgttcgga      360

gggggggacca agctggagat cacaggtggc ggtggctcgg gcggtggtgg gtcgggtggc      420

ggcggatctg aggtgaaact gcaggagtca ggacctggcc tggtggcgcc ctcacagagc      480

ctgtccgtca catgcactgt ctcaggggtc tcattacccg actatggtgt aagctggatt      540

cgccagcctc cacgaaaggg tctggagtgg ctgggagtaa tatggggtag tgaaaccaca      600
```

tactataatt cagctctcaa atccagactg accatcatca aggacaactc caagagccaa 660

gttttcttaa aaatgaacag tctgcaaact gatgacacag ccatttacta ctgtgccaaa 720

cattattact acggtggtag ctatgctatg gactactggg gccaaggaac ctcagtcacc 780

gtctcctcaa ccacgacgcc agcgccgcga ccaccaacac cggcgcccac catcgcgtcg 840

cagcccctgt ccctgcgccc agaggcgtgc cggccagcgg cgggggcgc agtgcacacg 900

agggggctgg acttcgcctg tgatatctac atctgggcgc ccttggccgg gacttgtggg 960

gtccttctcc tgtcactggt tatcaccctt tactgcaaac ggggcagaaa gaaactcctg 1020

tatatattca aacaaccatt tatgagacca gtacaaacta ctcaagagga agatggctgt 1080

agctgccgat ttccagaaga agaagaagga ggatgtgaac tgagagtgaa gttcagcagg 1140

agcgcagacg cccccgcgta caagcagggc cagaaccagc tctataacga gctcaatcta 1200

ggacgaagag aggagtacga tgttttggac aagagacgtg gccgggaccc tgagatgggg 1260

ggaaagccga gaaggaagaa ccctcaggaa ggcctgtaca atgaactgca gaaagataag 1320

atggcggagg cctacagtga gattgggatg aaaggcgagc gccggagggg caaggggcac 1380

gatggccttt accagggtct cagtacagcc accaaggaca cctacgacgc ccttcacatg 1440

caggccctgc cccctcgc 1458

<210> 100
<211> 1184
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 100
cgtgaggctc cggtgcccgt cagtgggcag agcgcacatc gcccacagtc cccgagaagt 60

tgggggggagg ggtcggcaat tgaaccggtg cctagagaag gtggcgcggg gtaaactggg 120

aaagtgatgt cgtgtactgg ctccgccttt ttcccgaggg tgggggagaa ccgtatataa 180

gtgcagtagt cgccgtgaac gttctttttc gcaacgggtt tgccgccaga acacaggtaa 240

gtgccgtgtg tggttcccgc gggcctggcc tctttacggg ttatggccct tgcgtgcctt 300

gaattacttc cacctggctg cagtacgtga ttcttgatcc cgagcttcgg gttggaagtg 360

ggtgggagag ttcgaggcct tgcgcttaag gagccccttc gcctcgtgct tgagttgagg 420

cctggcctgg gcgctggggc cgccgcgtgc gaatctggtg gcaccttcgc gcctgtctcg 480

ctgctttcga taagtctcta gccatttaaa atttttgatg acctgctgcg acgcttttt 540

tctggcaaga tagtcttgta aatgcgggcc aagatctgca cactggtatt tcggtttttg 600

gggccgcggg cggcgacggg gcccgtgcgt cccagcgcac atgttcggcg aggcggggcc 660

tgcgagcgcg gccaccgaga atcggacggg ggtagtctca agctggccgg cctgctctgg 720

tgcctggcct cgcgccgccg tgtatcgccc cgccctgggc ggcaaggctg gcccggtcgg 780

caccagttgc gtgagcggaa agatggccgc ttcccggccc tgctgcaggg agctcaaaat 840

ggaggacgcg gcgctcggga gagcgggcgg gtgagtcacc cacacaaagg aaaagggcct 900

ttccgtcctc agccgtcgct tcatgtgact ccacggagta ccgggcgccg tccaggcacc 960

tcgattagtt ctcgagcttt tggagtacgt cgtctttagg ttgggggggag gggttttatg 1020

cgatggagtt tccccacact gagtgggtgg agactgaagt taggccagct tggcacttga 1080

tgtaattctc cttggaattt gccctttttg agtttggatc ttggttcatt ctcaagcctc 1140

agacagtggt tcaaagtttt tttcttccat ttcaggtgtc gtga 1184

<210> 101
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 101
agagtgaagt tcagcaggag cgcagacgcc cccgcgtaca agcagggcca gaaccagctc 60

tataacgagc tcaatctagg acgaagagag gagtacgatg ttttggacaa gagacgtggc 120

cgggaccctg agatgggggg aaagccgaga aggaagaacc ctcaggaagg cctgtacaat 180

gaactgcaga aagataagat ggcggaggcc tacagtgaga ttgggatgaa aggcgagcgc 240

cggaggggca aggggcacga tggcctttac cagggtctca gtacagccac caaggacacc 300

tacgacgccc ttcacatgca ggccctgccc cctcgc 336

<210> 102
<211> 230
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 102
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
1 5 10 15

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
20 25 30

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
35 40 45

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
50 55 60

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65 70 75 80

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
85 90 95

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser

100 105 110

Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
115 120 125

Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
130 135 140

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
145 150 155 160

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
165 170 175

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
180 185 190

Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
195 200 205

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
210 215 220

Leu Ser Leu Gly Lys Met
225 230

<210> 103
<211> 690
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 103
gagagcaagt acggccctcc ctgcccccct tgccctgccc ccgagttcct gggcggaccc 60

agcgtgttcc tgttcccccc caagcccaag gacaccctga tgatcagccg gacccccgag 120

gtgacctgtg tggtggtgga cgtgtcccag gaggaccccg aggtccagtt caactggtac 180

gtggacggcg tggaggtgca caacgccaag accaagcccc gggaggagca gttcaatagc 240

acctaccggg tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaggaa 300

tacaagtgta aggtgtccaa caagggcctg cccagcagca tcgagaaaac catcagcaag 360

gccaagggcc agcctcggga gccccaggtg tacaccctgc cccctagcca agaggagatg 420

accaagaacc aggtgtccct gacctgcctg gtgaagggct tctaccccag cgacatcgcc 480

gtggagtggg agagcaacgg ccagcccgag aacaactaca agaccacccc ccctgtgctg 540

gacagcgacg gcagcttctt cctgtacagc cggctgaccg tggacaagag ccggtggcag 600

gagggcaacg tctttagctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag 660

aagagcctga gcctgtccct gggcaagatg 690

<210> 104
<211> 400
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (1)..(400)
<223> /note="This sequence may encompass 100-400 nucleotides"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 104
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 180

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 240

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 300

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 360

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 400

<210> 105
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>
<221> MISC_FEATURE
<222> (1)..(40)
<223> /note="This sequence may encompass 1-10 'Gly-Gly-Gly-Ser' repeating units"

<220>
<221> source
<223> /note="See specification as filed for detailed description of substitutions and preferred embodiments"

<400> 105
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
20 25 30

Gly Gly Gly Ser Gly Gly Gly Ser
35 40

<210> 106

<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 106
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser
20

<210> 107
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 107
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 108
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 108
Gly Gly Gly Ser
1

<210> 109
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 109
Gln Val Gln Leu Leu Glu Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
20 25 30

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
50 55 60

Lys Gly Gln Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Gly Leu Thr Ser Glu Asp Ser Ala Val Tyr Ser Cys
85 90 95

Ala Arg Lys Thr Ile Ser Ser Val Val Asp Phe Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Gly Gly Gly Ser Gly Gly Gly Ser Gly
115 120 125

Gly Gly Ser Gly Gly Gly Ser Glu Leu Val Leu Thr Gln Ser Pro Lys
130 135 140

Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser Val Thr Cys Lys Ala

145 150 155 160

Ser Gln Asn Val Gly Thr Asn Val Ala Trp Tyr Gln Gln Lys Pro Gly
165 170 175

Gln Ser Pro Lys Pro Leu Ile Tyr Ser Ala Thr Tyr Arg Asn Ser Gly
180 185 190

Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
195 200 205

Thr Ile Thr Asn Val Gln Ser Lys Asp Leu Ala Asp Tyr Phe Cys Gln
210 215 220

Tyr Asn Arg Tyr Pro Tyr Thr Ser Phe Phe Phe Thr Lys Leu Glu Ile
225 230 235 240

Lys Arg Arg Ser

<210> 110
<211> 464
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 110
Gln Val Gln Leu Leu Glu Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
20 25 30

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

```
Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
    50                  55                  60

Lys Gly Gln Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Gly Leu Thr Ser Glu Asp Ser Ala Val Tyr Ser Cys
                85                  90                  95

Ala Arg Lys Thr Ile Ser Ser Val Val Asp Phe Tyr Phe Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Gly Gly Gly Ser Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Ser Glu Leu Val Leu Thr Gln Ser Pro Lys
    130                 135                 140

Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser Val Thr Cys Lys Ala
145                 150                 155                 160

Ser Gln Asn Val Gly Thr Asn Val Ala Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175

Gln Ser Pro Lys Pro Leu Ile Tyr Ser Ala Thr Tyr Arg Asn Ser Gly
            180                 185                 190

Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        195                 200                 205

Thr Ile Thr Asn Val Gln Ser Lys Asp Leu Ala Asp Tyr Phe Cys Gln
    210                 215                 220

Tyr Asn Arg Tyr Pro Tyr Thr Ser Phe Phe Phe Thr Lys Leu Glu Ile
225                 230                 235                 240
```

```
Lys Arg Arg Ser Lys Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp
                245                 250                 255

Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly Lys His Leu
            260                 265                 270

Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu
        275                 280                 285

Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val
    290                 295                 300

Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg Leu Leu His
305                 310                 315                 320

Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys
                325                 330                 335

His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser
            340                 345                 350

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
        355                 360                 365

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
    370                 375                 380

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
385                 390                 395                 400

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
                405                 410                 415

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
            420                 425                 430
```

```
Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
        435                 440                 445


Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
    450                 455                 460


<210> 111
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 111
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1               5                   10                  15


Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
            20                  25                  30


Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45


Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65                  70                  75                  80


Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly
            100                 105                 110
```

```
Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys
        115                 120                 125


Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser
    130                 135                 140


Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser
145                 150                 155                 160


Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile
                165                 170                 175


Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu
            180                 185                 190


Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn
        195                 200                 205


Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr
    210                 215                 220


Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
225                 230                 235                 240


Val Thr Val Ser Ser Glu
                245
```

<210> 112
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 112

```
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1               5                  10                  15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly
            100                 105                 110

Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys
        115                 120                 125

Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser
    130                 135                 140

Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser
145                 150                 155                 160

Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile
                165                 170                 175

Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu
            180                 185                 190
```

```
Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn
        195                 200                 205

Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr
    210                 215                 220

Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
225                 230                 235                 240

Val Thr Val Ser Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
                245                 250                 255

Pro Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr
            260                 265                 270

Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Lys Arg Gly
        275                 280                 285

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
    290                 295                 300

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Glu Glu Glu
305                 310                 315                 320

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
                325                 330                 335

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
            340                 345                 350

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
        355                 360                 365

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
    370                 375                 380
```

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
385 390 395 400

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
405 410 415

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
420 425 430

Gln Ala Leu Pro Pro Arg Leu
435

<210> 113
<211> 819
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 113
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65 70 75 80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr

85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly
100 105 110

Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys
115 120 125

Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser
130 135 140

Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser
145 150 155 160

Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile
165 170 175

Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu
180 185 190

Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn
195 200 205

Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr
210 215 220

Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
225 230 235 240

Val Thr Val Ser Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
245 250 255

Pro Met Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr
260 265 270

Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val Lys Arg Gly

```
        275                 280                 285

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
    290                 295                 300

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Glu Glu Glu
305                 310                 315                 320

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
                325                 330                 335

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
            340                 345                 350

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
        355                 360                 365

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
    370                 375                 380

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
385                 390                 395                 400

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
                405                 410                 415

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
            420                 425                 430

Gln Ala Leu Pro Pro Arg Leu Glu Gly Gly Gly Glu Gly Arg Gly Ser
        435                 440                 445

Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro Gly Pro Arg Met Leu
    450                 455                 460

Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro Ala Phe
```

```
465                 470                 475                 480

Leu Leu Ile Pro Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Phe
                485                 490                 495

Lys Asp Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys Asn
            500                 505                 510

Cys Thr Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg
        515                 520                 525

Gly Asp Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp
    530                 535                 540

Ile Leu Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala
545                 550                 555                 560

Trp Pro Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn Leu Glu Ile
                565                 570                 575

Ile Arg Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val Val
            580                 585                 590

Ser Leu Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser
        595                 600                 605

Asp Gly Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn
    610                 615                 620

Thr Ile Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys
625                 630                 635                 640

Ile Ile Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln Val
                645                 650                 655

Cys His Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg
```

660 665 670

Asp Cys Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val Asp
675 680 685

Lys Cys Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn Ser
690 695 700

Glu Cys Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn Ile
705 710 715 720

Thr Cys Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His Tyr
725 730 735

Ile Asp Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val Met Gly
740 745 750

Glu Asn Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His Val Cys
755 760 765

His Leu Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly Leu
770 775 780

Glu Gly Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile Ala Thr Gly
785 790 795 800

Met Val Gly Ala Leu Leu Leu Leu Leu Val Val Ala Leu Gly Ile Gly
805 810 815

Leu Phe Met

<210> 114
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 114

```
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1               5                  10                  15

Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly
            100                 105                 110

Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys
        115                 120                 125

Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser
    130                 135                 140

Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser
145                 150                 155                 160

Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile
                165                 170                 175
```

```
Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu
            180                 185                 190


Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn
        195                 200                 205


Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr
    210                 215                 220


Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
225                 230                 235                 240


Val Thr Val Ser Ser
                245


<210> 115
<211> 467
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 115
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
1               5                   10                  15


Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
            20                  25                  30


Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45


Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

```
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Gly Ser Thr Ser Gly
            100                 105                 110

Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr Lys Gly Glu Val Lys
        115                 120                 125

Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln Ser Leu Ser
    130                 135                 140

Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser
145                 150                 155                 160

Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu Gly Val Ile
                165                 170                 175

Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys Ser Arg Leu
            180                 185                 190

Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu Lys Met Asn
        195                 200                 205

Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala Lys His Tyr
    210                 215                 220

Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
225                 230                 235                 240

Val Thr Val Ser Ser Ala Ala Ala Ile Glu Val Met Tyr Pro Pro Pro
                245                 250                 255
```

```
Tyr Leu Asp Asn Glu Lys Ser Asn Gly Thr Ile Ile His Val Lys Gly
            260                 265                 270

Lys His Leu Cys Pro Ser Pro Leu Phe Pro Gly Pro Ser Lys Pro Phe
        275                 280                 285

Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu Leu
    290                 295                 300

Val Thr Val Ala Phe Ile Ile Phe Trp Val Arg Ser Lys Arg Ser Arg
305                 310                 315                 320

Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro
                325                 330                 335

Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala
            340                 345                 350

Tyr Arg Ser Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
        355                 360                 365

Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
    370                 375                 380

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
385                 390                 395                 400

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
                405                 410                 415

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
            420                 425                 430

Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
        435                 440                 445
```

Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
450 455 460

Pro Pro Arg
465

<210> 116
<211> 735
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 116
gaagtgcaac ttgtggaatc tggtggagga cttgtgcaac ctggaagatc actgagactg 60

tcatgtgcag cctcggggtt taccttcgac gactacgcca tgcactgggt gcgccaggct 120

ccggggaagg gcctcgaatg ggtgtcgggc atcagctgga actccggttc cattggctat 180

gcggactccg tgaaaggacg cttcacaatt tcccgggata acgccaagaa cagcctgtac 240

ttgcagatga actccctgcg ggccgaggat accgccctgt actactgcgc taaggacaag 300

ggcggtggat actacgactt ctggagcgga agcgactact ggggacaggg aactctggtc 360

accgtgtcct ccggcggagg gggctccggc ggcggtggta gcgggggtgg agggtcgtcg 420

tcggagctga cccaggaccc cgcagtgtcc gtcgccctgg ggcagactgt gcggatcact 480

tgccaaggag acagcctgcg gtcctactac gcgtcctggt atcagcagaa gccggggcag 540

gccccagtcc tcgtcatcta cggaaagaac aataggccca gcggaatccc tgaccgcttc 600

tcgggctcat cctccggcaa caccgcctcc ctgaccatca cgggcgcgca ggccgaggac 660

gaagccgatt actactgcaa ctcacgggat tccagcggat gggtgttcgg aggaggaacc 720

aagctcactg tgctc 735

<210> 117

<211> 744
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 117
caagtccaac tcgtccagtc cggtgcagaa gtcaagaaac ccggagcttc cgtgaaagtg 60

tcctgcaagg cctcggggta taccttcact tcctactaca tgcactgggt ccggcaggcg 120

ccgggacagg gactggaatg gatgggtatc atcaacccct cgggcggttc cactagctac 180

gcccagaagt tccagggaag agtgaccatg acccgggaca cttccacttc gaccgtgtac 240

atggaactga gcagcctgag gagcgaggac accgccgtgt actactgtgc ccggcccgag 300

ggagtgtcct actacgattc ctccgtgctg gattactggg gacagggaac acttgtgacc 360

gtgtcctcgg gaggaggcgg aagcgggggc ggagggtctg ggggaggcgg ctcccagtcc 420

gctctgacgc agcctgcgtc cgtgtccggg agccctggcc agagcattac tatttcatgc 480

accggtacca gctccgacgt gggcggatat aagcacgtgt catggtacca gcatcacccg 540

ggaaaggccc caaagctgat gatctacgac gtgtcgaaca gaccgagcgg ggtgtcaaat 600

cgcttttccg gttcaaagtc gggcaacact gcctcactca ccgtgtcggg cctccaagcg 660

gaggacgaag cccactacta ctgcgtgtcc taccgcaact tcaactcctt ggtgttcggc 720

accggcacca aggtcaccgt cctg 744

<210> 118
<211> 2000
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<220>
<221> misc_feature
<222> (1)..(2000)
<223> /note="This sequence may encompass 50-2000 nucleotides"

<220>
<221> source
<223> /note="See specification as filed for detailed description of
substitutions and preferred embodiments"

<400> 118
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 180

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 240

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 300

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 360

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 420

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 600

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 660

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 720

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 840

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 900

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 960

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1020

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1080

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1140

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1200

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1260

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1320

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1380

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1440

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1500

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1560

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1680

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1740

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1800

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1860

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1920

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1980

aaaaaaaaaa aaaaaaaaaa 2000

<210> 119
<211> 373
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 119
Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro Trp Asn Pro Pro Thr
1 5 10 15

Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp Asn Ala Thr Phe

```
            20                  25                  30

Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val Leu Asn Trp Tyr
        35                  40                  45

Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala Ala Phe Pro Glu
    50                  55                  60

Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg Val Thr Gln Leu
65                  70                  75                  80

Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg Ala Arg Arg Asn
                85                  90                  95

Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu Ala Pro Lys Ala
            100                 105                 110

Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val Thr Glu Arg Arg
        115                 120                 125

Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro Arg Pro Ala Gly
    130                 135                 140

Gln Phe Gln Thr Leu Val Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
145                 150                 155                 160

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
                165                 170                 175

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
            180                 185                 190

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
        195                 200                 205

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
```

210 215 220

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
225 230 235 240

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
245 250 255

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
260 265 270

Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
275 280 285

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
290 295 300

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
305 310 315 320

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
325 330 335

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
340 345 350

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
355 360 365

Ala Leu Pro Pro Arg
370

<210> 120
<211> 1182
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 120
atggccctcc ctgtcactgc cctgcttctc cccctcgcac tcctgctcca cgccgctaga 60

ccacccggat ggtttctgga ctctccggat cgcccgtgga atcccccaac cttctcaccg 120

gcactcttgg ttgtgactga gggcgataat gcgaccttca cgtgctcgtt ctccaacacc 180

tccgaatcat tcgtgctgaa ctggtaccgc atgagcccgt caaaccagac cgacaagctc 240

gccgcgtttc cggaagatcg gtcgcaaccg ggacaggatt gtcggttccg cgtgactcaa 300

ctgccgaatg gcagagactt ccacatgagc gtggtccgcg ctaggcgaaa cgactccggg 360

acctacctgt gcggagccat ctcgctggcg cctaaggccc aaatcaaaga gagcttgagg 420

gccgaactga gagtgaccga gcgcagagct gaggtgccaa ctgcacatcc atccccatcg 480

cctcggcctg cggggcagtt tcagaccctg gtcacgacca ctccggcgcc gcgcccaccg 540

actccggccc caactatcgc gagccagccc ctgtcgctga ggccggaagc atgccgccct 600

gccgccggag gtgctgtgca tacccgggga ttggacttcg catgcgacat ctacatttgg 660

gctcctctcg ccggaacttg tggcgtgctc cttctgtccc tggtcatcac cctgtactgc 720

aagcggggtc ggaaaaagct tctgtacatt ttcaagcagc ccttcatgag gcccgtgcaa 780

accacccagg aggaggacgg ttgctcctgc cggttccccg aagaggaaga aggaggttgc 840

gagctgcgcg tgaagttctc ccggagcgcc gacgcccccg cctataagca gggccagaac 900

cagctgtaca acgaactgaa cctgggacgg cgggaagagt acgatgtgct ggacaagcgg 960

cgcggccggg accccgaaat gggcgggaag cctagaagaa agaaccctca ggaaggcctg 1020

tataacgagc tgcagaagga caagatggcc gaggcctact ccgaaattgg gatgaaggga 1080

gagcggcgga ggggaaaggg gcacgacggc ctgtaccaag gactgtccac cgccaccaag 1140

gacacatacg atgccctgca catgcaggcc cttccccctc gc 1182

<210> 121

<211> 394
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 121

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Pro Gly Trp Phe Leu Asp Ser Pro Asp Arg Pro
            20                  25                  30

Trp Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly
        35                  40                  45

Asp Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe
    50                  55                  60

Val Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu
65                  70                  75                  80

Ala Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe
                85                  90                  95

Arg Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val
            100                 105                 110

Arg Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser
        115                 120                 125

Leu Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg
    130                 135                 140

Val Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser
145                 150                 155                 160
```

```
Pro Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Thr Thr Thr Pro Ala
                165                 170                 175

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
            180                 185                 190

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
        195                 200                 205

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
    210                 215                 220

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
225                 230                 235                 240

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
                245                 250                 255

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
            260                 265                 270

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
        275                 280                 285

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
    290                 295                 300

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
305                 310                 315                 320

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
                325                 330                 335

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
            340                 345                 350
```

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
355 360 365

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
370 375 380

Ala Leu His Met Gln Ala Leu Pro Pro Arg
385 390

<210> 122
<211> 132
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 122
Asp Val Pro Asp Tyr Ala Ser Leu Gly Gly Pro Ser Ser Pro Lys Lys
1 5 10 15

Lys Arg Lys Val Ser Arg Gly Val Gln Val Glu Thr Ile Ser Pro Gly
20 25 30

Asp Gly Arg Thr Phe Pro Lys Arg Gly Gln Thr Cys Val Val His Tyr
35 40 45

Thr Gly Met Leu Glu Asp Gly Lys Lys Phe Asp Ser Ser Arg Asp Arg
50 55 60

Asn Lys Pro Phe Lys Phe Met Leu Gly Lys Gln Glu Val Ile Arg Gly
65 70 75 80

Trp Glu Glu Gly Val Ala Gln Met Ser Val Gly Gln Arg Ala Lys Leu
85 90 95

Thr Ile Ser Pro Asp Tyr Ala Tyr Gly Ala Thr Gly His Pro Gly Ile
100 105 110

Ile Pro Pro His Ala Thr Leu Val Phe Asp Val Glu Leu Leu Lys Leu
115 120 125

Glu Thr Ser Tyr
130

<210> 123
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 123
Val Gln Val Glu Thr Ile Ser Pro Gly Asp Gly Arg Thr Phe Pro Lys
1 5 10 15

Arg Gly Gln Thr Cys Val Val His Tyr Thr Gly Met Leu Glu Asp Gly
20 25 30

Lys Lys Phe Asp Ser Ser Arg Asp Arg Asn Lys Pro Phe Lys Phe Met
35 40 45

Leu Gly Lys Gln Glu Val Ile Arg Gly Trp Glu Glu Gly Val Ala Gln
50 55 60

Met Ser Val Gly Gln Arg Ala Lys Leu Thr Ile Ser Pro Asp Tyr Ala
65 70 75 80

Tyr Gly Ala Thr Gly His Pro Gly Ile Ile Pro Pro His Ala Thr Leu
85 90 95

Val Phe Asp Val Glu Leu Leu Lys Leu Glu Thr Ser
100 105

<210> 124
<211> 93
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 124
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg
1 5 10 15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
20 25 30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr
35 40 45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
50 55 60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala
65 70 75 80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys
85 90

<210> 125
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 125
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Ile Glu Ala Ser Arg
1   5   10   15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
            20   25   30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr
        35   40   45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
    50   55   60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala
65   70   75   80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
                85   90   95

<210> 126
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 126
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Leu Glu Ala Ser Arg
1   5   10   15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
            20   25   30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr
        35   40   45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
    50   55   60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Thr Gln Ala
65   70   75   80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
                85   90   95

<210> 127
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 127
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Glu Glu Ala Ser Arg
1   5   10   15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
            20   25   30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr
        35   40   45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
    50   55   60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Leu Gln Ala
65   70   75   80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
                85   90   95

<210> 128
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<220>
<221> MOD_RES
<222> (12)..(12)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (78)..(78)
<223> Any amino acid

<400> 128

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Ile Leu Trp His Glu Met Trp His Glu Gly Leu Xaa Glu Ala Ser Arg
1               5                   10                  15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
            20                  25                  30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr
        35                  40                  45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
    50                  55                  60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Xaa Gln Ala
65                  70                  75                  80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
                85                  90                  95
```

<210> 129
<211> 95

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 129
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Ile Glu Ala Ser Arg
1 5 10 15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
20 25 30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr
35 40 45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
50 55 60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Leu Gln Ala
65 70 75 80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
85 90 95

<210> 130
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 130
Ile Leu Trp His Glu Met Trp His Glu Gly Leu Leu Glu Ala Ser Arg
1 5 10 15

Leu Tyr Phe Gly Glu Arg Asn Val Lys Gly Met Phe Glu Val Leu Glu
20 25 30

Pro Leu His Ala Met Met Glu Arg Gly Pro Gln Thr Leu Lys Glu Thr
35 40 45

Ser Phe Asn Gln Ala Tyr Gly Arg Asp Leu Met Glu Ala Gln Glu Trp
50 55 60

Cys Arg Lys Tyr Met Lys Ser Gly Asn Val Lys Asp Leu Leu Gln Ala
65 70 75 80

Trp Asp Leu Tyr Tyr His Val Phe Arg Arg Ile Ser Lys Thr Ser
85 90 95

<210> 131
<211> 254
<212> PRT
<213> Homo sapiens

<400> 131
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Ser Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

```
Tyr Tyr Cys Ala Arg Asp Pro Tyr Asp Phe Trp Ser Gly Tyr Pro Asp
            100                 105                 110

Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser
    130                 135                 140

Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile
145                 150                 155                 160

Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr
                165                 170                 175

Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Val Ile Ile
            180                 185                 190

Ser Glu Val Asn Asn Arg Pro Ser Gly Val Ser His Arg Phe Ser Gly
        195                 200                 205

Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
    210                 215                 220

Glu Asp Glu Ala Asp Tyr Phe Cys Ser Ser Tyr Thr Ser Gly Arg Thr
225                 230                 235                 240

Leu Tyr Val Phe Gly Thr Gly Ser Lys Val Thr Val Leu Gly
                245                 250
```

<210> 132
<211> 251
<212> PRT
<213> Homo sapiens

<400> 132

```
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                  10                  15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Asn Asn
            20                  25                  30

Asn Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asn Asp Tyr Val
    50                  55                  60

Gly Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65                  70                  75                  80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95

Tyr Tyr Cys Ala Arg Glu Thr Asp Tyr Gly Asp Tyr Gly Ala Phe Asp
            100                 105                 110

Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr
    130                 135                 140

Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser
145                 150                 155                 160

Cys Thr Gly Ser Arg Asn Asp Ile Gly Ala Tyr Glu Ser Val Ser Trp
                165                 170                 175

Tyr Gln Gln His Pro Gly Asn Ala Pro Lys Leu Ile Ile His Gly Val
            180                 185                 190
```

Asn Asn Arg Pro Ser Gly Val Phe Asp Arg Phe Ser Val Ser Gln Ser
195 200 205

Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu
210 215 220

Ala Asp Tyr Tyr Cys Ser Ser His Thr Thr Thr Ser Thr Leu Tyr Val
225 230 235 240

Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
245 250

<210> 133
<211> 247
<212> PRT
<213> Homo sapiens

<400> 133
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Asn Pro Ser Gln
1 5 10 15

Thr Leu Ser Ile Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Phe Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Gly Arg Ile Thr Ile Ser Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Gly Gly Asp Tyr Tyr Tyr Gly Leu Asp Val Trp Gly
100 105 110

```
Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala
    130                 135                 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly
145                 150                 155                 160

Ser Ser Ser Asp Val Gly Gly Tyr Asn Ser Val Ser Trp Tyr Gln Gln
                165                 170                 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Val Ile Asn Arg
            180                 185                 190

Pro Ser Gly Val Ser His Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr
        195                 200                 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr
    210                 215                 220

Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Tyr Val Phe Gly Thr Gly
225                 230                 235                 240

Thr Lys Val Thr Val Leu Gly
                245
```

<210> 134
<211> 254
<212> PRT
<213> Homo sapiens

<400> 134

```
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15
```

```
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
            20                  25                  30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
    50                  55                  60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65                  70                  75                  80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
                85                  90                  95

Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
            100                 105                 110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser
    130                 135                 140

Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile
145                 150                 155                 160

Thr Ile Ser Cys Thr Gly Ser Ser Ser Asp Ile Gly Gly Phe Asn Tyr
                165                 170                 175

Val Ser Trp Tyr Gln Gln His Ala Gly Glu Ala Pro Lys Leu Met Ile
            180                 185                 190

Tyr Glu Val Thr Asn Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly
        195                 200                 205
```

Ser Lys Ser Asp Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
210 215 220

Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Ser Gly Ser Pro
225 230 235 240

Leu Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
245 250

<210> 135
<211> 254
<212> PRT
<213> Homo sapiens

<400> 135
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
20 25 30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
50 55 60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65 70 75 80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
85 90 95

Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
100 105 110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
115 120 125

```
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Ser Gly Gly Ser Gln Ser
    130                 135                 140

Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile
145                 150                 155                 160

Thr Phe Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Gly Tyr Asn Tyr
                165                 170                 175

Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile
            180                 185                 190

Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly
        195                 200                 205

Thr Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
    210                 215                 220

Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr
225                 230                 235                 240

Leu Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu Gly
                245                 250
```

<210> 136
<211> 254
<212> PRT
<213> Homo sapiens

<400> 136

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
            20                  25                  30
```

```
Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
    50                  55                  60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65                  70                  75                  80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
                85                  90                  95

Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
            100                 105                 110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Ser Gly Gly Ser Gln Ser
    130                 135                 140

Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile
145                 150                 155                 160

Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr
                165                 170                 175

Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile
            180                 185                 190

Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly
        195                 200                 205

Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
    210                 215                 220
```

Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr
225 230 235 240

Leu Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
245 250

<210> 137
<211> 254
<212> PRT
<213> Homo sapiens

<400> 137
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
20 25 30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
50 55 60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65 70 75 80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
85 90 95

Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
100 105 110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser
130 135 140

```
Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile
145                 150                 155                 160


Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr
                165                 170                 175


Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile
            180                 185                 190


Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly
        195                 200                 205


Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
    210                 215                 220


Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr
225                 230                 235                 240


Leu Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
                245                 250


<210> 138
<211> 254
<212> PRT
<213> Homo sapiens

<400> 138
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
            20                  25                  30


Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45
```

```
Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
    50                  55                  60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65                  70                  75                  80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
                85                  90                  95

Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
            100                 105                 110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser
    130                 135                 140

Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile
145                 150                 155                 160

Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr
                165                 170                 175

Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile
            180                 185                 190

Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly
        195                 200                 205

Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
    210                 215                 220

Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr
225                 230                 235                 240
```

Leu Tyr Ile Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
245 250

<210> 139
<211> 253
<212> PRT
<213> Homo sapiens

<400> 139
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Pro Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
20 25 30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
50 55 60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65 70 75 80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
85 90 95

Tyr Tyr Cys Ala Arg Val Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
100 105 110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Pro Gln Ser
130 135 140

Ala Leu Thr Gln Pro Ala Ser Ala Ser Gly Ser Pro Gly Gln Ser Val
145 150 155 160

```
Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr
                165                 170                 175


Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile
            180                 185                 190


Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly
        195                 200                 205


Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
    210                 215                 220


Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr
225                 230                 235                 240


Leu Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu
                245                 250


<210> 140
<211> 253
<212> PRT
<213> Homo sapiens

<400> 140
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Met Leu Ser Asn
            20                  25                  30


Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45


Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
    50                  55                  60
```

```
Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65                  70                  75                  80


Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
                85                  90                  95


Tyr Tyr Cys Ala Arg Val Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
            100                 105                 110


Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
        115                 120                 125


Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser
    130                 135                 140


Ala Leu Thr Gln Pro Ala Ser Ala Ser Gly Ser Pro Gly Gln Ser Val
145                 150                 155                 160


Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr
                165                 170                 175


Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile
            180                 185                 190


Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly
        195                 200                 205


Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
    210                 215                 220


Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr
225                 230                 235                 240


Leu Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu
                245                 250
```

<210> 141
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
<221> MOD_RES
<222> (1)..(1)
<223> Any amino acid

<400> 141
Xaa Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp Ala Phe Asp Val
1 5 10 15

<210> 142
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 142
Gly Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn
1 5 10

<210> 143
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 143
Gly Phe Thr Val Ser Ser Asn Tyr Met Ser

1 5 10

<210> 144
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 144
Gly Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn
1 5 10

<210> 145
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 145
Gly Asp Ser Val Leu Ser Asn Ser Asp Thr Trp Asn
1 5 10

<210> 146
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 146
Gly Phe Thr Phe Asp Asp Tyr Ala Met His
1 5 10

<210> 147
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 147
Gly Phe Thr Phe Asp Asp Tyr Ala Met His
1 5 10

<210> 148
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 148
Gly Asp Ser Val Ser Ser Asn Ser Ala Thr Trp Thr
1 5 10

<210> 149
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 149
Gly Tyr Thr Phe Thr Gly Tyr Tyr Met His
1 5 10

<210> 150
<211> 10
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 150
Gly Tyr Thr Phe Thr Ser Tyr Gly Ile Ser
1 5 10

<210> 151
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 151
Gly Phe Thr Phe Ser Asn Ala Trp Met Asn
1 5 10

<210> 152
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 152
Gly Asp Ser Val Leu Ser Asn Ser Asp Thr Trp Asn
1 5 10

<210> 153
<211> 12
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 153
Gly Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn
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<210> 154
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 154
Gly Asp Ser Val Leu Ser Asn Ser Asp Thr Trp Asn
1 5 10

<210> 155
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 155
Gly Gly Ser Ile Ser Ser Ser Ser Tyr Tyr Trp Gly
1 5 10

<210> 156
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 156
Gly Tyr Thr Phe Thr Ser Tyr Tyr Met His
1 5 10

<210> 157
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 157
Gly Phe Thr Phe Ser Ser Tyr Ala Met His
1 5 10

<210> 158
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 158
Gly Tyr Thr Phe Thr Ser Tyr Tyr Met His
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<210> 159
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 159
Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser

1 5 10

<210> 160
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 160
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<220>
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<400> 161
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<210> 162
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<220>
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<400> 162
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<210> 163
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<400> 163
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<220>
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<400> 164
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<400> 165
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<400> 166
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1 5 10

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<400> 171
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<220>
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<400> 175
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<210> 177
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<220>
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<400> 178
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 179
Gly Tyr Thr Phe Thr Ser Tyr Tyr Met His
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 180
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1 5 10

<210> 181
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 181
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Lys Ser

<210> 182
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 182
Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> 183
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<220>
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<400> 183
Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 184
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 184
Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala Ser Ser Val
1 5 10 15

Arg Gly

<210> 185
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 185
Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 186
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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 186
Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 187
<211> 18
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 187
Arg Thr Tyr Tyr Arg Ser Thr Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 188
<211> 17
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic
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<400> 188
Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 189
<211> 17
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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 189
Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> 190
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 190
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1 5 10 15

Val Lys Gly

<210> 191
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 191
Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala Ser Ser Val
1 5 10 15

Arg Gly

<210> 192
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 192
Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 193
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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 193
Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala Ser Ser Val
1 5 10 15

Arg Gly

<210> 194
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<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 194
Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 195
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 195
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 196
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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 196
Ala Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asn Ser Val Lys
1 5 10 15

Asp

<210> 197
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 197
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 198
<211> 17
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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 198
Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 199
<211> 17
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 199
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 200

<211> 9211
<212> DNA
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

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acttggttga gtactcacca gtcacagaaa agcatcttac ggatggcatg acagtaagag 240

aattatgcag tgctgccata accatgagtg ataacactgc ggccaactta cttctgacaa 300

cgatcggagg accgaaggag ctaaccgctt ttttgcacaa catgggggat catgtaactc 360

gccttgatcg ttgggaaccg gagctgaatg aagccatacc aaacgacgag cgtgacacca 420

cgatgcctgt agcaatggca acaacgttgc gcaaactatt aactggcgaa ctacttactc 480

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ggagtacgat gttttggaca agagacgtgg ccgggaccct gagatggggg gaaagccgag 6840

aaggaagaac cctcaggaag gcctgtacaa tgaactgcag aaagataaga tggcggaggc 6900

ctacagtgag attgggatga aaggcgagcg ccggaggggc aaggggcacg atggccttta 6960

ccagggtctc agtacagcca ccaaggacac ctacgacgcc cttcacatgc aggccctgcc 7020

ccctcgctaa gtcgacaatc aacctctgga ttacaaaatt tgtgaaagat tgactggtat 7080

tcttaactat gttgctcctt ttacgctatg tggatacgct gctttaatgc ctttgtatca 7140

tgctattgct tcccgtatgg ctttcatttt ctcctccttg tataaatcct ggttgctgtc 7200

tctttatgag gagttgtggc ccgttgtcag gcaacgtggc gtggtgtgca ctgtgtttgc 7260

tgacgcaacc cccactggtt ggggcattgc caccacctgt cagctccttt ccgggacttt 7320

cgctttcccc ctccctattg ccacggcgga actcatcgcc gcctgccttg cccgctgctg 7380

gacaggggct cggctgttgg gcactgacaa ttccgtggtg ttgtcgggga agctgacgtc 7440

ctttccatgg ctgctcgcct gtgttgccac ctggattctg cgcgggacgt ccttctgcta 7500

cgtcccttcg gccctcaatc cagcggacct tccttcccgc ggcctgctgc cggctctgcg 7560

gcctcttccg cgtcttcgcc ttcgccctca gacgagtcgg atctcccttt gggccgcctc 7620

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cttagccact ttttaaaaga aaaggggggа ctggaagggc taattcactc ccaacgaaga 7740

caagatctgc tttttgcttg tactgggtct ctctggttag accagatctg agcctgggag 7800

ctctctggct aactagggaa cccactgctt aagcctcaat aaagcttgcc ttgagtgctt 7860

caagtagtgt gtgcccgtct gttgtgtgac tctggtaact agagatccct cagacccttt 7920

tagtcagtgt ggaaaatctc tagcagtagt agttcatgtc atcttattat tcagtattta 7980

taacttgcaa agaaatgaat atcagagagt gagaggaact tgtttattgc agcttataat 8040

ggttacaaat aaagcaatag catcacaaat ttcacaaata aagcattttt ttcactgcat 8100

tctagttgtg gtttgtccaa actcatcaat gtatcttatc atgtctggct ctagctatcc 8160

cgcccctaac tccgcccagt tccgcccatt ctccgcccca tggctgacta attttttta 8220

tttatgcaga ggccgaggcc gcctcggcct ctgagctatt ccagaagtag tgaggaggct 8280

tttttggagg cctaggcttt tgcgtcgaga cgtacccaat tcgccctata gtgagtcgta 8340

ttacgcgcgc tcactggccg tcgttttaca acgtcgtgac tgggaaaacc ctggcgttac 8400

ccaacttaat cgccttgcag cacatccccc tttcgccagc tggcgtaata gcgaagaggc 8460

ccgcaccgat cgcccttccc aacagttgcg cagcctgaat ggcgaatggg acgcgccctg 8520

tagcggcgca ttaagcgcgg cgggtgtggt ggttacgcgc agcgtgaccg ctacacttgc 8580

cagcgcccta gcgcccgctc ctttcgcttt cttcccttcc tttctcgcca cgttcgccgg 8640

ctttccccgt caagctctaa atcgggggct ccctttaggg ttccgattta gtgctttacg 8700

gcacctcgac cccaaaaaac ttgattaggg tgatggttca cgtagtgggc catcgccctg 8760

atagacggtt tttcgccctt tgacgttgga gtccacgttc tttaatagtg gactcttgtt 8820

ccaaactgga acaacactca accctatctc ggtctattct tttgatttat aagggatttt 8880

gccgatttcg gcctattggt taaaaaatga gctgatttaa caaaaattta acgcgaattt 8940

taacaaaata ttaacgctta caatttaggt ggcacttttc ggggaaatgt gcgcggaacc 9000

cctatttgtt tatttttcta atacattca aatatgtatc cgctcatgag acaataaccc 9060

tgataaatgc ttcaataata ttgaaaaagg aagagtatga gtattcaaca tttccgtgtc 9120

gcccttattc cctttttgc ggcattttgc cttcctgttt ttgctcaccc agaaacgctg 9180

gtgaaagtaa aagatgctga agatcagttg g 9211

<210> 201
<211> 235
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 201
Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

```
Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
    50                  55                  60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65                  70                  75                  80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95

Tyr Tyr Cys Ala Arg Glu Val Thr Gly Asp Leu Glu Asp Ala Phe Asp
            100                 105                 110

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys
        115                 120                 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
    130                 135                 140

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145                 150                 155                 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
                165                 170                 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
            180                 185                 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
        195                 200                 205

Val Ser His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
    210                 215                 220
```

Lys Ser Cys Asp Lys Thr Ser Gly Gln Ala Gly
225 230 235

<210> 202
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 202
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Trp Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Arg Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Arg Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ile Pro Gln
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

```
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140


Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160


Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175


Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190


Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205


Phe Asn Arg Gly Glu Cys
    210


<210> 203
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 203
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
            20                  25                  30


Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

```
Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65                  70                  75                  80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Ser Gln Ser Thr Pro Tyr Asp Ser Ser Gly Tyr Tyr Ser Gly Asp Ala
            100                 105                 110

Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Val
    130                 135                 140

Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln Arg Val Thr
145                 150                 155                 160

Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Tyr Val Tyr
                165                 170                 175

Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Arg
            180                 185                 190

Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205

Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg Ser Glu Asp
    210                 215                 220

Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu Ser Gly Tyr
225                 230                 235                 240
```

Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
245 250

<210> 204
<211> 753
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 204
caagtgcaac tcgtccaatc cggcggcgga ctgattcaac caggaggttc ccttagactc 60

tcatgtgccg ctagcggatt cactgtgtcc tcaaactaca tgagctgggt ccgccaggcg 120

cccggaaagg gcctggaatg ggtgtccgtg atctactcgg gcggatcaac ctactacgcc 180

gattccgtga aggggcggtt caccatctcg cgggataact ccaagaacac cctgtacttg 240

caaatgaact cactgagggc cgaagatacc gccgtctact actgcgcgag ccagtccact 300

ccctacgact cgagcgggta ctactccggg gacgccttcg acatctgggg acagggaact 360

atggtcacgg tgtcgtcggg aggaggggc agcggcggcg gaggaagcgg gggaggggt 420

tcgtcctatg tgctgaccca gccgccgagc gcctccggga ctccgggcca gcgcgtgacc 480

atttcctgct ccggctcctc atccaacatc ggttcgaatt atgtgtactg gtaccagcag 540

ctgcctggta ctgcccctaa gcttctcatc taccggaaca accagcgccc gtctggcgtg 600

cccgaccggt tctccggctc gaagtccggc accagcgcct ccctggctat ctccgggctg 660

agatccgagg atgaggccga ctactattgc gcagcgtggg acgacagcct gtcgggatac 720

gtgtttggaa ccggaaccaa gctcaccgtg ctg 753

<210> 205
<211> 846
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 205
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aactcgtcca atccggcggc ggactgattc aaccaggagg ttcccttaga 120

ctctcatgtg ccgctagcgg attcactgtg tcctcaaact acatgagctg ggtccgccag 180

gcgcccggaa agggcctgga atgggtgtcc gtgatctact cgggcggatc aacctactac 240

gccgattccg tgaaggggcg gttcaccatc tcgcgggata actccaagaa caccctgtac 300

ttgcaaatga actcactgag ggccgaagat accgccgtct actactgcgc gagccagtcc 360

actccctacg actcgagcgg gtactactcc ggggacgcct tcgacatctg gggacaggga 420

actatggtca cggtgtcgtc gggaggaggg ggcagcggcg gcggaggaag cgggggaggg 480

ggttcgtcct atgtgctgac ccagccgccg agcgcctccg ggactccggg ccagcgcgtg 540

accatttcct gctccggctc ctcatccaac atcggttcga attatgtgta ctggtaccag 600

cagctgcctg gtactgcccc taagcttctc atctaccgga acaaccagcg cccgtctggc 660

gtgcccgacc ggttctccgg ctcgaagtcc ggcaccagcg cctccctggc tatctccggg 720

ctgagatccg aggatgaggc cgactactat tgcgcagcgt gggacgacag cctgtcggga 780

tacgtgtttg gaaccggaac caagctcacc gtgctgggat cgcaccacca tcaccatcat 840

catcac 846

<210> 206
<211> 282
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 206
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu

```
1               5                   10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu
            20                  25                  30

Ile Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45

Thr Val Ser Ser Asn Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr
65                  70                  75                  80

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys
                85                  90                  95

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Ser Gln Ser Thr Pro Tyr Asp Ser Ser Gly Tyr
        115                 120                 125

Tyr Ser Gly Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr
    130                 135                 140

Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
145                 150                 155                 160

Gly Ser Ser Tyr Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro
                165                 170                 175

Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly
            180                 185                 190

Ser Asn Tyr Val Tyr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys
```

195 200 205

Leu Leu Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg
210 215 220

Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly
225 230 235 240

Leu Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp
245 250 255

Ser Leu Ser Gly Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
260 265 270

Gly Ser His His His His His His His His
275 280

<210> 207
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 207
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu
20 25 30

Ile Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Val Ser Ser Asn Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

```
Gly Leu Glu Trp Val Ser Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr
65                  70                  75                  80

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys
                85                  90                  95

Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Ser Gln Ser Thr Pro Tyr Asp Ser Ser Gly Tyr
        115                 120                 125

Tyr Ser Gly Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr
    130                 135                 140

Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
145                 150                 155                 160

Gly Ser Ser Tyr Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro
                165                 170                 175

Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly
            180                 185                 190

Ser Asn Tyr Val Tyr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys
        195                 200                 205

Leu Leu Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg
    210                 215                 220

Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly
225                 230                 235                 240

Leu Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp
                245                 250                 255
```

```
Ser Leu Ser Gly Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445
```

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 208
<211> 1485
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 208
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aactcgtcca atccggcggc ggactgattc aaccaggagg ttcccttaga 120

ctctcatgtg ccgctagcgg attcactgtg tcctcaaact acatgagctg ggtccgccag 180

gcgcccggaa agggcctgga atgggtgtcc gtgatctact cgggcggatc aacctactac 240

gccgattccg tgaaggggcg gttcaccatc tcgcgggata actccaagaa caccctgtac 300

ttgcaaatga actcactgag ggccgaagat accgccgtct actactgcgc gagccagtcc 360

actccctacg actcgagcgg gtactactcc ggggacgcct tcgacatctg gggacaggga 420

actatggtca cggtgtcgtc gggaggaggg ggcagcggcg gcggaggaag cgggggaggg 480

ggttcgtcct atgtgctgac ccagccgccg agcgcctccg ggactccggg ccagcgcgtg 540

accatttcct gctccggctc ctcatccaac atcggttcga attatgtgta ctggtaccag 600

cagctgcctg gtactgcccc taagcttctc atctaccgga acaaccagcg cccgtctggc 660

gtgcccgacc ggttctccgg ctcgaagtcc ggcaccagcg cctccctggc tatctccggg 720

ctgagatccg aggatgaggc cgactactat tgcgcagcgt gggacgacag cctgtcggga 780

tacgtgtttg gaaccggaac caagctcacc gtgctgacca ctaccccagc accgaggcca 840

cccaccccgg ctcctaccat cgcctcccag cctctgtccc tgcgtccgga ggcatgtaga 900

cccgcagctg gtggggccgt gcatacccgg ggtcttgact tcgcctgcga tatctacatt 960

tgggcccctc tggctggtac ttgcggggtc ctgctgcttt cactcgtgat cactctttac 1020

tgtaagcgcg gtcggaagaa gctgctgtac atctttaagc aacccttcat gaggcctgtg 1080

cagactactc aagaggagga cggctgttca tgccggttcc cagaggagga ggaaggcggc 1140

tgcgaactgc gcgtgaaatt cagccgcagc gcagatgctc cagcctacaa gcaggggcag 1200

aaccagctct acaacgaact caatcttggt cggagagagg agtacgacgt gctggacaag 1260

cggagaggac gggacccaga aatgggcggg aagccgcgca gaaagaatcc ccaagagggc 1320

ctgtacaacg agctccaaaa ggataagatg gcagaagcct atagcgagat tggtatgaaa 1380

ggggaacgca gaagaggcaa aggccacgac ggactgtacc agggactcag caccgccacc 1440

aaggacacct atgacgctct tcacatgcag gccctgccgc ctcgg 1485

<210> 209
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 209
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu

```
        35                  40                  45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
    50                  55                  60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65                  70                  75                  80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95

Tyr Tyr Cys Ala Arg Asp Leu Gly Trp Ile Ala Val Ala Gly Thr Phe
            100                 105                 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160

Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp
            180                 185                 190

Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys
        195                 200                 205

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220

Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Leu Asn His
```

225 230 235 240

Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
245 250

<210> 210
<211> 753
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 210
gaagtgcaac tccaacagag cggacccgga cttgtgaaac catcccagac tctcagcctg 60

acgtgtgcga tcagcgggga ctctgtgtcc tccaactccg ccgcctggaa ctggattagg 120

cagtcgccgt cgagagggct ggagtggttg ggtagaacct actaccggtc caagtggtac 180

aatgactacg ccgtgtccgt gaagtcccgg atcactatta acccggatac ctcaaagaac 240

cagttctccc tgcaactgaa ctcggtgacc cctgaggaca ccgcagtgta ctactgcgcc 300

cgggatctgg gttggatcgc tgtcgccggc accttcgact attggggaca gggcactctc 360

gtgaccgtgt cgtcgggtgg aggagggagc ggagggggcg gaagcggtgg cggcggttcc 420

cagtccgcgc tgacccagcc tgctagcgtg tccgggtcgc ccggacagtc aatcaccatc 480

tcctgcactg ggactagcag cgacgtgggc ggctacaact acgtgtcatg gtaccagcag 540

cacccgggaa aggcgcccaa gctgatgatc tacgacgtgt ccaagcgccc ttcgggagtc 600

tccaaccgct ttagcggctc caagtcgggc aacactgcct ccctgaccat tagcggactg 660

caggccgaag atgaggccga ctattactgc tcatcctaca cctcctcctc actgaaccat 720

gtgttcggca ccggaaccaa ggtcacagtc ctc 753

<210> 211
<211> 846
<212> DNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 211
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aactccaaca gagcggaccc ggacttgtga aaccatccca gactctcagc 120

ctgacgtgtg cgatcagcgg ggactctgtg tcctccaact ccgccgcctg gaactggatt 180

aggcagtcgc cgtcgagagg gctggagtgg ttgggtagaa cctactaccg gtccaagtgg 240

tacaatgact acgccgtgtc cgtgaagtcc cggatcacta ttaacccgga tacctcaaag 300

aaccagttct ccctgcaact gaactcggtg acccctgagg acaccgcagt gtactactgc 360

gcccgggatc tgggttggat cgctgtcgcc ggcaccttcg actattgggg acagggcact 420

ctcgtgaccg tgtcgtcggg tggaggaggg agcggagggg gcggaagcgg tggcggcggt 480

tcccagtccg cgctgaccca gcctgctagc gtgtccgggt cgcccggaca gtcaatcacc 540

atctcctgca ctgggactag cagcgacgtg ggcggctaca actacgtgtc atggtaccag 600

cagcacccgg gaaaggcgcc caagctgatg atctacgacg tgtccaagcg cccttcggga 660

gtctccaacc gctttagcgg ctccaagtcg ggcaacactg cctccctgac cattagcgga 720

ctgcaggccg aagatgaggc cgactattac tgctcatcct acacctcctc ctcactgaac 780

catgtgttcg gcaccggaac caaggtcaca gtcctcggat cgcaccacca tcaccatcat 840

catcac 846

<210> 212
<211> 282
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 212
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp
35 40 45

Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro
50 55 60

Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp
65 70 75 80

Tyr Asn Asp Tyr Ala Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro
85 90 95

Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro
100 105 110

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Leu Gly Trp Ile Ala
115 120 125

Val Ala Gly Thr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
130 135 140

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145 150 155 160

Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly
165 170 175

Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly
180 185 190

```
Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys
        195                 200                 205

Leu Met Ile Tyr Asp Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg
    210                 215                 220

Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly
225                 230                 235                 240

Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser
                245                 250                 255

Ser Ser Leu Asn His Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            260                 265                 270

Gly Ser His His His His His His His His
        275                 280
```

<210> 213
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 213

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu
            20                  25                  30

Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp
        35                  40                  45
```

```
Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro
    50                  55                  60

Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp
65                  70                  75                  80

Tyr Asn Asp Tyr Ala Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro
                85                  90                  95

Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro
            100                 105                 110

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Leu Gly Trp Ile Ala
        115                 120                 125

Val Ala Gly Thr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
    130                 135                 140

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly
                165                 170                 175

Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly
            180                 185                 190

Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys
        195                 200                 205

Leu Met Ile Tyr Asp Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg
    210                 215                 220

Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly
225                 230                 235                 240
```

```
Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser
                245                 250                 255

Ser Ser Leu Asn His Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430
```

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 214
<211> 1485
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 214
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aactccaaca gagcggaccc ggacttgtga aaccatccca gactctcagc 120

ctgacgtgtg cgatcagcgg ggactctgtg tcctccaact ccgccgcctg gaactggatt 180

aggcagtcgc cgtcgagagg gctggagtgg ttgggtagaa cctactaccg gtccaagtgg 240

tacaatgact acgccgtgtc cgtgaagtcc cggatcacta ttaacccgga tacctcaaag 300

aaccagttct ccctgcaact gaactcggtg acccctgagg acaccgcagt gtactactgc 360

gcccgggatc tgggttggat cgctgtcgcc ggcaccttcg actattgggg acagggcact 420

ctcgtgaccg tgtcgtcggg tggaggaggg agcggagggg gcggaagcgg tggcggcggt 480

tcccagtccg cgctgaccca gcctgctagc gtgtccgggt cgcccggaca gtcaatcacc 540

atctcctgca ctgggactag cagcgacgtg ggcggctaca actacgtgtc atggtaccag 600

cagcacccgg gaaaggcgcc caagctgatg atctacgacg tgtccaagcg cccttcggga 660

gtctccaacc gctttagcgg ctccaagtcg ggcaacactg cctccctgac cattagcgga 720

ctgcaggccg aagatgaggc cgactattac tgctcatcct acacctcctc ctcactgaac 780

catgtgttcg gcaccggaac caaggtcaca gtcctcacca ctaccccagc accgaggcca 840

cccaccccgg ctcctaccat cgcctcccag cctctgtccc tgcgtccgga ggcatgtaga 900

cccgcagctg gtggggccgt gcatacccgg ggtcttgact tcgcctgcga tatctacatt 960

tgggcccctc tggctggtac ttgcggggtc ctgctgcttt cactcgtgat cactctttac 1020

tgtaagcgcg gtcggaagaa gctgctgtac atctttaagc aacccttcat gaggcctgtg 1080

cagactactc aagaggagga cggctgttca tgccggttcc cagaggagga ggaaggcggc 1140

tgcgaactgc gcgtgaaatt cagccgcagc gcagatgctc cagcctacaa gcaggggcag 1200

aaccagctct acaacgaact caatcttggt cggagagagg agtacgacgt gctggacaag 1260

cggagaggac gggacccaga aatgggcggg aagccgcgca gaaagaatcc ccaagagggc 1320

ctgtacaacg agctccaaaa ggataagatg gcagaagcct atagcgagat tggtatgaaa 1380

ggggaacgca gaagaggcaa aggccacgac ggactgtacc agggactcag caccgccacc 1440

aaggacacct atgacgctct tcacatgcag gccctgccgc ctcgg 1485

<210> 215
<211> 253
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 215
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
20 25 30

```
Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
    50                  55                  60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65                  70                  75                  80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Ala
                85                  90                  95

Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
            100                 105                 110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser
    130                 135                 140

Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile
145                 150                 155                 160

Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr
                165                 170                 175

Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile
            180                 185                 190

Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly
        195                 200                 205

Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
    210                 215                 220
```

Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr
225 230 235 240

Pro Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu
245 250

<210> 216
<211> 759
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 216
gaagtgcaac tccaacagag cggacccgga cttgtgaaac cttcccaaac tctctccctg 60

acctgtgcga tctctgggga ttcggtgctg tcgaatagcg acacctggaa ctggatcaga 120

cagtcaccct cccggggcct ggagtggctc gggagaactt accaccggtc cacttggtac 180

gacgactatg ccagctcagt gcgcggaagg gtgtccatta acgtggacac ctccaagaac 240

cagtacagcc tgcagttgaa cgctgtgacc ccggaagata ccggagccta ctactgcgcc 300

cgcgaccggc tgcaggacgg aaactcctgg tccgatgcct tcgacgtctg gggccaggga 360

accatggtca ctgtgtcatc cggcggtggc ggttcgggcg gtggtggcag cggtggaggc 420

ggctcccagt cggcactgac tcagccagct tcagtctccg gctcgccggg acagtccatc 480

accatttcct gcactggaac cagctccgat gtcgggggt ataactacgt gtcgtggtac 540

cagcaacatc ctggaaaggc ccccaagctc atgatctacg acgtgtccaa tcgccctagc 600

ggagtgtcaa accggttttc cggctccaag tccgggaaca ccgcgtccct gacaatcagc 660

ggactgcagg ccgaggacga agccgactac tactgctcga gctacaccag ctcgtccacg 720

ccgtacgtgt tcggaactgg gacccagctg accgtgctg 759

<210> 217
<211> 852
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 217
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aactccaaca gagcggaccc ggacttgtga aaccttccca aactctctcc 120

ctgacctgtg cgatctctgg ggattcggtg ctgtcgaata gcgacacctg gaactggatc 180

agacagtcac cctcccgggg cctggagtgg ctcgggagaa cttaccaccg gtccacttgg 240

tacgacgact atgccagctc agtgcgcgga agggtgtcca ttaacgtgga cacctccaag 300

aaccagtaca gcctgcagtt gaacgctgtg accccggaag ataccggagc ctactactgc 360

gcccgcgacc ggctgcagga cggaaactcc tggtccgatg ccttcgacgt ctggggccag 420

ggaaccatgg tcactgtgtc atccggcggt ggcggttcgg gcggtggtgg cagcggtgga 480

ggcggctccc agtcggcact gactcagcca gcttcagtct ccggctcgcc gggacagtcc 540

atcaccattt cctgcactgg aaccagctcc gatgtcgggg ggtataacta cgtgtcgtgg 600

taccagcaac atcctggaaa ggcccccaag ctcatgatct acgacgtgtc caatcgccct 660

agcggagtgt caaaccggtt ttccggctcc aagtccggga acaccgcgtc cctgacaatc 720

agcggactgc aggccgagga cgaagccgac tactactgct cgagctacac cagctcgtcc 780

acgccgtacg tgttcggaac tgggacccag ctgaccgtgc tgggatcgca ccaccatcac 840

catcatcatc ac 852

<210> 218
<211> 284
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 218

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu
            20                  25                  30

Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp
        35                  40                  45

Ser Val Leu Ser Asn Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro
    50                  55                  60

Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp
65                  70                  75                  80

Tyr Asp Asp Tyr Ala Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val
                85                  90                  95

Asp Thr Ser Lys Asn Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro
            100                 105                 110

Glu Asp Thr Gly Ala Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly
        115                 120                 125

Asn Ser Trp Ser Asp Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val
    130                 135                 140

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser
                165                 170                 175
```

```
Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val
            180                 185                 190


Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala
        195                 200                 205


Pro Lys Leu Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser
    210                 215                 220


Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile
225                 230                 235                 240


Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr
                245                 250                 255


Thr Ser Ser Ser Thr Pro Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr
            260                 265                 270


Val Leu Gly Ser His His His His His His His His
        275                 280


<210> 219
<211> 497
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 219
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu
            20                  25                  30
```

```
Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp
        35                  40                  45

Ser Val Leu Ser Asn Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro
    50                  55                  60

Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp
65                  70                  75                  80

Tyr Asp Asp Tyr Ala Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val
                85                  90                  95

Asp Thr Ser Lys Asn Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro
            100                 105                 110

Glu Asp Thr Gly Ala Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly
        115                 120                 125

Asn Ser Trp Ser Asp Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val
    130                 135                 140

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser
                165                 170                 175

Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val
            180                 185                 190

Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala
        195                 200                 205

Pro Lys Leu Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser
    210                 215                 220
```

```
Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile
225                 230                 235                 240


Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr
                245                 250                 255


Thr Ser Ser Ser Thr Pro Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr
            260                 265                 270


Val Leu Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
        275                 280                 285


Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
    290                 295                 300


Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
305                 310                 315                 320


Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
                325                 330                 335


Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr
            340                 345                 350


Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
        355                 360                 365


Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
    370                 375                 380


Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln
385                 390                 395                 400


Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
                405                 410                 415
```

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
420 425 430

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
435 440 445

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
450 455 460

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
465 470 475 480

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
485 490 495

Arg

<210> 220
<211> 1491
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 220
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aactccaaca gagcggaccc ggacttgtga aaccttccca aactctctcc 120

ctgacctgtg cgatctctgg ggattcggtg ctgtcgaata gcgacacctg gaactggatc 180

agacagtcac cctcccgggg cctggagtgg ctcgggagaa cttaccaccg gtccacttgg 240

tacgacgact atgccagctc agtgcgcgga agggtgtcca ttaacgtgga cacctccaag 300

aaccagtaca gcctgcagtt gaacgctgtg accccggaag ataccggagc ctactactgc 360

gcccgcgacc ggctgcagga cggaaactcc tggtccgatg ccttcgacgt ctggggccag 420

ggaaccatgg tcactgtgtc atccggcggt ggcggttcgg gcggtggtgg cagcggtgga 480

ggcggctccc agtcggcact gactcagcca gcttcagtct ccggctcgcc gggacagtcc 540

atcaccattt cctgcactgg aaccagctcc gatgtcgggg ggtataacta cgtgtcgtgg 600

taccagcaac atcctggaaa ggcccccaag ctcatgatct acgacgtgtc caatcgccct 660

agcggagtgt caaaccggtt ttccggctcc aagtccggga acaccgcgtc cctgacaatc 720

agcggactgc aggccgagga cgaagccgac tactactgct cgagctacac cagctcgtcc 780

acgccgtacg tgttcggaac tgggacccag ctgaccgtgc tgaccactac cccagcaccg 840

aggccaccca ccccggctcc taccatcgcc tcccagcctc tgtccctgcg tccggaggca 900

tgtagacccg cagctggtgg ggccgtgcat acccggggtc ttgacttcgc ctgcgatatc 960

tacatttggg cccctctggc tggtacttgc ggggtcctgc tgctttcact cgtgatcact 1020

ctttactgta agcgcggtcg gaagaagctg ctgtacatct ttaagcaacc cttcatgagg 1080

cctgtgcaga ctactcaaga ggaggacggc tgttcatgcc ggttcccaga ggaggaggaa 1140

ggcggctgcg aactgcgcgt gaaattcagc cgcagcgcag atgctccagc ctacaagcag 1200

gggcagaacc agctctacaa cgaactcaat cttggtcgga gagaggagta cgacgtgctg 1260

gacaagcgga gaggacggga cccagaaatg ggcgggaagc cgcgcagaaa gaatccccaa 1320

gagggcctgt acaacgagct ccaaaaggat aagatggcag aagcctatag cgagattggt 1380

atgaaagggg aacgcagaag aggcaaaggc cacgacggac tgtaccaggg actcagcacc 1440

gccaccaagg acacctatga cgctcttcac atgcaggccc tgccgcctcg g 1491

<210> 221
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 221

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Lys Gly Leu Ser Ser Trp His Phe His Asp Ala Leu Asp Ile Trp
            100                 105                 110

Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Ser Glu Leu Thr Gln Asp
    130                 135                 140

Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln
145                 150                 155                 160

Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro
                165                 170                 175

Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser
            180                 185                 190
```

```
Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser
        195                 200                 205


Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
    210                 215                 220


Asn Ser Arg Asp Ser Ser Gly Asn His Leu Trp Val Phe Gly Gly Gly
225                 230                 235                 240


Thr Lys Leu Thr Val Leu
                245


<210> 222
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"

<400> 222
gaagtgcagt tggtggaatc aggaggagga cttgtgcaac ctggaagatc tctcagactc       60

tcgtgtgcgg cctccggttt caccttcgac gactacgcca tgcattgggt cagacaggcc      120

ccgggaaagg gcctggagtg ggtgtcaggc atctcatgga acagcggctc cattggctac      180

gccgactcgg tcaagggaag gttcactatc tcccgggaca acgccaagaa ctccctgtac      240

ctccaaatga acagcctgcg cgccgaggat actgccctgt actactgcgc caaggggctg      300

tccagctggc actttcacga cgcacttgat atctggggac agggtaccat ggtcaccgtg      360

tcctccggtg gcggaggctc agggggagga ggaagcgggg gcggtggttc ctcctccgaa      420

ctgacccagg acccggccgt gtccgtggcg ctgggacaaa ccgtgcgcat tacttgccag      480

ggcgacagct tgcggtcgta ctacgcctcg tggtaccagc agaagcccgg ccaggctccc      540

gtgctggtca tctatggcaa aaacaaccgc ccgagcggaa ttccagaccg gttctccggg      600
```

agctcgtccg ggaacaccgc ttcgctcacc atcacggggg cccaggcgga ggacgaagca 660

gattactact gcaactcgcg ggattccagc ggcaatcacc tctgggtgtt cgggggcgga 720

accaagctga ctgtgctg 738

<210> 223
<211> 831
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 223
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agttggtgga atcaggagga ggacttgtgc aacctggaag atctctcaga 120

ctctcgtgtg cggcctccgg tttcaccttc gacgactacg ccatgcattg ggtcagacag 180

gccccgggaa agggcctgga gtgggtgtca ggcatctcat ggaacagcgg ctccattggc 240

tacgccgact cggtcaaggg aaggttcact atctcccggg acaacgccaa gaactccctg 300

tacctccaaa tgaacagcct gcgcgccgag gatactgccc tgtactactg cgccaagggg 360

ctgtccagct ggcactttca cgacgcactt gatatctggg gacagggtac catggtcacc 420

gtgtcctccg gtggcggagg ctcaggggga ggaggaagcg ggggcggtgg ttcctcctcc 480

gaactgaccc aggacccggc cgtgtccgtg gcgctgggac aaaccgtgcg cattacttgc 540

cagggcgaca gcttgcggtc gtactacgcc tcgtggtacc agcagaagcc cggccaggct 600

cccgtgctgg tcatctatgg caaaaacaac cgcccgagcg gaattccaga ccggttctcc 660

gggagctcgt ccgggaacac cgcttcgctc accatcacgg gggcccaggc ggaggacgaa 720

gcagattact actgcaactc gcgggattcc agcggcaatc acctctgggt gttcgggggc 780

ggaaccaagc tgactgtgct gggatcgcac caccatcacc atcatcatca c 831

<210> 224

<211> 277
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 224

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45

Thr Phe Asp Asp Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
                85                  90                  95

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Leu Tyr Tyr Cys Ala Lys Gly Leu Ser Ser Trp His Phe His Asp
        115                 120                 125

Ala Leu Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Ser
145                 150                 155                 160
```

```
Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val
                165                 170                 175


Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp
            180                 185                 190


Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys
        195                 200                 205


Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser
    210                 215                 220


Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu
225                 230                 235                 240


Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His Leu Trp
                245                 250                 255


Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser His His His
            260                 265                 270


His His His His His
        275


<210> 225
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 225
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15
```

```
His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45

Thr Phe Asp Asp Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
                85                  90                  95

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Leu Tyr Tyr Cys Ala Lys Gly Leu Ser Ser Trp His Phe His Asp
        115                 120                 125

Ala Leu Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Ser
145                 150                 155                 160

Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val
                165                 170                 175

Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys
        195                 200                 205
```

```
Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser
    210                 215                 220

Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu
225                 230                 235                 240

Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His Leu Trp
                245                 250                 255

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400
```

```
Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415


Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430


Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445


Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460


Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480


Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 226
<211> 1470
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"

<400> 226
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg       60

cccgaagtgc agttggtgga atcaggagga ggacttgtgc aacctggaag atctctcaga      120

ctctcgtgtg cggcctccgg tttcaccttc gacgactacg ccatgcattg ggtcagacag      180

gccccgggaa agggcctgga gtgggtgtca ggcatctcat ggaacagcgg ctccattggc      240

tacgccgact cggtcaaggg aaggttcact atctcccggg acaacgccaa gaactccctg      300

tacctccaaa tgaacagcct gcgcgccgag gatactgccc tgtactactg cgccaagggg      360
```

ctgtccagct ggcactttca cgacgcactt gatatctggg gacagggtac catggtcacc 420

gtgtcctccg gtggcggagg ctcaggggga ggaggaagcg ggggcggtgg ttcctcctcc 480

gaactgaccc aggacccggc cgtgtccgtg gcgctgggac aaaccgtgcg cattacttgc 540

cagggcgaca gcttgcggtc gtactacgcc tcgtggtacc agcagaagcc cggccaggct 600

cccgtgctgg tcatctatgg caaaaacaac cgcccgagcg gaattccaga ccggttctcc 660

gggagctcgt ccgggaacac cgcttcgctc accatcacgg gggcccaggc ggaggacgaa 720

gcagattact actgcaactc gcgggattcc agcggcaatc acctctgggt gttcgggggc 780

ggaaccaagc tgactgtgct gaccactacc ccagcaccga ggccacccac cccggctcct 840

accatcgcct cccagcctct gtccctgcgt ccggaggcat gtagacccgc agctggtggg 900

gccgtgcata cccggggtct tgacttcgcc tgcgatatct acatttgggc ccctctggct 960

ggtacttgcg gggtcctgct gctttcactc gtgatcactc tttactgtaa gcgcggtcgg 1020

aagaagctgc tgtacatctt taagcaaccc ttcatgaggc ctgtgcagac tactcaagag 1080

gaggacggct gttcatgccg gttcccagag gaggaggaag gcggctgcga actgcgcgtg 1140

aaattcagcc gcagcgcaga tgctccagcc tacaagcagg ggcagaacca gctctacaac 1200

gaactcaatc ttggtcggag agaggagtac gacgtgctgg acaagcggag aggacgggac 1260

ccagaaatgg gcgggaagcc gcgcagaaag aatccccaag agggcctgta caacgagctc 1320

caaaaggata agatggcaga agcctatagc gagattggta tgaaagggga acgcagaaga 1380

ggcaaaggcc acgacggact gtaccaggga ctcagcaccg ccaccaagga cacctatgac 1440

gctcttcaca tgcaggccct gccgcctcgg 1470

<210> 227
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 227

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Lys Asp Lys Gly Gly Gly Tyr Tyr Asp Phe Trp Ser Gly Ser Asp
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Ser Glu Leu Thr
    130                 135                 140

Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr
145                 150                 155                 160

Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln
                165                 170                 175

Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg
            180                 185                 190
```

Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr
195 200 205

Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr
210 215 220

Tyr Cys Asn Ser Arg Asp Ser Ser Gly Trp Val Phe Gly Gly Gly Thr
225 230 235 240

Lys Leu Thr Val Leu
245

<210> 228
<211> 828
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 228
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aacttgtgga atctggtgga ggacttgtgc aacctggaag atcactgaga 120

ctgtcatgtg cagcctcggg gtttaccttc gacgactacg ccatgcactg ggtgcgccag 180

gctccgggga agggcctcga atgggtgtcg ggcatcagct ggaactccgg ttccattggc 240

tatgcggact ccgtgaaagg acgcttcaca atttcccggg ataacgccaa gaacagcctg 300

tacttgcaga tgaactccct gcgggccgag gataccgccc tgtactactg cgctaaggac 360

aagggcggtg gatactacga cttctggagc ggaagcgact actggggaca gggaactctg 420

gtcaccgtgt cctccggcgg agggggctcc ggcggcggtg gtagcggggg tggagggtcg 480

tcgtcggagc tgacccagga ccccgcagtg tccgtcgccc tggggcagac tgtgcggatc 540

acttgccaag gagacagcct gcggtcctac tacgcgtcct ggtatcagca gaagccgggg 600

caggccccag tcctcgtcat ctacggaaag aacaataggc ccagcggaat ccctgaccgc 660

ttctcgggct catcctccgg caacaccgcc tccctgacca tcacgggcgc gcaggccgag 720

gacgaagccg attactactg caactcacgg gattccagcg gatgggtgtt cggaggagga 780

accaagctca ctgtgctcgg atcgcaccac catcaccatc atcatcac 828

<210> 229
<211> 276
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 229
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Asp Asp Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
85 90 95

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

```
Ala Leu Tyr Tyr Cys Ala Lys Asp Lys Gly Gly Gly Tyr Tyr Asp Phe
        115                 120                 125


Trp Ser Gly Ser Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
    130                 135                 140


Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145                 150                 155                 160


Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
                165                 170                 175


Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
            180                 185                 190


Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        195                 200                 205


Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    210                 215                 220


Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
225                 230                 235                 240


Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Trp Val
                245                 250                 255


Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser His His His His
            260                 265                 270


His His His His
        275


<210> 230
<211> 489
<212> PRT
```

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 230

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45

Thr Phe Asp Asp Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
                85                  90                  95

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Leu Tyr Tyr Cys Ala Lys Asp Lys Gly Gly Gly Tyr Tyr Asp Phe
        115                 120                 125

Trp Ser Gly Ser Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145                 150                 155                 160
```

```
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
                165                 170                 175

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
            180                 185                 190

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        195                 200                 205

Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    210                 215                 220

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
225                 230                 235                 240

Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Trp Val
                245                 250                 255

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Thr Thr Thr Pro Ala Pro
            260                 265                 270

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
        275                 280                 285

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
    290                 295                 300

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
305                 310                 315                 320

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
                325                 330                 335

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
            340                 345                 350
```

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
355 360 365

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
370 375 380

Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu
385 390 395 400

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
405 410 415

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
420 425 430

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
435 440 445

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
450 455 460

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
465 470 475 480

Leu His Met Gln Ala Leu Pro Pro Arg
485

<210> 231
<211> 1467
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 231
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aacttgtgga atctggtgga ggacttgtgc aacctggaag atcactgaga 120

ctgtcatgtg cagcctcggg gtttaccttc gacgactacg ccatgcactg ggtgcgccag 180

gctccgggga agggcctcga atgggtgtcg ggcatcagct ggaactccgg ttccattggc 240

tatgcggact ccgtgaaagg acgcttcaca atttcccggg ataacgccaa gaacagcctg 300

tacttgcaga tgaactccct gcgggccgag gataccgccc tgtactactg cgctaaggac 360

aagggcggtg gatactacga cttctggagc ggaagcgact actggggaca gggaactctg 420

gtcaccgtgt cctccggcgg agggggctcc ggcggcggtg gtagcggggg tggagggtcg 480

tcgtcggagc tgacccagga ccccgcagtg tccgtcgccc tggggcagac tgtgcggatc 540

acttgccaag gagacagcct gcggtcctac tacgcgtcct ggtatcagca gaagccgggg 600

caggccccag tcctcgtcat ctacggaaag aacaataggc ccagcggaat ccctgaccgc 660

ttctcgggct catcctccgg caacaccgcc tccctgacca tcacgggcgc gcaggccgag 720

gacgaagccg attactactg caactcacgg gattccagcg gatgggtgtt cggaggagga 780

accaagctca ctgtgctcac cactacccca gcaccgaggc cacccacccc ggctcctacc 840

atcgcctccc agcctctgtc cctgcgtccg gaggcatgta gacccgcagc tggtggggcc 900

gtgcataccc ggggtcttga cttcgcctgc gatatctaca tttgggcccc tctggctggt 960

acttgcgggg tcctgctgct ttcactcgtg atcactcttt actgtaagcg cggtcggaag 1020

aagctgctgt acatctttaa gcaacccttc atgaggcctg tgcagactac tcaagaggag 1080

gacggctgtt catgccggtt cccagaggag gaggaaggcg gctgcgaact gcgcgtgaaa 1140

ttcagccgca gcgcagatgc tccagcctac aagcaggggc agaaccagct ctacaacgaa 1200

ctcaatcttg gtcggagaga ggagtacgac gtgctggaca agcggagagg acgggaccca 1260

gaaatgggcg ggaagccgcg cagaaagaat ccccaagagg gcctgtacaa cgagctccaa 1320

aaggataaga tggcagaagc ctatagcgag attggtatga aaggggaacg cagaagaggc 1380

aaaggccacg acggactgta ccagggactc agcaccgcca ccaaggacac ctatgacgct 1440

cttcacatgc aggccctgcc gcctcgg 1467

<210> 232
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 232
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Leu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Thr Trp Thr Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Thr Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Glu Gly Ser Gly Ser Tyr Tyr Ala Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala
130 135 140

```
Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly
145                 150                 155                 160


Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln
                165                 170                 175


His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser Asn Arg
            180                 185                 190


Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr
        195                 200                 205


Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr
    210                 215                 220


Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr Val Phe Gly Thr
225                 230                 235                 240


Gly Thr Lys Val Thr Val Leu
                245


<210> 233
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"

<400> 233
gaagtgcaac tccaacaatc aggtccagga ctcgtcaaac cctcgcttac tctgtcgctg       60

acttgtgcta tctcgggaga ctccgtgagc tccaacagcg ccacctggac ttggattaga      120

cagtccccgt cacggggcct cgaatggctg ggaaggacct actaccggag cacctggtac      180

aacgactatg ctgtgtccgt gaagtcccgc atcaccatca accccgatac ctccaagaac      240
```

cagttcagct tgcaactgaa ctccgtgacc cctgaggata cggccgtcta ttactgcgcc 300

cgcgaggggt ccggttccta ctacgcctac tggggacagg gtactctggt caccgtgtcg 360

agcggagggg gggggtccgg cggaggagga tctggtggcg gaggctccca gtccgcgctg 420

acccagcctg cgtccgtgtc cggctcaccg ggccagtcta tcaccattag ctgcaccggc 480

actagctcag acgtgggagg gtacaactac gtgtcgtggt accagcagca ccctggaaag 540

gccccgaagc tgatgatcta cgacgtgtcc aaccggccca gcggggtgtc gaatcgcttc 600

tccggctcaa agtccggcaa cacagccagc ctgaccatta gcggactgca ggccgaggat 660

gaagcagact actactgctc gtcctacacc tcctcctcga ctctctacgt gtttggcacc 720

ggaactaagg tcaccgtgct g 741

<210> 234
<211> 834
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 234
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aactccaaca atcaggtcca ggactcgtca aaccctcgct tactctgtcg 120

ctgacttgtg ctatctcggg agactccgtg agctccaaca gcgccacctg gacttggatt 180

agacagtccc cgtcacgggg cctcgaatgg ctgggaagga cctactaccg gagcacctgg 240

tacaacgact atgctgtgtc cgtgaagtcc cgcatcacca tcaaccccga tacctccaag 300

aaccagttca gcttgcaact gaactccgtg acccctgagg atacggccgt ctattactgc 360

gcccgcgagg ggtccggttc ctactacgcc tactggggac agggtactct ggtcaccgtg 420

tcgagcggag gggggggggtc cggcggagga ggatctggtg gcggaggctc ccagtccgcg 480

ctgacccagc ctgcgtccgt gtccggctca ccgggccagt ctatcaccat tagctgcacc 540

ggcactagct cagacgtggg agggtacaac tacgtgtcgt ggtaccagca gcaccctgga 600

aaggccccga agctgatgat ctacgacgtg tccaaccggc ccagcggggt gtcgaatcgc 660

ttctccggct caaagtccgg caacacagcc agcctgacca ttagcggact gcaggccgag 720

gatgaagcag actactactg ctcgtcctac acctcctcct cgactctcta cgtgtttggc 780

accggaacta aggtcaccgt gctgggatcg caccaccatc accatcatca tcac 834

<210> 235
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 235
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Leu Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp
35 40 45

Ser Val Ser Ser Asn Ser Ala Thr Trp Thr Trp Ile Arg Gln Ser Pro
50 55 60

Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Thr Trp
65 70 75 80

Tyr Asn Asp Tyr Ala Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro
85 90 95

Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro
100 105 110

```
Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu Gly Ser Gly Ser Tyr
        115                 120                 125

Tyr Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala
145                 150                 155                 160

Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr
                165                 170                 175

Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val
            180                 185                 190

Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr
        195                 200                 205

Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser
    210                 215                 220

Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu
225                 230                 235                 240

Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu
                245                 250                 255

Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Ser His His
            260                 265                 270

His His His His His His His
        275
```

<210> 236
<211> 491

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 236

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu
            20                  25                  30

Val Lys Pro Ser Leu Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp
        35                  40                  45

Ser Val Ser Ser Asn Ser Ala Thr Trp Thr Trp Ile Arg Gln Ser Pro
    50                  55                  60

Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Thr Trp
65                  70                  75                  80

Tyr Asn Asp Tyr Ala Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro
                85                  90                  95

Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro
            100                 105                 110

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu Gly Ser Gly Ser Tyr
        115                 120                 125

Tyr Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala
145                 150                 155                 160
```

```
Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr
                165                 170                 175

Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val
            180                 185                 190

Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr
        195                 200                 205

Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser
    210                 215                 220

Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu
225                 230                 235                 240

Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu
                245                 250                 255

Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350
```

```
Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365


Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380


Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400


Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415


Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430


Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445


Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460


His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480


Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 237
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"

<400> 237
```

atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aactccaaca atcaggtcca ggactcgtca aaccctcgct tactctgtcg 120

ctgacttgtg ctatctcggg agactccgtg agctccaaca gcgccacctg gacttggatt 180

agacagtccc cgtcacgggg cctcgaatgg ctgggaagga cctactaccg gagcacctgg 240

tacaacgact atgctgtgtc cgtgaagtcc cgcatcacca tcaaccccga tacctccaag 300

aaccagttca gcttgcaact gaactccgtg acccctgagg atacggccgt ctattactgc 360

gcccgcgagg ggtccggttc ctactacgcc tactggggac agggtactct ggtcaccgtg 420

tcgagcggag gggggggtc cggcggagga ggatctggtg gcggaggctc ccagtccgcg 480

ctgacccagc ctgcgtccgt gtccggctca ccgggccagt ctatcaccat tagctgcacc 540

ggcactagct cagacgtggg agggtacaac tacgtgtcgt ggtaccagca gcaccctgga 600

aaggccccga agctgatgat ctacgacgtg tccaaccggc ccagcggggt gtcgaatcgc 660

ttctccggct caaagtccgg caacacagcc agcctgacca ttagcggact gcaggccgag 720

gatgaagcag actactactg ctcgtcctac acctcctcct cgactctcta cgtgtttggc 780

accggaacta aggtcaccgt gctgaccact accccagcac cgaggccacc caccccggct 840

cctaccatcg cctcccagcc tctgtccctg cgtccggagg catgtagacc cgcagctggt 900

ggggccgtgc atacccgggg tcttgacttc gcctgcgata tctacatttg ggcccctctg 960

gctggtactt gcggggtcct gctgctttca ctcgtgatca ctctttactg taagcgcggt 1020

cggaagaagc tgctgtacat ctttaagcaa cccttcatga ggcctgtgca gactactcaa 1080

gaggaggacg gctgttcatg ccggttccca gaggaggagg aaggcggctg cgaactgcgc 1140

gtgaaattca gccgcagcgc agatgctcca gcctacaagc aggggcagaa ccagctctac 1200

aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

gacccagaaa tgggcgggaa gccgcgcaga aagaatcccc aagagggcct gtacaacgag 1320

ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 238
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 238
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Trp Gly Tyr Tyr Gly Ser Gly Thr Leu Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro
130 135 140

```
Gly Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr
145                 150                 155                 160


Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln
                165                 170                 175


Gln His Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp Val Ser Ser
            180                 185                 190


Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Gln Ser Gly Asn
        195                 200                 205


Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp
    210                 215                 220


Tyr Ser Cys Ser Ser Tyr Ala Gly Ser Asn Thr Leu Val Phe Gly Thr
225                 230                 235                 240


Gly Thr Lys Val Thr Val Leu
                245


<210> 239
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"

<400> 239
caagtccaac tcgtccagtc cggtgcagaa gtcaagaagc caggagcgtc cgtgaaagtg       60

tcctgcaaag cctcgggcta caccttcacc ggatactaca tgcactgggt gcgccaggct      120

cccggacaag gattggagtg gatgggttgg atcaacccga actccggcgg aaccaactac      180

gcccagaagt tccagggacg cgtgactatg actcgggaca cgtccatcag cactgcctac      240
```

atggaactga gccggcttag atcagacgac accgccgtgt actactgcgc ccgcgattac 300

tggggctact acggaagcgg aaccctcgac tactggggac agggaactct cgtgactgtg 360

tcgagcggtg gaggcggctc cggcggaggg ggttccggtg gtggaggctc ccagtccgcg 420

ctgacccagc ctgggtcggt gtccggctca cctggccaat ccatcaccat ttcctgcacc 480

ggcacttcct ccgacgtggg agggtacaac tacgtgtcgt ggtaccagca gcatccggga 540

aaggccccca agctgatcat ctacgatgtg tcgtcccggc cgagcggagt gtcaaacagg 600

tttagcggga gccagtccgg gaatactgcc tcgctgacaa ttagcgggct gcaggctgag 660

gacgaggccg attattcgtg ttcctcatat gcgggctcta acaccctggt gttcggcacc 720

gggaccaagg tcaccgtgct g 741

<210> 240
<211> 834
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 240
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca gtccggtgca gaagtcaaga agccaggagc gtccgtgaaa 120

gtgtcctgca aagcctcggg ctacaccttc accggatact acatgcactg ggtgcgccag 180

gctcccggac aaggattgga gtggatgggt tggatcaacc cgaactccgg cggaaccaac 240

tacgcccaga agttccaggg acgcgtgact atgactcggg acacgtccat cagcactgcc 300

tacatggaac tgagccggct tagatcagac gacaccgccg tgtactactg cgcccgcgat 360

tactggggct actacggaag cggaaccctc gactactggg gacagggaac tctcgtgact 420

gtgtcgagcg gtggaggcgg ctccggcgga gggggttccg gtggtggagg ctcccagtcc 480

gcgctgaccc agcctgggtc ggtgtccggc tcacctggcc aatccatcac catttcctgc 540

accggcactt cctccgacgt gggagggtac aactacgtgt cgtggtacca gcagcatccg 600

ggaaaggccc ccaagctgat catctacgat gtgtcgtccc ggccgagcgg agtgtcaaac 660

aggtttagcg ggagccagtc cgggaatact gcctcgctga caattagcgg gctgcaggct 720

gaggacgagg ccgattattc gtgttcctca tatgcgggct ctaacaccct ggtgttcggc 780

accgggacca aggtcaccgt gctgggatcg caccaccatc accatcatca tcac 834

<210> 241
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 241
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr

100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Tyr Trp Gly Tyr Tyr Gly Ser Gly
115 120 125

Thr Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser
145 150 155 160

Ala Leu Thr Gln Pro Gly Ser Val Ser Gly Ser Pro Gly Gln Ser Ile
165 170 175

Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr
180 185 190

Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Ile Ile
195 200 205

Tyr Asp Val Ser Ser Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly
210 215 220

Ser Gln Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
225 230 235 240

Glu Asp Glu Ala Asp Tyr Ser Cys Ser Ser Tyr Ala Gly Ser Asn Thr
245 250 255

Leu Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Ser His His
260 265 270

His His His His His His His
275

<210> 242

<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 242

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Asp Tyr Trp Gly Tyr Tyr Gly Ser Gly
        115                 120                 125

Thr Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser
145                 150                 155                 160
```

```
Ala Leu Thr Gln Pro Gly Ser Val Ser Gly Ser Pro Gly Gln Ser Ile
                165                 170                 175

Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr
            180                 185                 190

Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Ile Ile
        195                 200                 205

Tyr Asp Val Ser Ser Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly
    210                 215                 220

Ser Gln Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
225                 230                 235                 240

Glu Asp Glu Ala Asp Tyr Ser Cys Ser Ser Tyr Ala Gly Ser Asn Thr
                245                 250                 255

Leu Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350
```

```
Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 243
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 243

atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca gtccggtgca gaagtcaaga agccaggagc gtccgtgaaa 120

gtgtcctgca aagcctcggg ctacaccttc accggatact acatgcactg ggtgcgccag 180

gctcccggac aaggattgga gtggatgggt tggatcaacc cgaactccgg cggaaccaac 240

tacgcccaga agttccaggg acgcgtgact atgactcggg acacgtccat cagcactgcc 300

tacatggaac tgagccggct tagatcagac gacaccgccg tgtactactg cgcccgcgat 360

tactggggct actacggaag cggaaccctc gactactggg gacagggaac tctcgtgact 420

gtgtcgagcg gtggaggcgg ctccggcgga gggggttccg gtggtggagg ctcccagtcc 480

gcgctgaccc agcctgggtc ggtgtccggc tcacctggcc aatccatcac catttcctgc 540

accggcactt cctccgacgt gggagggtac aactacgtgt cgtggtacca gcagcatccg 600

ggaaaggccc ccaagctgat catctacgat gtgtcgtccc ggccgagcgg agtgtcaaac 660

aggtttagcg ggagccagtc cgggaatact gcctcgctga caattagcgg gctgcaggct 720

gaggacgagg ccgattattc gtgttcctca tatgcgggct ctaacaccct ggtgttcggc 780

accgggacca aggtcaccgt gctgaccact accccagcac cgaggccacc caccccggct 840

cctaccatcg cctcccagcc tctgtccctg cgtccggagg catgtagacc cgcagctggt 900

ggggccgtgc atacccgggg tcttgacttc gcctgcgata tctacatttg ggcccctctg 960

gctggtactt gcggggtcct gctgctttca ctcgtgatca ctctttactg taagcgcggt 1020

cggaagaagc tgctgtacat ctttaagcaa cccttcatga ggcctgtgca gactactcaa 1080

gaggaggacg gctgttcatg ccggttccca gaggaggagg aaggcggctg cgaactgcgc 1140

gtgaaattca gccgcagcgc agatgctcca gcctacaagc aggggcagaa ccagctctac 1200

aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

gacccagaaa tgggcgggaa gccgcgcaga aagaatcccc aagagggcct gtacaacgag 1320

ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 244
<211> 254
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 244
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ala Gly Leu Ala Leu Tyr Ser Asn Tyr Val Pro Tyr Tyr Tyr
100 105 110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn

130 135 140

Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys Thr
145 150 155 160

Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Asn Tyr
165 170 175

Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr Val Ile
180 185 190

Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly
195 200 205

Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly Leu
210 215 220

Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
225 230 235 240

Asn Pro Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
245 250

<210> 245
<211> 762
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 245
caagtccaac tggtgcagtc gggagccgaa gtcaagaagc cgggggcctc cgtcaaagtg 60

tcctgcaaag ccagcggcta cactttcacc tcctatggga tctcatgggt cagacaggct 120

cccggccaag gactggaatg gatgggttgg atctccgcct acaacggcaa cactaactac 180

gcccagaagc tgcaggggag agtgaccatg acaactgaca cctcgacctc aaccgcgtac 240

atggaactgc gcagccttag gtccgacgat acggcggtgt actattgtgc acgggccggc 300

ttggccctct actcgaacta cgtgccctac tactactacg gaatggacgt ctggggacag 360

ggaaccactg tgaccgtgtc ctccgggggt ggaggctcag gcggaggagg aagcggcggg 420

ggtggaagca actttatgct gacccagcct cactcggtgt cggagagccc tggaaagact 480

gtgaccatct cctgcactcg gagctcgggc tccattgcgt caaactacgt gcagtggtac 540

cagcagcgcc ccggttcctc gccaaccacc gtgatctacg aggacaacca acgcccgtcc 600

ggggtgcctg accggttctc cggctccatc gattcctctt ccaactccgc ttccctgacc 660

attagcggcc tcaagaccga ggatgaagcc gactactact gccagtccta cgactcaagc 720

aatccgtggg tgttcggtgg aggaactaag ctgaccgtgc tc 762

<210> 246
<211> 855
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 246
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactggtgca gtcgggagcc gaagtcaaga agccgggggc ctccgtcaaa 120

gtgtcctgca aagccagcgg ctacactttc acctcctatg ggatctcatg ggtcagacag 180

gctcccggcc aaggactgga atggatgggt tggatctccg cctacaacgg caacactaac 240

tacgcccaga agctgcaggg gagagtgacc atgacaactg acacctcgac ctcaaccgcg 300

tacatggaac tgcgcagcct taggtccgac gatacggcgg tgtactattg tgcacgggcc 360

ggcttggccc tctactcgaa ctacgtgccc tactactact acggaatgga cgtctgggga 420

cagggaacca ctgtgaccgt gtcctccggg ggtggaggct caggcggagg aggaagcggc 480

ggggggtggaa gcaactttat gctgacccag cctcactcgg tgtcggagag ccctggaaag 540

actgtgacca tctcctgcac tcggagctcg ggctccattg cgtcaaacta cgtgcagtgg 600

taccagcagc gccccggttc ctcgccaacc accgtgatct acgaggacaa ccaacgcccg 660

tccggggtgc ctgaccggtt ctccggctcc atcgattcct cttccaactc cgcttccctg 720

accattagcg gcctcaagac cgaggatgaa gccgactact actgccagtc ctacgactca 780

agcaatccgt gggtgttcgg tggaggaact aagctgaccg tgctcggatc gcaccaccat 840

caccatcatc atcac 855

<210> 247
<211> 285
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 247
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn
65 70 75 80

Tyr Ala Gln Lys Leu Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser
85 90 95

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Thr Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Ala Gly Leu Ala Leu Tyr Ser Asn Tyr
        115                 120                 125

Val Pro Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
    130                 135                 140

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
145                 150                 155                 160

Gly Gly Gly Ser Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu
                165                 170                 175

Ser Pro Gly Lys Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser
            180                 185                 190

Ile Ala Ser Asn Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser
        195                 200                 205

Pro Thr Thr Val Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro
    210                 215                 220

Asp Arg Phe Ser Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu
225                 230                 235                 240

Thr Ile Ser Gly Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln
                245                 250                 255

Ser Tyr Asp Ser Ser Asn Pro Trp Val Phe Gly Gly Gly Thr Lys Leu
            260                 265                 270

Thr Val Leu Gly Ser His His His His His His His His
        275                 280                 285
```

<210> 248
<211> 498
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 248
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn
65 70 75 80

Tyr Ala Gln Lys Leu Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser
85 90 95

Thr Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Ala Gly Leu Ala Leu Tyr Ser Asn Tyr
115 120 125

Val Pro Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
130 135 140

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Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
145                 150                 155                 160

Gly Gly Gly Ser Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu
                165                 170                 175

Ser Pro Gly Lys Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser
            180                 185                 190

Ile Ala Ser Asn Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser
        195                 200                 205

Pro Thr Thr Val Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro
    210                 215                 220

Asp Arg Phe Ser Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu
225                 230                 235                 240

Thr Ile Ser Gly Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln
                245                 250                 255

Ser Tyr Asp Ser Ser Asn Pro Trp Val Phe Gly Gly Gly Thr Lys Leu
            260                 265                 270

Thr Val Leu Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
        275                 280                 285

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
    290                 295                 300

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
305                 310                 315                 320

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
                325                 330                 335
```

```
Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
            340                 345                 350

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
        355                 360                 365

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
    370                 375                 380

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys
385                 390                 395                 400

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
                405                 410                 415

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
            420                 425                 430

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
        435                 440                 445

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
    450                 455                 460

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
465                 470                 475                 480

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
                485                 490                 495

Pro Arg
```

<210> 249
<211> 1494
<212> DNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 249
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactggtgca gtcgggagcc gaagtcaaga agccgggggc ctccgtcaaa 120

gtgtcctgca aagccagcgg ctacactttc acctcctatg ggatctcatg ggtcagacag 180

gctcccggcc aaggactgga atggatgggt tggatctccg cctacaacgg caacactaac 240

tacgcccaga agctgcaggg gagagtgacc atgacaactg acacctcgac ctcaaccgcg 300

tacatggaac tgcgcagcct taggtccgac gatacggcgg tgtactattg tgcacgggcc 360

ggcttggccc tctactcgaa ctacgtgccc tactactact acggaatgga cgtctgggga 420

cagggaacca ctgtgaccgt gtcctccggg ggtggaggct caggcggagg aggaagcggc 480

gggggtggaa gcaactttat gctgacccag cctcactcgg tgtcggagag ccctggaaag 540

actgtgacca tctcctgcac tcggagctcg ggctccattg cgtcaaacta cgtgcagtgg 600

taccagcagc gccccggttc ctcgccaacc accgtgatct acgaggacaa ccaacgcccg 660

tccggggtgc ctgaccggtt ctccggctcc atcgattcct cttccaactc cgcttccctg 720

accattagcg gcctcaagac cgaggatgaa gccgactact actgccagtc ctacgactca 780

agcaatccgt gggtgttcgg tggaggaact aagctgaccg tgctcaccac taccccagca 840

ccgaggccac ccaccccggc tcctaccatc gcctcccagc ctctgtccct gcgtccggag 900

gcatgtagac ccgcagctgg tggggccgtg catacccggg gtcttgactt cgcctgcgat 960

atctacattt gggcccctct ggctggtact tgcggggtcc tgctgctttc actcgtgatc 1020

actctttact gtaagcgcgg tcggaagaag ctgctgtaca tctttaagca acccttcatg 1080

aggcctgtgc agactactca agaggaggac ggctgttcat gccggttccc agaggaggag 1140

gaaggcggct gcgaactgcg cgtgaaattc agccgcagcg cagatgctcc agcctacaag 1200

caggggcaga accagctcta caacgaactc aatcttggtc ggagagagga gtacgacgtg 1260

ctggacaagc ggagaggacg ggacccagaa atgggcggga agccgcgcag aaagaatccc 1320

caagagggcc tgtacaacga gctccaaaag gataagatgg cagaagccta tagcgagatt 1380

ggtatgaaag gggaacgcag aagaggcaaa ggccacgacg gactgtacca gggactcagc 1440

accgccacca aggacaccta tgacgctctt cacatgcagg ccctgccgcc tcgg 1494

<210> 250
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 250
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr Ala Asp Tyr Ala Ala
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Met Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Gly Val Tyr
85 90 95

Tyr Cys Ile Thr Gly Ala Thr Asp Val Trp Gly Gln Gly Thr Thr Val
100 105 110

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Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Ser Tyr Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr
    130                 135                 140

Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile
145                 150                 155                 160

Gly Ser Asn Tyr Val Tyr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro
                165                 170                 175

Lys Leu Leu Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp
            180                 185                 190

Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser
        195                 200                 205

Gly Leu Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp
    210                 215                 220

Asp Ser Leu Ser Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val
225                 230                 235                 240

Leu
```

<210> 251
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 251
gaagtgcagc tcgtggaatc gggcggtgga ctggtcaagc caggaggttc cctgcggctg 60

tcctgcgtgg cctccggttt cacattctcc aacgcgtgga tgaattgggt gcgccaagcc 120

cctggaaagg gacttgaatg ggtcggacgg atcaagagca aaaccgacgg aggaactgcc 180

gattacgccg cacccgtgaa gggcagattc accatttcgc gggatgactc gaagaacacc 240

atgtacctcc agatgaactc gctcaagacc gaggataccg gcgtctacta ctgcatcacc 300

ggcgctactg acgtctgggg acagggaact accgtgactg tgtcctccgg cggaggcgga 360

agcggaggag ggggcagcgg gggcggggga tcatcctacg tgctcactca gccgccttca 420

gcctccggta ccccgggcca gcgcgtgacc atttcatgct cgggctcctc ctcaaacatc 480

gggagcaact acgtgtactg gtaccagcag ctgcccggta ctgcccccaa gctgctgatc 540

taccggaaca accaacgccc gagcggagtg ccggacagat tctccgggtc caagtctggg 600

acctccgcta gcctggcgat ctccggtctg aggagcgagg acgaggcaga ctactattgt 660

gcggcctggg acgattccct gtcggggcct gtgtttggag gcggcacgaa gttgaccgtg 720

ctg 723

<210> 252
<211> 816
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 252
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agctcgtgga atcgggcggt ggactggtca agccaggagg ttccctgcgg 120

ctgtcctgcg tggcctccgg tttcacattc tccaacgcgt ggatgaattg ggtgcgccaa 180

gcccctggaa agggacttga atgggtcgga cggatcaaga gcaaaaccga cggaggaact 240

gccgattacg ccgcacccgt gaagggcaga ttcaccattt cgcgggatga ctcgaagaac 300

accatgtacc tccagatgaa ctcgctcaag accgaggata ccggcgtcta ctactgcatc 360

accggcgcta ctgacgtctg gggacaggga actaccgtga ctgtgtcctc cggcggaggc 420

ggaagcggag gaggggcag cgggggcggg ggatcatcct acgtgctcac tcagccgcct 480

tcagcctccg gtaccccggg ccagcgcgtg accatttcat gctcgggctc ctcctcaaac 540

atcgggagca actacgtgta ctggtaccag cagctgcccg gtactgcccc caagctgctg 600

atctaccgga acaaccaacg cccgagcgga gtgccggaca gattctccgg gtccaagtct 660

gggacctccg ctagcctggc gatctccggt ctgaggagcg aggacgaggc agactactat 720

tgtgcggcct gggacgattc cctgtcgggg cctgtgtttg gaggcggcac gaagttgacc 780

gtgctgggat cgcaccacca tcaccatcat catcac 816

<210> 253
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 253
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe
35 40 45

Thr Phe Ser Asn Ala Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Gly Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr

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65                  70                  75                  80

Ala Asp Tyr Ala Ala Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
                85                  90                  95

Asp Ser Lys Asn Thr Met Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu
            100                 105                 110

Asp Thr Gly Val Tyr Tyr Cys Ile Thr Gly Ala Thr Asp Val Trp Gly
        115                 120                 125

Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu Thr Gln Pro Pro
145                 150                 155                 160

Ser Ala Ser Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly
                165                 170                 175

Ser Ser Ser Asn Ile Gly Ser Asn Tyr Val Tyr Trp Tyr Gln Gln Leu
            180                 185                 190

Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Arg Asn Asn Gln Arg Pro
        195                 200                 205

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala
    210                 215                 220

Ser Leu Ala Ile Ser Gly Leu Arg Ser Glu Asp Glu Ala Asp Tyr Tyr
225                 230                 235                 240

Cys Ala Ala Trp Asp Asp Ser Leu Ser Gly Pro Val Phe Gly Gly Gly
                245                 250                 255

Thr Lys Leu Thr Val Leu Gly Ser His His His His His His His His
```

260 265 270

<210> 254
<211> 485
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 254
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe
35 40 45

Thr Phe Ser Asn Ala Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Gly Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr
65 70 75 80

Ala Asp Tyr Ala Ala Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
85 90 95

Asp Ser Lys Asn Thr Met Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu
100 105 110

Asp Thr Gly Val Tyr Tyr Cys Ile Thr Gly Ala Thr Asp Val Trp Gly
115 120 125

Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
130 135 140

```
Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu Thr Gln Pro Pro
145                 150                 155                 160

Ser Ala Ser Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly
                165                 170                 175

Ser Ser Ser Asn Ile Gly Ser Asn Tyr Val Tyr Trp Tyr Gln Gln Leu
            180                 185                 190

Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Arg Asn Asn Gln Arg Pro
        195                 200                 205

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala
    210                 215                 220

Ser Leu Ala Ile Ser Gly Leu Arg Ser Glu Asp Glu Ala Asp Tyr Tyr
225                 230                 235                 240

Cys Ala Ala Trp Asp Asp Ser Leu Ser Gly Pro Val Phe Gly Gly Gly
                245                 250                 255

Thr Lys Leu Thr Val Leu Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
            260                 265                 270

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
        275                 280                 285

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
    290                 295                 300

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
305                 310                 315                 320

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
                325                 330                 335
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Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
            340                 345                 350

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
        355                 360                 365

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
    370                 375                 380

Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
385                 390                 395                 400

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
                405                 410                 415

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
            420                 425                 430

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
        435                 440                 445

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
    450                 455                 460

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
465                 470                 475                 480

Ala Leu Pro Pro Arg
                485
```

<210> 255
<211> 1455
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 255
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agctcgtgga atcgggcggt ggactggtca agccaggagg ttccctgcgg 120

ctgtcctgcg tggcctccgg tttcacattc tccaacgcgt ggatgaattg ggtgcgccaa 180

gcccctggaa agggacttga atgggtcgga cggatcaaga gcaaaaccga cggaggaact 240

gccgattacg ccgcacccgt gaagggcaga ttcaccattt cgcgggatga ctcgaagaac 300

accatgtacc tccagatgaa ctcgctcaag accgaggata ccggcgtcta ctactgcatc 360

accggcgcta ctgacgtctg gggacaggga actaccgtga ctgtgtcctc cggcggaggc 420

ggaagcggag gaggggcag cgggggcggg ggatcatcct acgtgctcac tcagccgcct 480

tcagcctccg gtaccccggg ccagcgcgtg accatttcat gctcgggctc ctcctcaaac 540

atcgggagca actacgtgta ctggtaccag cagctgcccg gtactgcccc caagctgctg 600

atctaccgga acaaccaacg cccgagcgga gtgccggaca gattctccgg gtccaagtct 660

gggacctccg ctagcctggc gatctccggt ctgaggagcg aggacgaggc agactactat 720

tgtgcggcct gggacgattc cctgtcgggg cctgtgtttg gaggcggcac gaagttgacc 780

gtgctgacca ctaccccagc accgaggcca cccaccccgg ctcctaccat cgcctcccag 840

cctctgtccc tgcgtccgga ggcatgtaga cccgcagctg gtggggccgt gcatacccgg 900

ggtcttgact tcgcctgcga tatctacatt tgggcccctc tggctggtac ttgcggggtc 960

ctgctgcttt cactcgtgat cactctttac tgtaagcgcg gtcggaagaa gctgctgtac 1020

atctttaagc aacccttcat gaggcctgtg cagactactc aagaggagga cggctgttca 1080

tgccggttcc cagaggagga ggaaggcggc tgcgaactgc gcgtgaaatt cagccgcagc 1140

gcagatgctc cagcctacaa gcaggggcag aaccagctct acaacgaact caatcttggt 1200

cggagagagg agtacgacgt gctggacaag cggagaggac gggacccaga aatgggcggg 1260

aagccgcgca gaaagaatcc ccaagagggc ctgtacaacg agctccaaaa ggataagatg 1320

gcagaagcct atagcgagat tggtatgaaa ggggaacgca gaagaggcaa aggccacgac 1380

ggactgtacc agggactcag caccgccacc aaggacacct atgacgctct tcacatgcag 1440

gccctgccgc ctcgg 1455

<210> 256
<211> 254
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 256
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
20 25 30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
50 55 60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65 70 75 80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
85 90 95

Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
100 105 110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly

115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser
130 135 140

Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile
145 150 155 160

Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr
165 170 175

Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile
180 185 190

Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly
195 200 205

Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
210 215 220

Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr
225 230 235 240

Leu Val Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
245 250

<210> 257
<211> 762
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 257
gaagtgcagc ttcagcagtc tggtcccggg cttgtcaaac catcgcagac cctgtccctg 60

acttgcgcga tcagcggcga tagcgtgctg tcaaactcgg acacctggaa ctggatcagg 120

cagtcccctt cccgcggact ggaatggttg ggccggacgt accatcgctc cacttggtac 180

gacgactatg ccagctccgt gagaggccgg gtgtcgatca acgtggatac ttcaaagaac 240

cagtactccc tccaactcaa tgctgtgacc ccggaggaca ccggagtgta ctactgtgcc 300

cgggatagac tgcaggacgg aaactcatgg agcgacgcct tcgacgtgtg gggacagggc 360

accatggtca ccgtgtccag cggtggagga ggctccggcg gtggaggttc gggggagga 420

gggagccaat cggctctgac ccaaccggcc tcagtcagcg gttcgcccgg acagtccatt 480

actattagct gcaccggaac ctccagcgac gtgggcggct acaactatgt gtcgtggtac 540

cagcagcacc cggggaaggc ccctaagctg atgatctacg acgtgtccaa tcggccctcc 600

ggggtgtcca accgcttctc cggctcgaag tccggcaaca ctgcatcact gacaatcagc 660

ggactgcaag ccgaggacga agcggattac tactgctcct cctacacctc ctcctccact 720

ctcgtctacg tgtttggaac cgggaccaag gtcaccgtgc tg 762

<210> 258
<211> 855
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 258
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agcttcagca gtctggtccc gggcttgtca aaccatcgca gaccctgtcc 120

ctgacttgcg cgatcagcgg cgatagcgtg ctgtcaaact cggacacctg gaactggatc 180

aggcagtccc cttcccgcgg actggaatgg ttgggccgga cgtaccatcg ctccacttgg 240

tacgacgact atgccagctc cgtgagaggc cgggtgtcga tcaacgtgga tacttcaaag 300

aaccagtact ccctccaact caatgctgtg accccggagg acaccggagt gtactactgt 360

gcccgggata gactgcagga cggaaactca tggagcgacg ccttcgacgt gtggggacag 420

ggcaccatgg tcaccgtgtc cagcggtgga ggaggctccg gcggtggagg ttcgggggga 480

ggagggagcc aatcggctct gacccaaccg gcctcagtca gcggttcgcc cggacagtcc 540

attactatta gctgcaccgg aacctccagc gacgtgggcg gctacaacta tgtgtcgtgg 600

taccagcagc acccggggaa ggcccctaag ctgatgatct acgacgtgtc caatcggccc 660

tccggggtgt ccaaccgctt ctccggctcg aagtccggca acactgcatc actgacaatc 720

agcggactgc aagccgagga cgaagcggat tactactgct cctcctacac ctcctcctcc 780

actctcgtct acgtgtttgg aaccgggacc aaggtcaccg tgctgggatc gcaccaccat 840

caccatcatc atcac 855

<210> 259
<211> 285
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 259
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp
35 40 45

Ser Val Leu Ser Asn Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro
50 55 60

Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp
65 70 75 80

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Tyr Asp Asp Tyr Ala Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val
                85                  90                  95

Asp Thr Ser Lys Asn Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro
            100                 105                 110

Glu Asp Thr Gly Val Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly
        115                 120                 125

Asn Ser Trp Ser Asp Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val
    130                 135                 140

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser
                165                 170                 175

Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val
            180                 185                 190

Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala
        195                 200                 205

Pro Lys Leu Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser
    210                 215                 220

Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile
225                 230                 235                 240

Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr
                245                 250                 255

Thr Ser Ser Ser Thr Leu Val Tyr Val Phe Gly Thr Gly Thr Lys Val
            260                 265                 270
```

Thr Val Leu Gly Ser His His His His His His His His
275 280 285

<210> 260
<211> 498
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 260
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp
35 40 45

Ser Val Leu Ser Asn Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro
50 55 60

Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp
65 70 75 80

Tyr Asp Asp Tyr Ala Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val
85 90 95

Asp Thr Ser Lys Asn Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro
100 105 110

Glu Asp Thr Gly Val Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly
115 120 125

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Asn Ser Trp Ser Asp Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val
    130                 135                 140

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser
                165                 170                 175

Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val
            180                 185                 190

Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala
        195                 200                 205

Pro Lys Leu Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser
    210                 215                 220

Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile
225                 230                 235                 240

Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr
                245                 250                 255

Thr Ser Ser Ser Thr Leu Val Tyr Val Phe Gly Thr Gly Thr Lys Val
            260                 265                 270

Thr Val Leu Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
        275                 280                 285

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
    290                 295                 300

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
305                 310                 315                 320
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Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
                325                 330                 335

Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
            340                 345                 350

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
        355                 360                 365

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
    370                 375                 380

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys
385                 390                 395                 400

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
                405                 410                 415

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
            420                 425                 430

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
        435                 440                 445

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
    450                 455                 460

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
465                 470                 475                 480

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
                485                 490                 495

Pro Arg
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<210> 261
<211> 1494
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 261
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agcttcagca gtctggtccc gggcttgtca aaccatcgca gaccctgtcc 120

ctgacttgcg cgatcagcgg cgatagcgtg ctgtcaaact cggacacctg gaactggatc 180

aggcagtccc cttcccgcgg actggaatgg ttgggccgga cgtaccatcg ctccacttgg 240

tacgacgact atgccagctc cgtgagaggc cgggtgtcga tcaacgtgga tacttcaaag 300

aaccagtact ccctccaact caatgctgtg accccggagg acaccggagt gtactactgt 360

gcccgggata gactgcagga cggaaactca tggagcgacg ccttcgacgt gtggggacag 420

ggcaccatgg tcaccgtgtc cagcggtgga ggaggctccg gcggtggagg ttcgggggga 480

ggagggagcc aatcggctct gacccaaccg gcctcagtca gcggttcgcc cggacagtcc 540

attactatta gctgcaccgg aacctccagc gacgtgggcg gctacaacta tgtgtcgtgg 600

taccagcagc acccggggaa ggcccctaag ctgatgatct acgacgtgtc caatcggccc 660

tccggggtgt ccaaccgctt ctccggctcg aagtccggca acactgcatc actgacaatc 720

agcggactgc aagccgagga cgaagcggat tactactgct cctcctacac ctcctcctcc 780

actctcgtct acgtgtttgg aaccgggacc aaggtcaccg tgctgaccac taccccagca 840

ccgaggccac ccaccccggc tcctaccatc gcctcccagc ctctgtccct gcgtccggag 900

gcatgtagac ccgcagctgg tggggccgtg catacccggg gtcttgactt cgcctgcgat 960

atctacattt gggcccctct ggctggtact tgcggggtcc tgctgctttc actcgtgatc 1020

actctttact gtaagcgcgg tcggaagaag ctgctgtaca tctttaagca acccttcatg 1080

aggcctgtgc agactactca agaggaggac ggctgttcat gccggttccc agaggaggag 1140

gaaggcggct gcgaactgcg cgtgaaattc agccgcagcg cagatgctcc agcctacaag 1200

caggggcaga accagctcta caacgaactc aatcttggtc ggagagagga gtacgacgtg 1260

ctggacaagc ggagaggacg ggacccagaa atgggcggga agccgcgcag aaagaatccc 1320

caagagggcc tgtacaacga gctccaaaag gataagatgg cagaagccta tagcgagatt 1380

ggtatgaaag gggaacgcag aagaggcaaa ggccacgacg gactgtacca gggactcagc 1440

accgccacca aggacaccta tgacgctctt cacatgcagg ccctgccgcc tcgg 1494

<210> 262
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 262
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

```
Tyr Tyr Cys Ala Arg Glu Glu Ser Ser Ser Gly Trp Tyr Glu Gly Asn
            100                 105                 110

Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Ser
    130                 135                 140

Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val
145                 150                 155                 160

Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys
            180                 185                 190

Asn His Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser
        195                 200                 205

Gly Asp Thr Asp Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu
    210                 215                 220

Ala Asp Tyr Tyr Cys His Ser Arg Asp Ser Ser Gly Asn His Leu Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu
                245
```

<210> 263
<211> 747
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 263
gaagtgcaac ttcagcagtc cggtcctggc ttggtcaagc cgtcacagac cctgtcgctg 60

acttgtgcta ttagcgggga ctctgtgtcc tcaaactccg ccgcatggaa ctggattaga 120

cagtcgccct cccggggact ggagtggctg ggccgcacct actaccggtc caagtggtac 180

aatgactacg ccgtgtccgt gaagtcccgc attactatca accccgacac ttcgaagaac 240

cagttttcgc tgcaactcaa ctccgtcacc cctgaggata ccgccgtgta ctattgcgcc 300

cgggaagaat cctccagcgg ttggtacgaa ggaaactggt tcgacccatg gggccagggc 360

accctggtca ctgtgtcctc gggaggaggg ggcagcggtg gcggaggaag cggaggagga 420

ggctccagct ccgagctcac ccaggacccg gcggtgtcag tggccctggg ccaaacggtc 480

cgcatcacat gccaggggga ttccctgagg tcatactacg cgagctggta tcagcagaaa 540

cccggacaag cccctgtgct cgtgatctac gggaagaacc acaggccgag cggaatcccg 600

gatagattct ccgggtcctc atcgggagac actgacagcc tcaccatcac cggcgcgcag 660

gccgaggacg aagctgatta ctactgccat tcccgggact cgagcgggaa ccacctttc 720

ggtggcggaa ccaagctgac cgtgctg 747

<210> 264
<211> 840
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 264
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aacttcagca gtccggtcct ggcttggtca agccgtcaca gaccctgtcg 120

ctgacttgtg ctattagcgg ggactctgtg tcctcaaact ccgccgcatg gaactggatt 180

agacagtcgc cctcccgggg actggagtgg ctgggccgca cctactaccg gtccaagtgg 240

tacaatgact acgccgtgtc cgtgaagtcc cgcattacta tcaaccccga cacttcgaag 300

aaccagtttt cgctgcaact caactccgtc acccctgagg ataccgccgt gtactattgc 360

gcccgggaag aatcctccag cggttggtac gaaggaaact ggttcgaccc atggggccag 420

ggcaccctgg tcactgtgtc ctcgggagga gggggcagcg gtggcggagg aagcggagga 480

ggaggctcca gctccgagct cacccaggac ccggcggtgt cagtggccct gggccaaacg 540

gtccgcatca catgccaggg ggattccctg aggtcatact acgcgagctg gtatcagcag 600

aaacccggac aagcccctgt gctcgtgatc tacgggaaga accacaggcc gagcggaatc 660

ccggatagat tctccgggtc ctcatcggga gacactgaca gcctcaccat caccggcgcg 720

caggccgagg acgaagctga ttactactgc cattcccggg actcgagcgg gaaccacctt 780

ttcggtggcg gaaccaagct gaccgtgctg ggatcgcacc accatcacca tcatcatcac 840

<210> 265
<211> 280
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 265
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp
35 40 45

Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro

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    50                  55                  60

Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp
65                  70                  75                  80

Tyr Asn Asp Tyr Ala Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro
                85                  90                  95

Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro
            100                 105                 110

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu Glu Ser Ser Ser Gly
        115                 120                 125

Trp Tyr Glu Gly Asn Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val
    130                 135                 140

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala
                165                 170                 175

Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser
            180                 185                 190

Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu
        195                 200                 205

Val Ile Tyr Gly Lys Asn His Arg Pro Ser Gly Ile Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Ser Ser Gly Asp Thr Asp Ser Leu Thr Ile Thr Gly Ala
225                 230                 235                 240

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys His Ser Arg Asp Ser Ser
```

245 250 255

Gly Asn His Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser
260 265 270

His His His His His His His His
275 280

<210> 266
<211> 493
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 266
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp
35 40 45

Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro
50 55 60

Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp
65 70 75 80

Tyr Asn Asp Tyr Ala Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro
85 90 95

Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro
100 105 110

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Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu Glu Ser Ser Ser Gly
        115                 120                 125

Trp Tyr Glu Gly Asn Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val
    130                 135                 140

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala
                165                 170                 175

Leu Gly Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser
            180                 185                 190

Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu
        195                 200                 205

Val Ile Tyr Gly Lys Asn His Arg Pro Ser Gly Ile Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Ser Ser Gly Asp Thr Asp Ser Leu Thr Ile Thr Gly Ala
225                 230                 235                 240

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys His Ser Arg Asp Ser Ser
                245                 250                 255

Gly Asn His Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Thr Thr
            260                 265                 270

Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln
        275                 280                 285

Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala
    290                 295                 300
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Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala
305                 310                 315                 320

Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr
                325                 330                 335

Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln
            340                 345                 350

Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser
        355                 360                 365

Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys
    370                 375                 380

Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln
385                 390                 395                 400

Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu
                405                 410                 415

Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg
            420                 425                 430

Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
        435                 440                 445

Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
    450                 455                 460

Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
465                 470                 475                 480

Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 267
<211> 1479
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 267
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aacttcagca gtccggtcct ggcttggtca agccgtcaca gaccctgtcg 120

ctgacttgtg ctattagcgg ggactctgtg tcctcaaact ccgccgcatg gaactggatt 180

agacagtcgc cctcccgggg actggagtgg ctgggccgca cctactaccg gtccaagtgg 240

tacaatgact acgccgtgtc cgtgaagtcc cgcattacta tcaaccccga cacttcgaag 300

aaccagtttt cgctgcaact caactccgtc acccctgagg ataccgccgt gtactattgc 360

gcccgggaag aatcctccag cggttggtac gaaggaaact ggttcgaccc atggggccag 420

ggcaccctgg tcactgtgtc ctcgggagga gggggcagcg gtggcggagg aagcggagga 480

ggaggctcca gctccgagct cacccaggac ccggcggtgt cagtggccct gggccaaacg 540

gtccgcatca catgccaggg ggattccctg aggtcatact acgcgagctg gtatcagcag 600

aaacccggac aagcccctgt gctcgtgatc tacgggaaga accacaggcc gagcggaatc 660

ccggatagat tctccgggtc ctcatcggga gacactgaca gcctcaccat caccggcgcg 720

caggccgagg acgaagctga ttactactgc cattcccggg actcgagcgg gaaccacctt 780

ttcggtggcg gaaccaagct gaccgtgctg accactaccc cagcaccgag gccacccacc 840

ccggctccta ccatcgcctc ccagcctctg tccctgcgtc cggaggcatg tagacccgca 900

gctggtgggg ccgtgcatac ccggggtctt gacttcgcct gcgatatcta catttgggcc 960

cctctggctg gtacttgcgg ggtcctgctg ctttcactcg tgatcactct ttactgtaag 1020

cgcggtcgga agaagctgct gtacatcttt aagcaaccct tcatgaggcc tgtgcagact 1080

actcaagagg aggacggctg ttcatgccgg ttcccagagg aggaggaagg cggctgcgaa 1140

ctgcgcgtga aattcagccg cagcgcagat gctccagcct acaagcaggg gcagaaccag 1200

ctctacaacg aactcaatct tggtcggaga gaggagtacg acgtgctgga caagcggaga 1260

ggacgggacc cagaaatggg cgggaagccg cgcagaaaga atccccaaga gggcctgtac 1320

aacgagctcc aaaaggataa gatggcagaa gcctatagcg agattggtat gaaaggggaa 1380

cgcagaagag gcaaaggcca cgacggactg taccagggac tcagcaccgc caccaaggac 1440

acctatgacg ctcttcacat gcaggccctg ccgcctcgg 1479

<210> 268
<211> 253
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 268
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
20 25 30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
50 55 60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65 70 75 80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val

85 90 95

Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
100 105 110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser
130 135 140

Ala Leu Thr Gln Pro Ala Ser Ala Ser Gly Ser Pro Gly Gln Ser Val
145 150 155 160

Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr
165 170 175

Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile
180 185 190

Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly
195 200 205

Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
210 215 220

Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr
225 230 235 240

Leu Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu
245 250

<210> 269
<211> 759
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 269
gaagtgcagc tgcagcagag cggaccgggc ctggtcaaac cctcccaaac cctgtccctc 60

acttgcgcga tctccgggga ctccgtgctc tcgaactccg acacctggaa ctggattcgg 120

cagagcccat cgaggggcct ggaatggctg ggaagaacct accaccggtc cacttggtac 180

gatgactacg cgagctcagt gcgcggacgc gtgtcgatta acgtggacac ctccaagaac 240

cagtacagct tgcaactgaa cgccgtgacc cctgaggaca ccggagtgta ctattgcgcc 300

cgggatagac ttcaggacgg aaacagctgg tccgacgcct ttgacgtctg gggacagggc 360

accatggtca ctgtgtcctc gggtggcggg gggtccggtg gaggaggttc aggcggaggc 420

ggctcacagt cagcactgac gcagccggct tccgcttccg ggagccctgg acagagcgtg 480

accatctcgt gtaccgggac ttccagcgat gtcggcgggt acaactacgt gtcttggtac 540

caacagcatc cgggaaaggc ccccaagctc atgatctacg acgtgtcaaa ccggcccagc 600

ggagtgtcca atcgcttctc cggctccaag tcgggcaata ctgcctcgct gactatcagc 660

ggtctgcaag ccgaagatga ggccgactat tactgctcct cctacacctc gtcctccaca 720

ctctacgtgt tcggaaccgg tactcagctg accgtgctt 759

<210> 270
<211> 852
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 270
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agctgcagca gagcggaccg ggcctggtca aaccctccca aaccctgtcc 120

ctcacttgcg cgatctccgg ggactccgtg ctctcgaact ccgacacctg gaactggatt 180

cggcagagcc catcgagggg cctggaatgg ctgggaagaa cctaccaccg gtccacttgg 240

tacgatgact acgcgagctc agtgcgcgga cgcgtgtcga ttaacgtgga cacctccaag 300

aaccagtaca gcttgcaact gaacgccgtg acccctgagg acaccggagt gtactattgc 360

gcccgggata gacttcagga cggaaacagc tggtccgacg cctttgacgt ctggggacag 420

ggcaccatgg tcactgtgtc ctcgggtggc gggggtccg gtggaggagg ttcaggcgga 480

ggcggctcac agtcagcact gacgcagccg gcttccgctt ccgggagccc tggacagagc 540

gtgaccatct cgtgtaccgg gacttccagc gatgtcggcg ggtacaacta cgtgtcttgg 600

taccaacagc atccgggaaa ggcccccaag ctcatgatct acgacgtgtc aaaccggccc 660

agcggagtgt ccaatcgctt ctccggctcc aagtcgggca atactgcctc gctgactatc 720

agcggtctgc aagccgaaga tgaggccgac tattactgct cctcctacac ctcgtcctcc 780

acactctacg tgttcggaac cggtactcag ctgaccgtgc ttggatcgca ccaccatcac 840

catcatcatc ac 852

<210> 271
<211> 284
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 271
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp
35 40 45

```
Ser Val Leu Ser Asn Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro
    50                  55                  60

Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp
65                  70                  75                  80

Tyr Asp Asp Tyr Ala Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val
                85                  90                  95

Asp Thr Ser Lys Asn Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro
            100                 105                 110

Glu Asp Thr Gly Val Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly
        115                 120                 125

Asn Ser Trp Ser Asp Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val
    130                 135                 140

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Ala Ser Gly Ser
                165                 170                 175

Pro Gly Gln Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val
            180                 185                 190

Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala
        195                 200                 205

Pro Lys Leu Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser
    210                 215                 220

Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile
225                 230                 235                 240
```

```
Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr
                245                 250                 255


Thr Ser Ser Ser Thr Leu Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr
            260                 265                 270


Val Leu Gly Ser His His His His His His His His
        275                 280


<210> 272
<211> 497
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 272
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu
            20                  25                  30


Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp
        35                  40                  45


Ser Val Leu Ser Asn Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro
    50                  55                  60


Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp
65                  70                  75                  80


Tyr Asp Asp Tyr Ala Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val
                85                  90                  95
```

```
Asp Thr Ser Lys Asn Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro
            100                 105                 110

Glu Asp Thr Gly Val Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly
        115                 120                 125

Asn Ser Trp Ser Asp Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val
    130                 135                 140

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Ala Ser Gly Ser
                165                 170                 175

Pro Gly Gln Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val
            180                 185                 190

Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala
        195                 200                 205

Pro Lys Leu Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser
    210                 215                 220

Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile
225                 230                 235                 240

Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr
                245                 250                 255

Thr Ser Ser Ser Thr Leu Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr
            260                 265                 270

Val Leu Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
        275                 280                 285
```

```
Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
    290                 295                 300

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
305                 310                 315                 320

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
                325                 330                 335

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr
            340                 345                 350

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
        355                 360                 365

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
    370                 375                 380

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln
385                 390                 395                 400

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
                405                 410                 415

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
            420                 425                 430

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
        435                 440                 445

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
    450                 455                 460

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
465                 470                 475                 480
```

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
485 490 495

Arg

<210> 273
<211> 1491
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 273
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agctgcagca gagcggaccg ggcctggtca aaccctccca aaccctgtcc 120

ctcacttgcg cgatctccgg ggactccgtg ctctcgaact ccgacacctg gaactggatt 180

cggcagagcc catcgagggg cctggaatgg ctgggaagaa cctaccaccg gtccacttgg 240

tacgatgact acgcgagctc agtgcgcgga cgcgtgtcga ttaacgtgga cacctccaag 300

aaccagtaca gcttgcaact gaacgccgtg acccctgagg acaccggagt gtactattgc 360

gcccgggata gacttcagga cggaaacagc tggtccgacg cctttgacgt ctggggacag 420

ggcaccatgg tcactgtgtc ctcgggtggc ggggggtccg gtggaggagg ttcaggcgga 480

ggcggctcac agtcagcact gacgcagccg gcttccgctt ccgggagccc tggacagagc 540

gtgaccatct cgtgtaccgg gacttccagc gatgtcggcg ggtacaacta cgtgtcttgg 600

taccaacagc atccgggaaa ggcccccaag ctcatgatct acgacgtgtc aaaccggccc 660

agcggagtgt ccaatcgctt ctccggctcc aagtcgggca atactgcctc gctgactatc 720

agcggtctgc aagccgaaga tgaggccgac tattactgct cctcctacac ctcgtcctcc 780

acactctacg tgttcggaac cggtactcag ctgaccgtgc ttaccactac cccagcaccg 840

aggccaccca ccccggctcc taccatcgcc tcccagcctc tgtccctgcg tccggaggca 900

tgtagacccg cagctggtgg ggccgtgcat acccggggtc ttgacttcgc ctgcgatatc 960

tacatttggg cccctctggc tggtacttgc ggggtcctgc tgctttcact cgtgatcact 1020

ctttactgta agcgcggtcg gaagaagctg ctgtacatct ttaagcaacc cttcatgagg 1080

cctgtgcaga ctactcaaga ggaggacggc tgttcatgcc ggttcccaga ggaggaggaa 1140

ggcggctgcg aactgcgcgt gaaattcagc cgcagcgcag atgctccagc ctacaagcag 1200

gggcagaacc agctctacaa cgaactcaat cttggtcgga gagaggagta cgacgtgctg 1260

gacaagcgga gaggacggga cccagaaatg ggcgggaagc cgcgcagaaa gaatccccaa 1320

gagggcctgt acaacgagct ccaaaaggat aagatggcag aagcctatag cgagattggt 1380

atgaaagggg aacgcagaag aggcaaaggc cacgacggac tgtaccaggg actcagcacc 1440

gccaccaagg acacctatga cgctcttcac atgcaggccc tgccgcctcg g 1491

<210> 274
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 274
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

```
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Gly Arg Met Asp Thr Ala Met Ala Gln Ile Trp Gly Gln
            100                 105                 110

Gly Thr Met Val Thr Val Ser Ser Gly Asp Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Asn Phe Met Leu Thr Gln Pro His Ser
    130                 135                 140

Val Ser Glu Ser Pro Gly Lys Thr Val Thr Ile Pro Cys Thr Gly Ser
145                 150                 155                 160

Ser Gly Ser Phe Ala Ser Ser Tyr Val Gln Trp Tyr Gln Gln Arg Pro
                165                 170                 175

Gly Ser Ala Pro Ala Thr Val Ile Tyr Glu Asp Asn Gln Arg Pro Ser
            180                 185                 190

Gly Val Pro Asp Arg Phe Ser Gly Ser Val Asp Ser Ser Ser Asn Ser
        195                 200                 205

Ala Ser Leu Thr Ile Ser Gly Leu Lys Thr Glu Asp Glu Ala Val Tyr
    210                 215                 220

Tyr Cys Gln Ser Tyr Asp Gly Ala Thr Trp Val Phe Gly Gly Gly Thr
225                 230                 235                 240

Lys Leu Thr Val Leu
                245
```

<210> 275
<211> 735
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 275
caagtgcagc tccaagaatc aggtcccggc ctcgtgaagc cttccgaaac cctctccctt 60

acttgtaccg tgtccggggg aagcatctcg agcagctcct attactgggg atggatcagg 120

cagcctcccg gaaagggact ggagtggatt ggctccatct actactcggg gtccacctac 180

tacaacccgt cactgaagtc ccgcgtgacc atctcggtgg atacctccaa gaaccagttc 240

agcctgaagc tgtcctccgt gactgccgcc gacactgccg tgtactactg cgcgcggggt 300

cggatggaca cagcgatggc tcagatttgg ggacagggca ccatggtcac tgtgtcctcc 360

ggggatggag gctccggggg cggaggatct ggtggcgggg ggtcgaactt catgttgacc 420

cagccacact ccgtgtcgga aagcccagga aagaccgtca ccatcccttg cactggaagc 480

agcggttcgt tcgcatcaag ctacgtgcag tggtaccagc aaagacccgg cagcgctccg 540

gccaccgtca tctatgagga caatcagcgg ccgtccggcg tgccggaccg cttcagcgga 600

tcggtggact catcctcaaa ctccgcctcc ctgacgattt ccggtctgaa aaccgaggac 660

gaagccgtct actactgcca gtcgtacgat ggcgccactt gggtgtttgg aggaggcacc 720

aagctgaccg tgctg 735

<210> 276
<211> 828
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<400> 276
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agctccaaga atcaggtccc ggcctcgtga agccttccga aaccctctcc 120

cttacttgta ccgtgtccgg gggaagcatc tcgagcagct cctattactg gggatggatc 180

aggcagcctc ccggaaaggg actggagtgg attggctcca tctactactc ggggtccacc 240

tactacaacc cgtcactgaa gtcccgcgtg accatctcgg tggatacctc caagaaccag 300

ttcagcctga agctgtcctc cgtgactgcc gccgacactg ccgtgtacta ctgcgcgcgg 360

ggtcggatgg acacagcgat ggctcagatt tggggacagg gcaccatggt cactgtgtcc 420

tccggggatg gaggctccgg gggcggagga tctggtggcg gggggtcgaa cttcatgttg 480

acccagccac actccgtgtc ggaaagccca ggaaagaccg tcaccatccc ttgcactgga 540

agcagcggtt cgttcgcatc aagctacgtg cagtggtacc agcaaagacc cggcagcgct 600

ccggccaccg tcatctatga ggacaatcag cggccgtccg gcgtgccgga ccgcttcagc 660

ggatcggtgg actcatcctc aaactccgcc tccctgacga tttccggtct gaaaaccgag 720

gacgaagccg tctactactg ccagtcgtac gatggcgcca cttgggtgtt tggaggaggc 780

accaagctga ccgtgctggg atcgcaccac catcaccatc atcatcac 828

<210> 277
<211> 276
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 277
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu

```
            20                  25                  30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly
        35                  40                  45

Ser Ile Ser Ser Ser Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro
    50                  55                  60

Gly Lys Gly Leu Glu Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr
65                  70                  75                  80

Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr
                85                  90                  95

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg Gly Arg Met Asp Thr Ala Met Ala
        115                 120                 125

Gln Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Asp Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn Phe Met Leu
145                 150                 155                 160

Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys Thr Val Thr Ile
                165                 170                 175

Pro Cys Thr Gly Ser Ser Gly Ser Phe Ala Ser Ser Tyr Val Gln Trp
            180                 185                 190

Tyr Gln Gln Arg Pro Gly Ser Ala Pro Ala Thr Val Ile Tyr Glu Asp
        195                 200                 205

Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Val Asp
```

210 215 220

Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly Leu Lys Thr Glu
225 230 235 240

Asp Glu Ala Val Tyr Tyr Cys Gln Ser Tyr Asp Gly Ala Thr Trp Val
245 250 255

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser His His His His
260 265 270

His His His His
275

<210> 278
<211> 489
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 278
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly
35 40 45

Ser Ile Ser Ser Ser Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro
50 55 60

Gly Lys Gly Leu Glu Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr
65 70 75 80

```
Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr
                85                  90                  95

Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp
            100                 105                 110

Thr Ala Val Tyr Tyr Cys Ala Arg Gly Arg Met Asp Thr Ala Met Ala
        115                 120                 125

Gln Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Asp Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn Phe Met Leu
145                 150                 155                 160

Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys Thr Val Thr Ile
                165                 170                 175

Pro Cys Thr Gly Ser Ser Gly Ser Phe Ala Ser Ser Tyr Val Gln Trp
            180                 185                 190

Tyr Gln Gln Arg Pro Gly Ser Ala Pro Ala Thr Val Ile Tyr Glu Asp
        195                 200                 205

Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Val Asp
    210                 215                 220

Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly Leu Lys Thr Glu
225                 230                 235                 240

Asp Glu Ala Val Tyr Tyr Cys Gln Ser Tyr Asp Gly Ala Thr Trp Val
                245                 250                 255

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Thr Thr Thr Pro Ala Pro
            260                 265                 270
```

```
Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
        275                 280                 285

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
    290                 295                 300

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
305                 310                 315                 320

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
                325                 330                 335

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
            340                 345                 350

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
        355                 360                 365

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
    370                 375                 380

Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu
385                 390                 395                 400

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
                405                 410                 415

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
            420                 425                 430

Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
        435                 440                 445

Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
    450                 455                 460
```

Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
465 470 475 480

Leu His Met Gln Ala Leu Pro Pro Arg
485

<210> 279
<211> 1467
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 279
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agctccaaga atcaggtccc ggcctcgtga agccttccga aaccctctcc 120

cttacttgta ccgtgtccgg gggaagcatc tcgagcagct cctattactg gggatggatc 180

aggcagcctc ccggaaaggg actggagtgg attggctcca tctactactc ggggtccacc 240

tactacaacc cgtcactgaa gtcccgcgtg accatctcgg tggatacctc caagaaccag 300

ttcagcctga agctgtcctc cgtgactgcc gccgacactg ccgtgtacta ctgcgcgcgg 360

ggtcggatgg acacagcgat ggctcagatt tggggacagg gcaccatggt cactgtgtcc 420

tccggggatg gaggctccgg gggcggagga tctggtggcg gggggtcgaa cttcatgttg 480

acccagccac actccgtgtc ggaaagccca ggaaagaccg tcaccatccc ttgcactgga 540

agcagcggtt cgttcgcatc aagctacgtg cagtggtacc agcaaagacc cggcagcgct 600

ccggccaccg tcatctatga ggacaatcag cggccgtccg gcgtgccgga ccgcttcagc 660

ggatcggtgg actcatcctc aaactccgcc tccctgacga tttccggtct gaaaaccgag 720

gacgaagccg tctactactg ccagtcgtac gatggcgcca cttgggtgtt tggaggaggc 780

accaagctga ccgtgctgac cactacccca gcaccgaggc cacccacccc ggctcctacc 840

atcgcctccc agcctctgtc cctgcgtccg gaggcatgta gacccgcagc tggtggggcc 900

gtgcataccc ggggtcttga cttcgcctgc gatatctaca tttgggcccc tctggctggt 960

acttgcgggg tcctgctgct ttcactcgtg atcactcttt actgtaagcg cggtcggaag 1020

aagctgctgt acatctttaa gcaacccttc atgaggcctg tgcagactac tcaagaggag 1080

gacggctgtt catgccggtt cccagaggag gaggaaggcg gctgcgaact gcgcgtgaaa 1140

ttcagccgca gcgcagatgc tccagcctac aagcaggggc agaaccagct ctacaacgaa 1200

ctcaatcttg gtcggagaga ggagtacgac gtgctggaca agcggagagg acgggaccca 1260

gaaatgggcg ggaagccgcg cagaaagaat ccccaagagg gcctgtacaa cgagctccaa 1320

aaggataaga tggcagaagc ctatagcgag attggtatga aaggggaacg cagaagaggc 1380

aaaggccacg acggactgta ccagggactc agcaccgcca ccaaggacac ctatgacgct 1440

cttcacatgc aggccctgcc gcctcgg 1467

<210> 280
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 280
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe

```
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Leu Asp Val Ser Leu Asp Ile Trp Gly Gln Gly Thr Met
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly
    130                 135                 140

Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Ser Gly Thr Ser Ser Asp
145                 150                 155                 160

Val Gly Gly Tyr Asn Ser Val Ser Trp Tyr Gln Gln Tyr Pro Gly Lys
                165                 170                 175

Ala Pro Lys Leu Met Ile Tyr Asp Val Asn Asn Arg Pro Ser Gly Val
            180                 185                 190

Ser Ser Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr
        195                 200                 205

Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser
    210                 215                 220

Tyr Thr Ser Ser Ser Thr Leu Phe Phe Gly Ala Gly Thr Lys Val Thr
225                 230                 235                 240

Val Leu
```

<210> 281
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 281
caagtgcaac ttgtccagag cggagcagaa gtcaagaaac caggagcaag cgtgaaggtg 60

tcctgcaaag cgtcaggcta cactttcacc tcctactata tgcactgggt ccgccaggcc 120

cctggacaag gcctggaatg gatgggtatc atcaacccgt ccggtggaag caccagctac 180

gcccagaagt ttcagggaag agtgaccatg actcgggaca cttcaacctc gacggtgtac 240

atggagctgt cctccctgcg gtcggaggac accgccgtgt actactgcgc gagggatctc 300

gatgtgtccc tggacatttg gggacagggc accatggtca ccgtgtcctc cgggggggggc 360

ggatcaggcg gcggaggttc agggggcggg ggctcccagt ccgcgctgac tcagccggct 420

agcgtgtccg gctcgccggg acagagcatt accatctcgt gctcgggtac cagctccgac 480

gtgggaggct ataactccgt gtcctggtac cagcagtacc ccggaaaggc ccccaagctg 540

atgatctacg acgtgaacaa tcgcccttct ggggtgtcct ctcggttctc cgggtcaaag 600

agcggaaaca ccgcctccct gaccatctcg ggactccaag ctgaggatga agccgactac 660

tactgttcga gctacacctc ctcctccact ctcttcttcg gtgccggaac taaggtcaca 720

gtgttg 726

<210> 282
<211> 819
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 282
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aacttgtcca gagcggagca gaagtcaaga aaccaggagc aagcgtgaag 120

gtgtcctgca aagcgtcagg ctacactttc acctcctact atatgcactg ggtccgccag 180

gcccctggac aaggcctgga atggatgggt atcatcaacc cgtccggtgg aagcaccagc 240

tacgcccaga agtttcaggg aagagtgacc atgactcggg acacttcaac ctcgacggtg 300

tacatggagc tgtcctccct gcggtcggag gacaccgccg tgtactactg cgcgagggat 360

ctcgatgtgt ccctggacat ttggggacag ggcaccatgg tcaccgtgtc ctccgggggg 420

ggcggatcag gcggcggagg ttcaggggggc gggggctccc agtccgcgct gactcagccg 480

gctagcgtgt ccggctcgcc gggacagagc attaccatct cgtgctcggg taccagctcc 540

gacgtgggag gctataactc cgtgtcctgg taccagcagt accccggaaa ggcccccaag 600

ctgatgatct acgacgtgaa caatcgccct tctggggtgt cctctcggtt ctccgggtca 660

aagagcggaa acaccgcctc cctgaccatc tcgggactcc aagctgagga tgaagccgac 720

tactactgtt cgagctacac ctcctcctcc actctcttct tcggtgccgg aactaaggtc 780

acagtgttgg gatcgcacca ccatcaccat catcatcac 819

<210> 283
<211> 273
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 283
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Asp Leu Asp Val Ser Leu Asp Ile Trp
        115                 120                 125

Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro
145                 150                 155                 160

Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Ser
                165                 170                 175

Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Ser Val Ser Trp Tyr Gln
            180                 185                 190

Gln Tyr Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Asn Asn
        195                 200                 205
```

Arg Pro Ser Gly Val Ser Ser Arg Phe Ser Gly Ser Lys Ser Gly Asn
210 215 220

Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp
225 230 235 240

Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Phe Phe Gly Ala
245 250 255

Gly Thr Lys Val Thr Val Leu Gly Ser His His His His His His His
260 265 270

His

<210> 284
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 284
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser

65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Leu Asp Val Ser Leu Asp Ile Trp
115 120 125

Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro
145 150 155 160

Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Ser
165 170 175

Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Ser Val Ser Trp Tyr Gln
180 185 190

Gln Tyr Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Asn Asn
195 200 205

Arg Pro Ser Gly Val Ser Ser Arg Phe Ser Gly Ser Lys Ser Gly Asn
210 215 220

Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp
225 230 235 240

Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Phe Phe Gly Ala
245 250 255

Gly Thr Lys Val Thr Val Leu Thr Thr Thr Pro Ala Pro Arg Pro Pro

```
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
```

450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 285
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 285
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aacttgtcca gagcggagca gaagtcaaga aaccaggagc aagcgtgaag 120

gtgtcctgca aagcgtcagg ctacactttc acctcctact atatgcactg ggtccgccag 180

gcccctggac aaggcctgga atggatgggt atcatcaacc cgtccggtgg aagcaccagc 240

tacgcccaga agtttcaggg aagagtgacc atgactcggg acacttcaac ctcgacggtg 300

tacatggagc tgtcctccct gcggtcggag gacaccgccg tgtactactg cgcgagggat 360

ctcgatgtgt ccctggacat ttggggacag ggcaccatgg tcaccgtgtc ctccgggggg 420

ggcggatcag gcggcggagg ttcaggggggc gggggctccc agtccgcgct gactcagccg 480

gctagcgtgt ccggctcgcc gggacagagc attaccatct cgtgctcggg taccagctcc 540

gacgtgggag gctataactc cgtgtcctgg taccagcagt accccggaaa ggcccccaag 600

ctgatgatct acgacgtgaa caatcgccct tctggggtgt cctctcggtt ctccgggtca 660

aagagcggaa acaccgcctc cctgaccatc tcgggactcc aagctgagga tgaagccgac 720

tactactgtt cgagctacac ctcctcctcc actctcttct tcggtgccgg aactaaggtc 780

acagtgttga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 286
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 286
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Tyr Val
35 40 45

```
Ser Ala Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asn Ser Val
    50                  55                  60

Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Gly Ser Leu Arg Ala Glu Asp Met Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Val His Ser Ser Gly Tyr Tyr His Pro Gly Pro Asn Asp Tyr
            100                 105                 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Ser Glu Leu Thr Gln
    130                 135                 140

Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys
145                 150                 155                 160

Gln Gly Asp Ser Leu Arg Thr Tyr Tyr Ala Thr Trp Tyr Gln Gln Lys
                165                 170                 175

Pro Gly Gln Ala Pro Val Leu Val Phe Tyr Asp Glu Asn Asn Arg Pro
            180                 185                 190

Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala
        195                 200                 205

Ser Leu Thr Ile Thr Gly Thr Gln Ala Glu Asp Glu Ala Asp Tyr Tyr
    210                 215                 220

Cys Ser Ser Arg Asp Ser Ser Gly Asn Pro Ser Cys Val Phe Gly Gly
225                 230                 235                 240
```

Gly Thr Lys Leu Thr Val Leu
245

<210> 287
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 287
gaagtgcagt tggtggagag cggtggagga cttgtgcaac ctggaggatc attgagactg 60

tcgtgtgcgg cctccggctt taccttctcg tcctacgcta tgcattgggt ccgccaggcc 120

cccgggaaag gactcgaata cgtcagcgcc atctcctcaa acgggggatc aacctactac 180

gccaattccg tgaaggatcg gttcaccatc tcccgggata acagcaagaa caccctgtat 240

ctgcaaatgg ggtccctgag ggcagaggac atggccgtct actactgcgc gcgcgtgcac 300

agctctggat actaccaccc tggaccgaac gattactggg gccagggcac tctcgtgacc 360

gtgtcctcgg ggggtggtgg aagcggcggc ggaggatcgg ggggaggcgg ctcctcgagc 420

gaactgacac aggaccctgc cgtgtccgtg gctctgggtc agactgtgcg cattacgtgt 480

caaggagact ccctgagaac ttattacgcg acctggtacc agcagaagcc gggacaggca 540

ccggtgctgg tgttctacga cgaaaacaac cggccatccg ggattcccga ccggttctcc 600

ggctcatcga gcggcaacac tgcctccctg accatcaccg ggacccaggc cgaggacgag 660

gccgattact actgctcctc gcgggactcc tccggcaacc cctcctgcgt gttcggcggt 720

ggaaccaagc tgactgtcct c 741

<210> 288
<211> 834
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 288
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agttggtgga gagcggtgga ggacttgtgc aacctggagg atcattgaga 120

ctgtcgtgtg cggcctccgg ctttaccttc tcgtcctacg ctatgcattg ggtccgccag 180

gcccccggga aaggactcga atacgtcagc gccatctcct caaacggggg atcaacctac 240

tacgccaatt ccgtgaagga tcggttcacc atctcccggg ataacagcaa gaacaccctg 300

tatctgcaaa tggggtccct gagggcagag gacatggccg tctactactg cgcgcgcgtg 360

cacagctctg gatactacca ccctggaccg aacgattact ggggccaggg cactctcgtg 420

accgtgtcct cgggggtgg tggaagcggc ggcggaggat cgggggggagg cggctcctcg 480

agcgaactga cacaggaccc tgccgtgtcc gtggctctgg gtcagactgt gcgcattacg 540

tgtcaaggag actccctgag aacttattac gcgacctggt accagcagaa gccgggacag 600

gcaccggtgc tggtgttcta cgacgaaaac aaccggccat ccgggattcc cgaccggttc 660

tccggctcat cgagcggcaa cactgcctcc ctgaccatca ccgggaccca ggccgaggac 720

gaggccgatt actactgctc ctcgcgggac tcctccggca acccctcctg cgtgttcggc 780

ggtggaacca agctgactgt cctcggatcg caccaccatc accatcatca tcac 834

<210> 289
<211> 278
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 289
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45

Thr Phe Ser Ser Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Tyr Val Ser Ala Ile Ser Ser Asn Gly Gly Ser Thr Tyr
65                  70                  75                  80

Tyr Ala Asn Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser
                85                  90                  95

Lys Asn Thr Leu Tyr Leu Gln Met Gly Ser Leu Arg Ala Glu Asp Met
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Val His Ser Ser Gly Tyr Tyr His Pro
        115                 120                 125

Gly Pro Asn Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser
145                 150                 155                 160

Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr
                165                 170                 175

Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Thr Tyr Tyr Ala Thr
            180                 185                 190

Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Phe Tyr Asp
        195                 200                 205
```

```
Glu Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser
    210                 215                 220


Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Thr Gln Ala Glu Asp
225                 230                 235                 240


Glu Ala Asp Tyr Tyr Cys Ser Ser Arg Asp Ser Ser Gly Asn Pro Ser
                245                 250                 255


Cys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser His His
            260                 265                 270


His His His His His His
        275


<210> 290
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 290
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30


Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45


Thr Phe Ser Ser Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60
```

```
Gly Leu Glu Tyr Val Ser Ala Ile Ser Ser Asn Gly Gly Ser Thr Tyr
65                  70                  75                  80

Tyr Ala Asn Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser
                85                  90                  95

Lys Asn Thr Leu Tyr Leu Gln Met Gly Ser Leu Arg Ala Glu Asp Met
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Val His Ser Ser Gly Tyr Tyr His Pro
        115                 120                 125

Gly Pro Asn Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser
145                 150                 155                 160

Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr
                165                 170                 175

Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Thr Tyr Tyr Ala Thr
            180                 185                 190

Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Phe Tyr Asp
        195                 200                 205

Glu Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser
    210                 215                 220

Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Thr Gln Ala Glu Asp
225                 230                 235                 240

Glu Ala Asp Tyr Tyr Cys Ser Ser Arg Asp Ser Ser Gly Asn Pro Ser
                245                 250                 255
```

```
Cys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445
```

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 291
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 291
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agttggtgga gagcggtgga ggacttgtgc aacctggagg atcattgaga 120

ctgtcgtgtg cggcctccgg ctttaccttc tcgtcctacg ctatgcattg ggtccgccag 180

gcccccggga aaggactcga atacgtcagc gccatctcct caaacggggg atcaacctac 240

tacgccaatt ccgtgaagga tcggttcacc atctcccggg ataacagcaa gaacaccctg 300

tatctgcaaa tggggtccct gagggcagag gacatggccg tctactactg cgcgcgcgtg 360

cacagctctg gatactacca ccctggaccg aacgattact ggggccaggg cactctcgtg 420

accgtgtcct cgggggtgg tggaagcggc ggcggaggat cgggggggagg cggctcctcg 480

agcgaactga cacaggaccc tgccgtgtcc gtggctctgg gtcagactgt gcgcattacg 540

tgtcaaggag actccctgag aacttattac gcgacctggt accagcagaa gccgggacag 600

gcaccggtgc tggtgttcta cgacgaaaac aaccggccat ccgggattcc cgaccggttc 660

tccggctcat cgagcggcaa cactgcctcc ctgaccatca ccgggaccca ggccgaggac 720

gaggccgatt actactgctc ctcgcgggac tcctccggca acccctcctg cgtgttcggc 780

ggtggaacca agctgactgt cctcaccact accccagcac cgaggccacc caccccggct 840

cctaccatcg cctcccagcc tctgtccctg cgtccggagg catgtagacc cgcagctggt 900

ggggccgtgc atacccgggg tcttgacttc gcctgcgata tctacatttg ggcccctctg 960

gctggtactt gcggggtcct gctgctttca ctcgtgatca ctctttactg taagcgcggt 1020

cggaagaagc tgctgtacat ctttaagcaa cccttcatga ggcctgtgca gactactcaa 1080

gaggaggacg gctgttcatg ccggttccca gaggaggagg aaggcggctg cgaactgcgc 1140

gtgaaattca gccgcagcgc agatgctcca gcctacaagc aggggcagaa ccagctctac 1200

aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

gacccagaaa tgggcgggaa gccgcgcaga aagaatcccc aagagggcct gtacaacgag 1320

ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 292
<211> 243
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 292
Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

```
Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Gly Val Val Ala Val Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser
    130                 135                 140

Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser
145                 150                 155                 160

Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly
                165                 170                 175

Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly
            180                 185                 190

Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu
        195                 200                 205

Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser
    210                 215                 220

Ser Tyr Thr Ser Ser Ser Thr Trp Val Phe Gly Gly Gly Thr Lys Leu
225                 230                 235                 240
```

Thr Val Leu

<210> 293
<211> 729
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 293
gaagtgcaac tcgtcgaatc tggagcggaa gtcaagaagc ctggagcaag cgtgaaagtg 60

tcctgtaaag cgtccggtta caccttcact tcgtattaca tgcactgggt ccgccaagct 120

ccgggacagg gactggaatg gatgggcatc atcaacccta gcggaggatc gacctcctac 180

gcccaaaagt tccagggcag agtgaccatg acccgggaca ccagcacatc aactgcctac 240

atggagctgt catcactgag gtccgaggat accgccgtgt actattgcgc ccgcgaggcc 300

ggcgtggtgg ccgtcgacta ctggggacag ggcactctcg tgaccgtgtc atcgggaggc 360

ggcggttccg gggggggagg gtcgggggggc ggaggctccc agtccgcact gacgcagccg 420

gcttccgtgt ctggttcgcc cggacagtcc atcaccattt cctgcactgg aaccagcagc 480

gacgtgggcg gttacaacta cgtgtcatgg taccagcagc atcccggaaa ggccccaaag 540

cttatgatct acgacgtgtc caatcggccg tcgggcgtca gcaaccggtt ctccggctcc 600

aagtccggga acactgccag cctgaccatt agcgggctgc aggccgagga cgaagcggat 660

tactactgct cctcctacac ttcctcctcg acctgggtgt ttggtggagg caccaagttg 720

actgtgctg 729

<210> 294
<211> 822
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 294
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aactcgtcga atctggagcg gaagtcaaga agcctggagc aagcgtgaaa 120

gtgtcctgta aagcgtccgg ttacaccttc acttcgtatt acatgcactg ggtccgccaa 180

gctccgggac agggactgga atggatgggc atcatcaacc ctagcggagg atcgacctcc 240

tacgcccaaa agttccaggg cagagtgacc atgacccggg acaccagcac atcaactgcc 300

tacatggagc tgtcatcact gaggtccgag gataccgccg tgtactattg cgcccgcgag 360

gccggcgtgg tggccgtcga ctactgggga cagggcactc tcgtgaccgt gtcatcggga 420

ggcggcggtt ccgggggggg agggtcgggg ggcggaggct cccagtccgc actgacgcag 480

ccggcttccg tgtctggttc gcccggacag tccatcacca tttcctgcac tggaaccagc 540

agcgacgtgg gcggttacaa ctacgtgtca tggtaccagc agcatcccgg aaaggcccca 600

aagcttatga tctacgacgt gtccaatcgg ccgtcgggcg tcagcaaccg gttctccggc 660

tccaagtccg ggaacactgc cagcctgacc attagcgggc tgcaggccga ggacgaagcg 720

gattactact gctcctccta cacttcctcc tcgacctggg tgtttggtgg aggcaccaag 780

ttgactgtgc tgggatcgca ccaccatcac catcatcatc ac 822

<210> 295
<211> 274
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 295
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Glu Ala Gly Val Val Ala Val Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln
145                 150                 155                 160

Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys
                165                 170                 175

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr
            180                 185                 190

Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser
        195                 200                 205
```

```
Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly
    210                 215                 220

Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala
225                 230                 235                 240

Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Trp Val Phe Gly
                245                 250                 255

Gly Gly Thr Lys Leu Thr Val Leu Gly Ser His His His His His His
            260                 265                 270

His His
```

<210> 296
<211> 487
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 296

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60
```

```
Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80


Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95


Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110


Ala Val Tyr Tyr Cys Ala Arg Glu Ala Gly Val Val Ala Val Asp Tyr
        115                 120                 125


Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
    130                 135                 140


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln
145                 150                 155                 160


Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys
                165                 170                 175


Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr
            180                 185                 190


Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser
        195                 200                 205


Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly
    210                 215                 220


Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala
225                 230                 235                 240


Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Trp Val Phe Gly
                245                 250                 255
```

```
Gly Gly Thr Lys Leu Thr Val Leu Thr Thr Thr Pro Ala Pro Arg Pro
            260                 265                 270

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
        275                 280                 285

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
    290                 295                 300

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
305                 310                 315                 320

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
                325                 330                 335

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
            340                 345                 350

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
        355                 360                 365

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
    370                 375                 380

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
385                 390                 395                 400

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
                405                 410                 415

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
            420                 425                 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
        435                 440                 445
```

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
450 455 460

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465 470 475 480

Met Gln Ala Leu Pro Pro Arg
485

<210> 297
<211> 1461
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 297
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aactcgtcga atctggagcg gaagtcaaga agcctggagc aagcgtgaaa 120

gtgtcctgta aagcgtccgg ttacaccttc acttcgtatt acatgcactg ggtccgccaa 180

gctccgggac agggactgga atggatgggc atcatcaacc ctagcggagg atcgacctcc 240

tacgcccaaa agttccaggg cagagtgacc atgacccggg acaccagcac atcaactgcc 300

tacatggagc tgtcatcact gaggtccgag gataccgccg tgtactattg cgcccgcgag 360

gccggcgtgg tggccgtcga ctactgggga cagggcactc tcgtgaccgt gtcatcggga 420

ggcggcggtt ccgggggggg agggtcgggg ggcggaggct cccagtccgc actgacgcag 480

ccggcttccg tgtctggttc gcccggacag tccatcacca tttcctgcac tggaaccagc 540

agcgacgtgg gcggttacaa ctacgtgtca tggtaccagc agcatcccgg aaaggcccca 600

aagcttatga tctacgacgt gtccaatcgg ccgtcgggcg tcagcaaccg gttctccggc 660

tccaagtccg ggaacactgc cagcctgacc attagcgggc tgcaggccga ggacgaagcg 720

gattactact gctcctccta cacttcctcc tcgacctggg tgtttggtgg aggcaccaag 780

ttgactgtgc tgaccactac cccagcaccg aggccaccca ccccggctcc taccatcgcc 840

tcccagcctc tgtccctgcg tccggaggca tgtagacccg cagctggtgg ggccgtgcat 900

acccggggtc ttgacttcgc ctgcgatatc tacatttggg cccctctggc tggtacttgc 960

ggggtcctgc tgctttcact cgtgatcact ctttactgta agcgcggtcg gaagaagctg 1020

ctgtacatct ttaagcaacc cttcatgagg cctgtgcaga ctactcaaga ggaggacggc 1080

tgttcatgcc ggttcccaga ggaggaggaa ggcggctgcg aactgcgcgt gaaattcagc 1140

cgcagcgcag atgctccagc ctacaagcag gggcagaacc agctctacaa cgaactcaat 1200

cttggtcgga gagaggagta cgacgtgctg gacaagcgga gaggacggga cccagaaatg 1260

ggcgggaagc cgcgcagaaa gaatccccaa gagggcctgt acaacgagct ccaaaaggat 1320

aagatggcag aagcctatag cgagattggt atgaaagggg aacgcagaag aggcaaaggc 1380

cacgacggac tgtaccaggg actcagcacc gccaccaagg acacctatga cgctcttcac 1440

atgcaggccc tgccgcctcg g 1461

<210> 298
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 298
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

```
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Glu Pro Leu Phe Gly Val Val Glu Glu Asp Val Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met Thr Gln Ser
    130                 135                 140

Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys
145                 150                 155                 160

Arg Ser Ser Gln Ser Leu Leu Ala Gly Asn Gly His Asn Tyr Leu Asp
                165                 170                 175

Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu
            180                 185                 190

Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
        195                 200                 205

Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp
    210                 215                 220

Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln Asn Pro Leu Thr Phe
225                 230                 235                 240
```

Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
245 250

<210> 299
<211> 750
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 299
caagtgcagt tggtccagag cggaggagga gtggtgcaac ccggaagatc attgaggctc 60

tcatgtgctg caagcggatt caccttctcg agctacgcaa tgtcctgggt gcgccaggcc 120

cctggaaagg gactggaatg ggtgtccgcc atctcgggct ccggcggatc aacgtactac 180

gccgactccg tgaagggccg ctttactatt tcaagagaca actccaagaa cactctgtac 240

ctccaaatga actctctgcg ggccgaggac accgccgtgt actactgcgc gaaggagccg 300

ctgttcggcg tggtggagga agatgtggac tactggggcc agggcactct cgtcaccgtg 360

tcctccggcg gtggaggatc gggaggcgga ggcagcgggg gtggtggctc cgacgtcgtg 420

atgacccagt cgcccctgtc cctgcccgtg acccctgggg aaccggcctc catttcctgc 480

cggtccagcc agtcgctgct ggctggaaac ggacacaatt accttgattg gtatctgcaa 540

aagcctgggc agtcaccgca gctgctgatc tacctcggaa gcaaccgggc gtccggggtg 600

ccggaccggt tctccggttc cgggagcggc accgacttca ccctgaaaat ctcgagggtg 660

gaggccgaag atgtcggagt gtactattgc atgcaggcgc ttcagaaccc actcactttc 720

gggggcggta ctaagctgga aatcaagcgc 750

<210> 300
<211> 843
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 300
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agttggtcca gagcggagga ggagtggtgc aacccggaag atcattgagg 120

ctctcatgtg ctgcaagcgg attcaccttc tcgagctacg caatgtcctg ggtgcgccag 180

gcccctggaa agggactgga atgggtgtcc gccatctcgg gctccggcgg atcaacgtac 240

tacgccgact ccgtgaaggg ccgctttact atttcaagag acaactccaa gaacactctg 300

tacctccaaa tgaactctct gcgggccgag gacaccgccg tgtactactg cgcgaaggag 360

ccgctgttcg gcgtggtgga ggaagatgtg gactactggg gccagggcac tctcgtcacc 420

gtgtcctccg gcggtggagg atcgggaggc ggaggcagcg ggggtggtgg ctccgacgtc 480

gtgatgaccc agtcgccccc gtccctgccc gtgaccctg gggaaccggc ctccatttcc 540

tgccggtcca gccagtcgct gctggctgga aacggacaca attaccttga ttggtatctg 600

caaaagcctg ggcagtcacc gcagctgctg atctacctcg gaagcaaccg ggcgtccggg 660

gtgccggacc ggttctccgg ttccgggagc ggcaccgact tcaccctgaa aatctcgagg 720

gtggaggccg aagatgtcgg agtgtactat tgcatgcagg cgcttcagaa cccactcact 780

ttcgggggcg gtactaagct ggaaatcaag cgcggatcgc accaccatca ccatcatcat 840

cac 843

<210> 301
<211> 281
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 301

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val
            20                  25                  30

Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45

Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
                85                  90                  95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Lys Glu Pro Leu Phe Gly Val Val Glu Glu
        115                 120                 125

Asp Val Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val
145                 150                 155                 160

Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro
                165                 170                 175

Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Ala Gly Asn Gly
            180                 185                 190
```

```
His Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln
        195                 200                 205


Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg
    210                 215                 220


Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg
225                 230                 235                 240


Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln
                245                 250                 255


Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Gly
            260                 265                 270


Ser His His His His His His His His
        275                 280


<210> 302
<211> 494
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 302
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val
            20                  25                  30


Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45
```

```
Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
                85                  90                  95

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Lys Glu Pro Leu Phe Gly Val Val Glu Glu
        115                 120                 125

Asp Val Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val
145                 150                 155                 160

Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro
                165                 170                 175

Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Ala Gly Asn Gly
            180                 185                 190

His Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln
        195                 200                 205

Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg
    210                 215                 220

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg
225                 230                 235                 240
```

```
Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln
                245                 250                 255

Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr
            260                 265                 270

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
        275                 280                 285

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
    290                 295                 300

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
305                 310                 315                 320

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
                325                 330                 335

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
            340                 345                 350

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
        355                 360                 365

Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
    370                 375                 380

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn
385                 390                 395                 400

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
                405                 410                 415

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
            420                 425                 430
```

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
435 440 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
450 455 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465 470 475 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 303
<211> 1482
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 303
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agttggtcca gagcggagga ggagtggtgc aacccggaag atcattgagg 120

ctctcatgtg ctgcaagcgg attcaccttc tcgagctacg caatgtcctg ggtgcgccag 180

gcccctggaa agggactgga atgggtgtcc gccatctcgg gctccggcgg atcaacgtac 240

tacgccgact ccgtgaaggg ccgctttact atttcaagag acaactccaa gaacactctg 300

tacctccaaa tgaactctct gcgggccgag gacaccgccg tgtactactg cgcgaaggag 360

ccgctgttcg gcgtggtgga ggaagatgtg gactactggg gccagggcac tctcgtcacc 420

gtgtcctccg gcggtggagg atcgggaggc ggaggcagcg ggggtggtgg ctccgacgtc 480

gtgatgaccc agtcgccccc gtccctgccc gtgaccctg gggaaccggc ctccatttcc 540

tgccggtcca gccagtcgct gctggctgga aacggacaca attaccttga ttggtatctg 600

caaaagcctg ggcagtcacc gcagctgctg atctacctcg gaagcaaccg ggcgtccggg 660

gtgccggacc ggttctccgg ttccgggagc ggcaccgact tcaccctgaa aatctcgagg 720

gtggaggccg aagatgtcgg agtgtactat tgcatgcagg cgcttcagaa cccactcact 780

ttcgggggcg gtactaagct ggaaatcaag cgcaccacta ccccagcacc gaggccaccc 840

accccggctc ctaccatcgc ctcccagcct ctgtccctgc gtccggaggc atgtagaccc 900

gcagctggtg gggccgtgca tacccggggt cttgacttcg cctgcgatat ctacatttgg 960

gcccctctgg ctggtacttg cggggtcctg ctgctttcac tcgtgatcac tctttactgt 1020

aagcgcggtc ggaagaagct gctgtacatc tttaagcaac ccttcatgag gcctgtgcag 1080

actactcaag aggaggacgg ctgttcatgc cggttcccag aggaggagga aggcggctgc 1140

gaactgcgcg tgaaattcag ccgcagcgca gatgctccag cctacaagca ggggcagaac 1200

cagctctaca acgaactcaa tcttggtcgg agagaggagt acgacgtgct ggacaagcgg 1260

agaggacggg acccagaaat gggcgggaag ccgcgcagaa agaatcccca agagggcctg 1320

tacaacgagc tccaaaagga taagatggca gaagcctata gcgagattgg tatgaaaggg 1380

gaacgcagaa gaggcaaagg ccacgacgga ctgtaccagg gactcagcac cgccaccaag 1440

gacacctatg acgctcttca catgcaggcc ctgccgcctc gg 1482

<210> 304
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 304
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

```
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Ser Gly Ser Leu Gly Asp Ala Phe Asp Ile Trp Gly Gln
            100                 105                 110

Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser
    130                 135                 140

Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Ser
145                 150                 155                 160

Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His
                165                 170                 175

Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Val Ser Asn Arg Pro
            180                 185                 190

Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala
        195                 200                 205

Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr
    210                 215                 220
```

Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Val Phe Gly Thr Gly Thr
225 230 235 240

Lys Val Thr Val Leu
245

<210> 305
<211> 735
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 305
caagtccaac tcgtccaaag cggagctgaa gtcaagaagc ctggagcgtc agtgaaagtg 60

tcctgcaagg cctccggcta cacgtttact tcctactaca tgcattgggt gcggcaggcc 120

ccaggtcaag gactggaatg gatgggcatc attaaccctt ccgggggtc cacctcgtat 180

gcgcagaagt tccagggcag agtgaccatg acccgcgaca cctccacctc cactgtgtac 240

atggaactgt ccagcctgag gtctgaggac actgccgtgt actactgtgc gcgcggtagc 300

ggatcactgg gcgatgcctt cgacatctgg ggccagggaa ctatggtcac cgtgtcctcc 360

gggggagggg gctcgggtgg aggaggttca ggcggaggag gctcccagag cgcattgaca 420

cagcccgctt cggtgtccgg ctccccggga cagtccatta ccatctcgtg caccggaagc 480

tcaagcgatg tcggagggta caactacgtg tcgtggtatc agcagcaccc gggaaaggcc 540

cccaagctca tgatctacga agtgtccaat cggccgtccg gggtgtcgaa ccggttcagc 600

ggttccaagt cgggcaacac tgccagcctg accatcagcg ggctgcaggc cgaggacgag 660

gccgactact actgctcctc gtacacctcc tcctcaaccc tggtgttcgg cactggaact 720

aaggtcaccg tgctt 735

<210> 306

<211> 828
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 306
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca aagcggagct gaagtcaaga agcctggagc gtcagtgaaa 120

gtgtcctgca aggcctccgg ctacacgttt acttcctact acatgcattg ggtgcggcag 180

gccccaggtc aaggactgga atggatgggc atcattaacc cttccggggg gtccacctcg 240

tatgcgcaga agttccaggg cagagtgacc atgacccgcg acacctccac ctccactgtg 300

tacatggaac tgtccagcct gaggtctgag gacactgccg tgtactactg tgcgcgcggt 360

agcggatcac tgggcgatgc cttcgacatc tggggccagg gaactatggt caccgtgtcc 420

tccgggggag ggggctcggg tggaggaggt tcaggcggag gaggctccca gagcgcattg 480

acacagcccg cttcggtgtc cggctccccg ggacagtcca ttaccatctc gtgcaccgga 540

agctcaagcg atgtcggagg gtacaactac gtgtcgtggt atcagcagca cccgggaaag 600

gcccccaagc tcatgatcta cgaagtgtcc aatcggccgt ccggggtgtc gaaccggttc 660

agcggttcca agtcgggcaa cactgccagc ctgaccatca gcgggctgca ggccgaggac 720

gaggccgact actactgctc ctcgtacacc tcctcctcaa ccctggtgtt cggcactgga 780

actaaggtca ccgtgcttgg atcgcaccac catcaccatc atcatcac 828

<210> 307
<211> 276
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 307

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Ser Gly Ser Leu Gly Asp Ala Phe
        115                 120                 125

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
145                 150                 155                 160

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
                165                 170                 175

Ser Cys Thr Gly Ser Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
            180                 185                 190
```

```
Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu
        195                 200                 205

Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys
    210                 215                 220

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
225                 230                 235                 240

Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Val
                245                 250                 255

Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Ser His His His His
            260                 265                 270

His His His His
        275


<210> 308
<211> 489
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 308
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45
```

```
Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Ser Gly Ser Leu Gly Asp Ala Phe
        115                 120                 125

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
145                 150                 155                 160

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
                165                 170                 175

Ser Cys Thr Gly Ser Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
            180                 185                 190

Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu
        195                 200                 205

Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys
    210                 215                 220

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
225                 230                 235                 240
```

```
Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Val
                245                 250                 255

Phe Gly Thr Gly Thr Lys Val Thr Val Leu Thr Thr Thr Pro Ala Pro
            260                 265                 270

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
        275                 280                 285

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
    290                 295                 300

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
305                 310                 315                 320

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
                325                 330                 335

Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg
            340                 345                 350

Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro
        355                 360                 365

Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser
    370                 375                 380

Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu
385                 390                 395                 400

Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg
                405                 410                 415

Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln
            420                 425                 430
```

```
Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr
        435                 440                 445


Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp
    450                 455                 460


Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala
465                 470                 475                 480


Leu His Met Gln Ala Leu Pro Pro Arg
                485
```

<210> 309
<211> 1467
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 309

```
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg       60

ccccaagtcc aactcgtcca aagcggagct gaagtcaaga agcctggagc gtcagtgaaa      120

gtgtcctgca aggcctccgg ctacacgttt acttcctact acatgcattg ggtgcggcag      180

gccccaggtc aaggactgga atggatgggc atcattaacc cttccggggg gtccacctcg      240

tatgcgcaga agttccaggg cagagtgacc atgacccgcg acacctccac ctccactgtg      300

tacatggaac tgtccagcct gaggtctgag gacactgccg tgtactactg tgcgcgcggt      360

agcggatcac tgggcgatgc cttcgacatc tggggccagg gaactatggt caccgtgtcc      420

tccgggggag ggggctcggg tggaggaggt tcaggcggag gaggctccca gagcgcattg      480

acacagcccg cttcggtgtc cggctccccg ggacagtcca ttaccatctc gtgcaccgga      540

agctcaagcg atgtcggagg gtacaactac gtgtcgtggt atcagcagca cccgggaaag      600
```

gcccccaagc tcatgatcta cgaagtgtcc aatcggccgt ccggggtgtc gaaccggttc 660

agcggttcca agtcgggcaa cactgccagc ctgaccatca gcgggctgca ggccgaggac 720

gaggccgact actactgctc ctcgtacacc tcctcctcaa ccctggtgtt cggcactgga 780

actaaggtca ccgtgcttac cactacccca gcaccgaggc cacccacccc ggctcctacc 840

atcgcctccc agcctctgtc cctgcgtccg gaggcatgta gacccgcagc tggtggggcc 900

gtgcataccc ggggtcttga cttcgcctgc gatatctaca tttgggcccc tctggctggt 960

acttgcgggg tcctgctgct ttcactcgtg atcactcttt actgtaagcg cggtcggaag 1020

aagctgctgt acatctttaa gcaacccttc atgaggcctg tgcagactac tcaagaggag 1080

gacggctgtt catgccggtt cccagaggag gaggaaggcg gctgcgaact gcgcgtgaaa 1140

ttcagccgca gcgcagatgc tccagcctac aagcaggggc agaaccagct ctacaacgaa 1200

ctcaatcttg gtcggagaga ggagtacgac gtgctggaca agcggagagg acgggaccca 1260

gaaatgggcg ggaagccgcg cagaaagaat ccccaagagg gcctgtacaa cgagctccaa 1320

aaggataaga tggcagaagc ctatagcgag attggtatga aaggggaacg cagaagaggc 1380

aaaggccacg acggactgta ccagggactc agcaccgcca ccaaggacac ctatgacgct 1440

cttcacatgc aggccctgcc gcctcgg 1467

<210> 310
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 310
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

```
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Phe Gly Glu Leu Ser Gly Ala Phe Asp Ile Trp Gly
            100                 105                 110

Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala
    130                 135                 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly
145                 150                 155                 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln
                165                 170                 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser Asn Arg
            180                 185                 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr
        195                 200                 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr
    210                 215                 220
```

Tyr Cys Ser Ser Tyr Ala Ser Ser Ser Thr Leu Val Phe Gly Gly Gly
225 230 235 240

Thr Lys Val Thr Val Leu
245

<210> 311
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 311
caagtgcaac tcgtccagtc cggtgcagaa gtcaagaaac ccggagcctc cgtgaaagtg 60

tcctgcaagg cctccggcta cacgttcact tcatactaca tgcactgggt ccgccaggcg 120

cccggacagg gactggagtg gatgggcatc atcaaccctt ccggcggctc gacctcctac 180

gcccaaaagt tccagggaag agtgacaatg accagggata cttcaaccag cactgtctac 240

atggaactgt ctagcttgcg gtccgaggac actgccgtgt actattgcgc tcgggacggt 300

ttcggggagc tgtccggggc ctttgacatc tggggccagg ggactatggt gaccgtgtcc 360

tcgggcggag gcggcagcgg aggaggaggt tcgggaggcg gaggaagcca gtcagcactg 420

acccagccag cctcggtgtc cgggagcccg ggccagagca tcactatttc ctgtaccggg 480

acctcctccg acgtgggagg gtacaattac gtgtcatggt atcaacagca tccgggaaag 540

gcgccgaagc tgatgatcta cgacgtgtcg aaccgcccta gcggagtgtc caaccggttc 600

tccggttcga agtccgggaa caccgcgagc ctgaccatta gcggactcca ggccgaggat 660

gaagccgact actactgctc ctcctacgct tcatcgtcca ccctggtgtt cggtggtggc 720

accaaggtca ccgtgctt 738

<210> 312
<211> 831
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 312
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aactcgtcca gtccggtgca gaagtcaaga aacccggagc ctccgtgaaa 120

gtgtcctgca aggcctccgg ctacacgttc acttcatact acatgcactg ggtccgccag 180

gcgcccggac agggactgga gtggatgggc atcatcaacc cttccggcgg ctcgacctcc 240

tacgcccaaa agttccaggg aagagtgaca atgaccaggg atacttcaac cagcactgtc 300

tacatggaac tgtctagctt gcggtccgag gacactgccg tgtactattg cgctcgggac 360

ggtttcgggg agctgtccgg ggcctttgac atctggggcc aggggactat ggtgaccgtg 420

tcctcgggcg gaggcggcag cggaggagga ggttcgggag gcggaggaag ccagtcagca 480

ctgacccagc cagcctcggt gtccgggagc ccgggccaga gcatcactat ttcctgtacc 540

gggacctcct ccgacgtggg agggtacaat tacgtgtcat ggtatcaaca gcatccggga 600

aaggcgccga agctgatgat ctacgacgtg tcgaaccgcc ctagcggagt gtccaaccgg 660

ttctccggtt cgaagtccgg gaacaccgcg agcctgacca ttagcggact ccaggccgag 720

gatgaagccg actactactg ctcctcctac gcttcatcgt ccaccctggt gttcggtggt 780

ggcaccaagg tcaccgtgct tggatcgcac caccatcacc atcatcatca c 831

<210> 313
<211> 277
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polypeptide"

<400> 313

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Asp Gly Phe Gly Glu Leu Ser Gly Ala
        115                 120                 125

Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala
145                 150                 155                 160

Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr
                165                 170                 175

Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val
```

180 185 190

Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr
195 200 205

Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser
210 215 220

Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu
225 230 235 240

Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Ser Ser Ser Thr Leu
245 250 255

Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Ser His His His
260 265 270

His His His His His
275

<210> 314
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 314
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

```
Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Asp Gly Phe Gly Glu Leu Ser Gly Ala
        115                 120                 125

Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala
145                 150                 155                 160

Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr
                165                 170                 175

Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val
            180                 185                 190

Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr
        195                 200                 205

Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser
    210                 215                 220

Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu
225                 230                 235                 240
```

```
Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Ser Ser Ser Thr Leu
                245                 250                 255

Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430
```

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
435 440 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
450 455 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465 470 475 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 315
<211> 1470
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 315
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aactcgtcca gtccggtgca gaagtcaaga aacccggagc ctccgtgaaa 120

gtgtcctgca aggcctccgg ctacacgttc acttcatact acatgcactg ggtccgccag 180

gcgcccggac agggactgga gtggatgggc atcatcaacc cttccggcgg ctcgacctcc 240

tacgcccaaa agttccaggg aagagtgaca atgaccaggg atacttcaac cagcactgtc 300

tacatggaac tgtctagctt gcggtccgag gacactgccg tgtactattg cgctcgggac 360

ggtttcgggg agctgtccgg ggcctttgac atctggggcc aggggactat ggtgaccgtg 420

tcctcgggcg gaggcggcag cggaggagga ggttcgggag gcggaggaag ccagtcagca 480

ctgacccagc cagcctcggt gtccgggagc ccgggccaga gcatcactat ttcctgtacc 540

gggacctcct ccgacgtggg agggtacaat tacgtgtcat ggtatcaaca gcatccggga 600

aaggcgccga agctgatgat ctacgacgtg tcgaaccgcc ctagcggagt gtccaaccgg 660

ttctccggtt cgaagtccgg gaacaccgcg agcctgacca ttagcggact ccaggccgag 720

gatgaagccg actactactg ctcctcctac gcttcatcgt ccaccctggt gttcggtggt 780

ggcaccaagg tcaccgtgct taccactacc ccagcaccga ggccacccac cccggctcct 840

accatcgcct cccagcctct gtccctgcgt ccggaggcat gtagacccgc agctggtggg 900

gccgtgcata cccggggtct tgacttcgcc tgcgatatct acatttgggc ccctctggct 960

ggtacttgcg gggtcctgct gctttcactc gtgatcactc tttactgtaa gcgcggtcgg 1020

aagaagctgc tgtacatctt taagcaaccc ttcatgaggc ctgtgcagac tactcaagag 1080

gaggacggct gttcatgccg gttcccagag gaggaggaag gcggctgcga actgcgcgtg 1140

aaattcagcc gcagcgcaga tgctccagcc tacaagcagg ggcagaacca gctctacaac 1200

gaactcaatc ttggtcggag agaggagtac gacgtgctgg acaagcggag aggacgggac 1260

ccagaaatgg gcgggaagcc gcgcagaaag aatccccaag agggcctgta caacgagctc 1320

caaaaggata agatggcaga agcctatagc gagattggta tgaaagggga acgcagaaga 1380

ggcaaaggcc acgacggact gtaccaggga ctcagcaccg ccaccaagga cacctatgac 1440

gctcttcaca tgcaggccct gccgcctcgg 1470

<210> 316
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 316
Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr

```
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Pro Ile Gly Cys Ser Gly Gly Ser Cys Leu Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro
    130                 135                 140

Ala Tyr Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr
145                 150                 155                 160

Gly Thr Asn Ser Asp Val Gly Arg Tyr Asn Tyr Val Ser Trp Tyr Gln
                165                 170                 175

Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Val Ser Tyr
            180                 185                 190

Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn
        195                 200                 205

Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp
```

210 215 220

Tyr Tyr Cys Ser Ser Tyr Thr Thr Ser Ser Thr Leu Asp Phe Gly Thr
225 230 235 240

Gly Thr Lys Val Thr Val Leu
245

<210> 317
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 317
gaagtgcaac tcgtcgaatc aggagcagaa gtcaagaaac caggagcctc cgtgaaagtc 60

agctgcaagg cctcgggcta cactttcact tcctactaca tgcattgggt gcgccaggcc 120

ccgggccagg gactggaatg gatgggcatc atcaatccct cgggaggttc cactagctac 180

gcgcagaagt tccagggaag agtgaccatg accagagaca cctcgacttc gacggtgtac 240

atggagctga gctccctgag gagcgaggac actgccgtgt actactgcgc ccggggcccg 300

atcggatgca gcgggggggtc ctgtctcgat tactggggcc agggcacact cgtgaccgtg 360

tccagcgggg gcggtggtag cggaggaggg ggatcgggcg gtggaggatc gcagtccgcc 420

ctgacccaac cggcgtacgt gtctggatca cccggacagt ccattaccat ctcctgcacc 480

ggaaccaact cggacgtggg ccgctacaac tacgtgtcat ggtaccagca gcaccccggg 540

aaggctccta agctgatgat ctacgaggtg tcctatcggc ctagcggtgt cagcaaccgg 600

ttctccggct ccaagtccgg caacactgct tcccttacca tttccgggtt gcaagccgag 660

gacgaggccg attactactg ttcctcctat accacttcat ccaccctgga ctttggaacc 720

ggcaccaagg tcaccgtgct g 741

<210> 318
<211> 834
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 318
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aactcgtcga atcaggagca gaagtcaaga aaccaggagc ctccgtgaaa 120

gtcagctgca aggcctcggg ctacactttc acttcctact acatgcattg ggtgcgccag 180

gccccgggcc agggactgga atggatgggc atcatcaatc cctcgggagg ttccactagc 240

tacgcgcaga agttccaggg aagagtgacc atgaccagag acacctcgac ttcgacggtg 300

tacatggagc tgagctccct gaggagcgag gacactgccg tgtactactg cgcccggggc 360

ccgatcggat gcagcggggg gtcctgtctc gattactggg gccagggcac actcgtgacc 420

gtgtccagcg ggggcggtgg tagcggagga gggggatcgg gcggtggagg atcgcagtcc 480

gccctgaccc aaccggcgta cgtgtctgga tcacccggac agtccattac catctcctgc 540

accggaacca actcggacgt gggccgctac aactacgtgt catggtacca gcagcacccc 600

gggaaggctc ctaagctgat gatctacgag gtgtcctatc ggcctagcgg tgtcagcaac 660

cggttctccg gctccaagtc cggcaacact gcttccctta ccatttccgg gttgcaagcc 720

gaggacgagg ccgattacta ctgttcctcc tataccactt catccaccct ggactttgga 780

accggcacca aggtcaccgt gctgggatcg caccaccatc accatcatca tcac 834

<210> 319
<211> 278
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 319
```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15


His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val
            20                  25                  30


Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45


Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60


Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80


Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95


Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110


Ala Val Tyr Tyr Cys Ala Arg Gly Pro Ile Gly Cys Ser Gly Gly Ser
        115                 120                 125


Cys Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
    130                 135                 140


Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser
145                 150                 155                 160


Ala Leu Thr Gln Pro Ala Tyr Val Ser Gly Ser Pro Gly Gln Ser Ile
                165                 170                 175
```

Thr Ile Ser Cys Thr Gly Thr Asn Ser Asp Val Gly Arg Tyr Asn Tyr
180 185 190

Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile
195 200 205

Tyr Glu Val Ser Tyr Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly
210 215 220

Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
225 230 235 240

Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Thr Ser Ser Thr
245 250 255

Leu Asp Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Ser His His
260 265 270

His His His His His His
275

<210> 320
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 320
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr

```
        35                  40                  45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Pro Ile Gly Cys Ser Gly Gly Ser
        115                 120                 125

Cys Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser
145                 150                 155                 160

Ala Leu Thr Gln Pro Ala Tyr Val Ser Gly Ser Pro Gly Gln Ser Ile
                165                 170                 175

Thr Ile Ser Cys Thr Gly Thr Asn Ser Asp Val Gly Arg Tyr Asn Tyr
            180                 185                 190

Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile
        195                 200                 205

Tyr Glu Val Ser Tyr Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly
    210                 215                 220

Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
```

225 230 235 240

Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Thr Ser Ser Thr
245 250 255

Leu Asp Phe Gly Thr Gly Thr Lys Val Thr Val Leu Thr Thr Thr Pro
260 265 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
275 280 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
290 295 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305 310 315 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
325 330 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
340 345 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
355 360 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn

420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 321
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 321
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aactcgtcga atcaggagca gaagtcaaga aaccaggagc ctccgtgaaa 120

gtcagctgca aggcctcggg ctacactttc acttcctact acatgcattg ggtgcgccag 180

gccccgggcc agggactgga atggatgggc atcatcaatc cctcgggagg ttccactagc 240

tacgcgcaga agttccaggg aagagtgacc atgaccagag acacctcgac ttcgacggtg 300

tacatggagc tgagctccct gaggagcgag gacactgccg tgtactactg cgcccggggc 360

ccgatcggat gcagcggggg gtcctgtctc gattactggg gccagggcac actcgtgacc 420

gtgtccagcg ggggcggtgg tagcggagga gggggatcgg gcggtggagg atcgcagtcc 480

gccctgaccc aaccggcgta cgtgtctgga tcacccggac agtccattac catctcctgc 540

accggaacca actcggacgt gggccgctac aactacgtgt catggtacca gcagcacccc 600

gggaaggctc ctaagctgat gatctacgag gtgtcctatc ggcctagcgg tgtcagcaac 660

cggttctccg gctccaagtc cggcaacact gcttccctta ccatttccgg gttgcaagcc 720

gaggacgagg ccgattacta ctgttcctcc tataccactt catccaccct ggactttgga 780

accggcacca aggtcaccgt gctgaccact accccagcac cgaggccacc caccccggct 840

cctaccatcg cctcccagcc tctgtccctg cgtccggagg catgtagacc cgcagctggt 900

ggggccgtgc atacccgggg tcttgacttc gcctgcgata tctacatttg ggcccctctg 960

gctggtactt gcggggtcct gctgctttca ctcgtgatca ctctttactg taagcgcggt 1020

cggaagaagc tgctgtacat ctttaagcaa cccttcatga ggcctgtgca gactactcaa 1080

gaggaggacg gctgttcatg ccggttccca gaggaggagg aaggcggctg cgaactgcgc 1140

gtgaaattca gccgcagcgc agatgctcca gcctacaagc aggggcagaa ccagctctac 1200

aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

gacccagaaa tgggcgggaa gccgcgcaga aagaatcccc aagagggcct gtacaacgag 1320

ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 322
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 322
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Ser Tyr Gly Asp Tyr Gly Asp Ala Phe Asp Ile Trp Gly
            100                 105                 110

Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Ser Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala
    130                 135                 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly
145                 150                 155                 160

Thr Ser Ser Asp Val Gly Gly Tyr Lys Tyr Val Ser Trp Tyr Gln Gln
                165                 170                 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser Asn Arg
            180                 185                 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr
        195                 200                 205
```

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr
210 215 220

Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Val Phe Gly Gly Gly
225 230 235 240

Thr Lys Leu Thr Val Leu
245

<210> 323
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 323
caagtgcaac tcgtccagtc cggtgcagaa gtcaagaaac ccggagcctc cgtgaaagtg 60

tcctgcaagg cctcgggcta caccttcacc tcctactaca tgcactgggt gcgccaggcg 120

ccgggccagg gacttgagtg gatgggtatc atcaacccgt ccggcggaag cacctcgtac 180

gcccaaaagt ttcaggggag agtgaccatg accagggaca cttcaaccag caccgtgtac 240

atggaactgt caagcttgcg ctccgaggat actgccgtct actactgcgc ccggggatcg 300

tacggagact acggcgacgc tttcgatatc tggggacagg gcacaaccgt gaccgtgtcc 360

tccggcggag ggggctcggg cggaggaggc tcaggttccg gcgggagcca gtccgcactg 420

actcagccag cgtccgtgag cggtagccct gggcagtcta tcacgatttc gtgcactggc 480

acctcctccg acgtgggagg ctataagtac gtcagctggt accaacagca tccgggaaag 540

gcgcctaagc tgatgatcta tgacgtcagc aaccggccct ccggggtgtc aaaccggttc 600

agcggttcca agtcgggaaa taccgcctcc ctgaccatta gcgggctgca ggccgaagat 660

gaggctgact actactgttc ctcctacact tcatcgtcca ctctcgtgtt cgggggagga 720

actaagctca ccgtgctg 738

<210> 324
<211> 831
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 324
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aactcgtcca gtccggtgca gaagtcaaga aacccggagc ctccgtgaaa 120

gtgtcctgca aggcctcggg ctacaccttc acctcctact acatgcactg ggtgcgccag 180

gcgccgggcc agggacttga gtggatgggt atcatcaacc cgtccggcgg aagcacctcg 240

tacgcccaaa agtttcaggg gagagtgacc atgaccaggg acacttcaac cagcaccgtg 300

tacatggaac tgtcaagctt gcgctccgag gatactgccg tctactactg cgcccgggga 360

tcgtacggag actacggcga cgctttcgat atctggggac agggcacaac cgtgaccgtg 420

tcctccggcg gaggggctc gggcggagga ggctcaggtt ccggcgggag ccagtccgca 480

ctgactcagc cagcgtccgt gagcggtagc cctgggcagt ctatcacgat ttcgtgcact 540

ggcacctcct ccgacgtggg aggctataag tacgtcagct ggtaccaaca gcatccggga 600

aaggcgccta agctgatgat ctatgacgtc agcaaccggc cctccggggt gtcaaaccgg 660

ttcagcggtt ccaagtcggg aaataccgcc tccctgacca ttagcgggct gcaggccgaa 720

gatgaggctg actactactg ttcctcctac acttcatcgt ccactctcgt gttcgggggga 780

ggaactaagc tcaccgtgct gggatcgcac caccatcacc atcatcatca c 831

<210> 325
<211> 277
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 325

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Ser Tyr Gly Asp Tyr Gly Asp Ala
        115                 120                 125

Phe Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Ser Gly Gly Ser Gln Ser Ala
145                 150                 155                 160

Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr
                165                 170                 175
```

```
Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Lys Tyr Val
            180                 185                 190


Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr
        195                 200                 205


Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser
    210                 215                 220


Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu
225                 230                 235                 240


Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu
                245                 250                 255


Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser His His His
            260                 265                 270


His His His His His
        275
```

<210> 326
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 326

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30
```

```
Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Ser Tyr Gly Asp Tyr Gly Asp Ala
        115                 120                 125

Phe Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Ser Gly Gly Ser Gln Ser Ala
145                 150                 155                 160

Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr
                165                 170                 175

Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Lys Tyr Val
            180                 185                 190

Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr
        195                 200                 205

Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser
    210                 215                 220
```

```
Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu
225                 230                 235                 240


Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu
                245                 250                 255


Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Thr Thr Thr Pro Ala
            260                 265                 270


Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285


Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300


Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320


Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335


Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350


Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365


Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380


Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400


Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415
```

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
420 425 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
435 440 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
450 455 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465 470 475 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 327
<211> 1470
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 327
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aactcgtcca gtccggtgca gaagtcaaga aacccggagc ctccgtgaaa 120

gtgtcctgca aggcctcggg ctacaccttc acctcctact acatgcactg ggtgcgccag 180

gcgccgggcc agggacttga gtggatgggt atcatcaacc cgtccggcgg aagcacctcg 240

tacgcccaaa agtttcaggg gagagtgacc atgaccaggg acacttcaac cagcaccgtg 300

tacatggaac tgtcaagctt gcgctccgag gatactgccg tctactactg cgcccgggga 360

tcgtacggag actacggcga cgctttcgat atctggggac agggcacaac cgtgaccgtg 420

tcctccggcg gaggggctc gggcggagga ggctcaggtt ccggcgggag ccagtccgca 480

ctgactcagc cagcgtccgt gagcggtagc cctgggcagt ctatcacgat ttcgtgcact 540

ggcacctcct ccgacgtggg aggctataag tacgtcagct ggtaccaaca gcatccggga 600

aaggcgccta agctgatgat ctatgacgtc agcaaccggc cctccggggt gtcaaaccgg 660

ttcagcggtt ccaagtcggg aaataccgcc tccctgacca ttagcgggct gcaggccgaa 720

gatgaggctg actactactg ttcctcctac acttcatcgt ccactctcgt gttcgggggga 780

ggaactaagc tcaccgtgct gaccactacc ccagcaccga ggccacccac cccggctcct 840

accatcgcct cccagcctct gtccctgcgt ccggaggcat gtagacccgc agctggtggg 900

gccgtgcata cccggggtct tgacttcgcc tgcgatatct acatttgggc ccctctggct 960

ggtacttgcg gggtcctgct gctttcactc gtgatcactc tttactgtaa gcgcggtcgg 1020

aagaagctgc tgtacatctt taagcaaccc ttcatgaggc ctgtgcagac tactcaagag 1080

gaggacggct gttcatgccg gttcccagag gaggaggaag gcggctgcga actgcgcgtg 1140

aaattcagcc gcagcgcaga tgctccagcc tacaagcagg ggcagaacca gctctacaac 1200

gaactcaatc ttggtcggag agaggagtac gacgtgctgg acaagcggag aggacgggac 1260

ccagaaatgg gcgggaagcc gcgcagaaag aatccccaag agggcctgta caacgagctc 1320

caaaaggata agatggcaga agcctatagc gagattggta tgaaaggggga acgcagaaga 1380

ggcaaaggcc acgacggact gtaccaggga ctcagcaccg ccaccaagga cacctatgac 1440

gctcttcaca tgcaggccct gccgcctcgg 1470

<210> 328
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 328
Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp His Lys Val Val Arg Phe Gly Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser His Val Ile Leu Thr Gln Pro Pro Ser Ala Ser
    130                 135                 140

Ala Ser Leu Gly Ala Ser Val Lys Leu Thr Cys Thr Leu Ser Ser Gly
145                 150                 155                 160

His Ser Ser Tyr Ala Ile Ala Trp His Gln Gln Gln Pro Glu Lys Gly
                165                 170                 175

Pro Arg Tyr Leu Met Lys Val Asn Ser Asp Gly Ser Leu Ser Lys Gly
            180                 185                 190

Asp Gly Ile Pro Asp Arg Phe Ser Gly Ser Thr Ser Gly Ala Glu Arg
        195                 200                 205
```

Tyr Leu Thr Ile Ser Ser Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr
210 215 220

Cys Gln Thr Trp Gly Ser Gly Met Ala Ile Phe Gly Gly Gly Thr Lys
225 230 235 240

Leu Thr Val Leu

<210> 329
<211> 732
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 329
gaagtgcaat tggtggaatc aggcgcagaa gtcaagaaac ccggaagcag cgtgaaagtg 60

tcctgcaagg cctcaggagg caccttctcg tcctatgcca tttcctgggt ccgccaggcc 120

ccgggacagg gcctggaatg gatgggcgga attatcccta tcttcggaac cgcgaactac 180

gcccagaagt ttcagggacg cgtgaccatc actgccgatg aatcaacctc cactgcgtac 240

atggaactgt cctccctgcg gagcgaggac accgccgtgt actactgcgc aagggatcat 300

aaggtcgtgc ggttcggata ctggggacag ggaacccttg tgaccgtgtc ctccggcggc 360

gggggtccg gcggaggggg ttccgggggga ggcggatcgc acgtgatcct gactcaacca 420

ccctcagcct ccgcctctct gggagccagc gtgaagctca cctgtactct gagctcggga 480

cactcgtcgt acgccatcgc ttggcaccag cagcagccgg agaaggggcc tagatacctg 540

atgaaggtca actccgacgg ttcgctgagc aagggcgacg gcatcccgga tcggttcagc 600

ggttccacgt ccggcgcgga gagatacctc acaatctcct cgctccaatc cgaggacgag 660

gctgactact actgccagac ctggggtagc ggcatggcga ttttcggggg tggaactaag 720

ctgaccgtgc tg 732

<210> 330
<211> 825
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 330
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aattggtgga atcaggcgca gaagtcaaga aacccggaag cagcgtgaaa 120

gtgtcctgca aggcctcagg aggcaccttc tcgtcctatg ccatttcctg ggtccgccag 180

gccccgggac agggcctgga atggatgggc ggaattatcc ctatcttcgg aaccgcgaac 240

tacgcccaga agtttcaggg acgcgtgacc atcactgccg atgaatcaac ctccactgcg 300

tacatggaac tgtcctccct gcggagcgag gacaccgccg tgtactactg cgcaagggat 360

cataaggtcg tgcggttcgg atactgggga cagggaaccc ttgtgaccgt gtcctccggc 420

ggcgggggt ccggcggagg gggttccggg ggaggcggat cgcacgtgat cctgactcaa 480

ccaccctcag cctccgcctc tctgggagcc agcgtgaagc tcacctgtac tctgagctcg 540

ggacactcgt cgtacgccat cgcttggcac cagcagcagc cggagaaggg gcctagatac 600

ctgatgaagg tcaactccga cggttcgctg agcaagggcg acggcatccc ggatcggttc 660

agcggttcca cgtccggcgc ggagagatac ctcacaatct cctcgctcca atccgaggac 720

gaggctgact actactgcca gacctggggt agcggcatgg cgattttcgg gggtggaact 780

aagctgaccg tgctgggatc gcaccaccat caccatcatc atcac 825

<210> 331
<211> 275
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 331

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly
        35                  40                  45

Thr Phe Ser Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser
                85                  90                  95

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Asp His Lys Val Val Arg Phe Gly Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser His Val Ile Leu Thr Gln
145                 150                 155                 160

Pro Pro Ser Ala Ser Ala Ser Leu Gly Ala Ser Val Lys Leu Thr Cys
                165                 170                 175
```

```
Thr Leu Ser Ser Gly His Ser Ser Tyr Ala Ile Ala Trp His Gln Gln
            180                 185                 190


Gln Pro Glu Lys Gly Pro Arg Tyr Leu Met Lys Val Asn Ser Asp Gly
        195                 200                 205


Ser Leu Ser Lys Gly Asp Gly Ile Pro Asp Arg Phe Ser Gly Ser Thr
    210                 215                 220


Ser Gly Ala Glu Arg Tyr Leu Thr Ile Ser Ser Leu Gln Ser Glu Asp
225                 230                 235                 240


Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Gly Ser Gly Met Ala Ile Phe
                245                 250                 255


Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser His His His His His
            260                 265                 270


His His His
        275


<210> 332
<211> 488
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 332
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val
            20                  25                  30
```

```
Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly
        35                  40                  45

Thr Phe Ser Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser
                85                  90                  95

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Asp His Lys Val Val Arg Phe Gly Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser His Val Ile Leu Thr Gln
145                 150                 155                 160

Pro Pro Ser Ala Ser Ala Ser Leu Gly Ala Ser Val Lys Leu Thr Cys
                165                 170                 175

Thr Leu Ser Ser Gly His Ser Ser Tyr Ala Ile Ala Trp His Gln Gln
            180                 185                 190

Gln Pro Glu Lys Gly Pro Arg Tyr Leu Met Lys Val Asn Ser Asp Gly
        195                 200                 205

Ser Leu Ser Lys Gly Asp Gly Ile Pro Asp Arg Phe Ser Gly Ser Thr
    210                 215                 220
```

```
Ser Gly Ala Glu Arg Tyr Leu Thr Ile Ser Ser Leu Gln Ser Glu Asp
225                 230                 235                 240


Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Gly Ser Gly Met Ala Ile Phe
                245                 250                 255


Gly Gly Gly Thr Lys Leu Thr Val Leu Thr Thr Thr Pro Ala Pro Arg
            260                 265                 270


Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
        275                 280                 285


Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
    290                 295                 300


Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
305                 310                 315                 320


Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg
                325                 330                 335


Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
            340                 345                 350


Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
        355                 360                 365


Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
    370                 375                 380


Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
385                 390                 395                 400


Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
                405                 410                 415
```

```
Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
            420                 425                 430

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
        435                 440                 445

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
    450                 455                 460

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
465                 470                 475                 480

His Met Gln Ala Leu Pro Pro Arg
                485
```

<210> 333
<211> 1464
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 333
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aattggtgga atcaggcgca gaagtcaaga aacccggaag cagcgtgaaa 120

gtgtcctgca aggcctcagg aggcaccttc tcgtcctatg ccatttcctg ggtccgccag 180

gccccgggac agggcctgga atggatgggc ggaattatcc ctatcttcgg aaccgcgaac 240

tacgcccaga agtttcaggg acgcgtgacc atcactgccg atgaatcaac ctccactgcg 300

tacatggaac tgtcctccct gcggagcgag gacaccgccg tgtactactg cgcaagggat 360

cataaggtcg tgcggttcgg atactgggga cagggaaccc ttgtgaccgt gtcctccggc 420

ggcgggggt ccggcggagg gggttccggg ggaggcggat cgcacgtgat cctgactcaa 480

ccaccctcag cctccgcctc tctgggagcc agcgtgaagc tcacctgtac tctgagctcg 540

ggacactcgt cgtacgccat cgcttggcac cagcagcagc cggagaaggg gcctagatac 600

ctgatgaagg tcaactccga cggttcgctg agcaagggcg acggcatccc ggatcggttc 660

agcggttcca cgtccggcgc ggagagatac ctcacaatct cctcgctcca atccgaggac 720

gaggctgact actactgcca gacctggggt agcggcatgg cgattttcgg gggtggaact 780

aagctgaccg tgctgaccac taccccagca ccgaggccac ccaccccggc tcctaccatc 840

gcctcccagc ctctgtccct gcgtccggag gcatgtagac ccgcagctgg tggggccgtg 900

catacccggg gtcttgactt cgcctgcgat atctacattt gggcccctct ggctggtact 960

tgcggggtcc tgctgctttc actcgtgatc actctttact gtaagcgcgg tcggaagaag 1020

ctgctgtaca tctttaagca acccttcatg aggcctgtgc agactactca agaggaggac 1080

ggctgttcat gccggttccc agaggaggag gaaggcggct gcgaactgcg cgtgaaattc 1140

agccgcagcg cagatgctcc agcctacaag caggggcaga accagctcta caacgaactc 1200

aatcttggtc ggagagagga gtacgacgtg ctggacaagc ggagaggacg ggacccagaa 1260

atgggcggga agccgcgcag aaagaatccc caagagggcc tgtacaacga gctccaaaag 1320

gataagatgg cagaagccta tagcgagatt ggtatgaaag gggaacgcag aagaggcaaa 1380

ggccacgacg gactgtacca gggactcagc accgccacca aggacaccta tgacgctctt 1440

cacatgcagg ccctgccgcc tcgg 1464

<210> 334
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 334
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Asp Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val
            100                 105                 110

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Ala Ser Gly Ser
    130                 135                 140

Pro Gly Gln Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val
145                 150                 155                 160

Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala
                165                 170                 175

Pro Lys Leu Met Ile Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Pro
            180                 185                 190

Asp Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile
        195                 200                 205
```

Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr
210 215 220

Thr Ser Ser Gly Thr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val
225 230 235 240

Leu

<210> 335
<211> 723
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 335
caagtgcaac tcgtccagtc cggtgcagaa gtcaagaaac ccggtgcttc cgtgaaagtg 60

tcctgcaagg cctcaggtta caccttcacc tcctactaca tgcattgggt ccgccaagcc 120

cccggacaag gcctggagtg gatgggaatt atcaacccgt ccggcggcag cacaagctac 180

gcccagaagt tccagggacg cgtgactatg accagagata cctccacctc caccgtgtac 240

atggaactgt cctcactccg gtcggaagat accgccgtgt actactgtgc ccggggagac 300

tactatatgg acgtctgggg aaagggcacc accgtgactg tgtcgtcggg cggcgggggt 360

tcgggaggag gaggaagcgg tggcgggggа agccagtccg cactgactca gcccgcgtcg 420

gccagcggga gccctggcca gagcgtgacc atttcgtgca ccggaacttc ctctgacgtc 480

ggcggataca actacgtgtc ctggtaccag cagcaccctg gaaaggcccc gaagctgatg 540

atctacgagg tgtccaagag gccatccggc gtgccggacc ggttttcggg atcaaagtcc 600

gggaacacgg ccagcctgac catcagcggg cttcaggctg aggacgaagc ggattactac 660

tgctcctcct atacttcatc cggcaccttg gtgttcggcg gagggactaa gctgactgtg 720

ctc 723

<210> 336
<211> 816
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 336
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aactcgtcca gtccggtgca gaagtcaaga aacccggtgc ttccgtgaaa 120

gtgtcctgca aggcctcagg ttacaccttc acctcctact acatgcattg ggtccgccaa 180

gcccccggac aaggcctgga gtggatggga attatcaacc cgtccggcgg cagcacaagc 240

tacgcccaga agttccaggg acgcgtgact atgaccagag atacctccac ctccaccgtg 300

tacatggaac tgtcctcact ccggtcggaa gataccgccg tgtactactg tgcccgggga 360

gactactata tggacgtctg gggaaagggc accaccgtga ctgtgtcgtc gggcggcggg 420

ggttcgggag gaggaggaag cggtggcggg ggaagccagt ccgcactgac tcagcccgcg 480

tcggccagcg ggagccctgg ccagagcgtg accatttcgt gcaccggaac ttcctctgac 540

gtcggcggat acaactacgt gtcctggtac cagcagcacc ctggaaaggc cccgaagctg 600

atgatctacg aggtgtccaa gaggccatcc ggcgtgccgg accggttttc gggatcaaag 660

tccgggaaca cggccagcct gaccatcagc gggcttcagg ctgaggacga agcggattac 720

tactgctcct cctatacttc atccggcacc ttggtgttcg gcggagggac taagctgact 780

gtgctcggat cgcaccacca tcaccatcat catcac 816

<210> 337
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 337
```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15


His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30


Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45


Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60


Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80


Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95


Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110


Ala Val Tyr Tyr Cys Ala Arg Gly Asp Tyr Tyr Met Asp Val Trp Gly
        115                 120                 125


Lys Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140


Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala
145                 150                 155                 160


Ser Ala Ser Gly Ser Pro Gly Gln Ser Val Thr Ile Ser Cys Thr Gly
```

```
                165                 170                 175

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln
            180                 185                 190

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Val Ser Lys Arg
        195                 200                 205

Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr
    210                 215                 220

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr
225                 230                 235                 240

Tyr Cys Ser Ser Tyr Thr Ser Ser Gly Thr Leu Val Phe Gly Gly Gly
                245                 250                 255

Thr Lys Leu Thr Val Leu Gly Ser His His His His His His His His
            260                 265                 270
```

<210> 338
<211> 485
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 338

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45
```

```
Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asp Tyr Tyr Met Asp Val Trp Gly
        115                 120                 125

Lys Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala
145                 150                 155                 160

Ser Ala Ser Gly Ser Pro Gly Gln Ser Val Thr Ile Ser Cys Thr Gly
                165                 170                 175

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln
            180                 185                 190

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Val Ser Lys Arg
        195                 200                 205

Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr
    210                 215                 220

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr
225                 230                 235                 240
```

```
Tyr Cys Ser Ser Tyr Thr Ser Ser Gly Thr Leu Val Phe Gly Gly Gly
                245                 250                 255

Thr Lys Leu Thr Val Leu Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
            260                 265                 270

Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
        275                 280                 285

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
    290                 295                 300

Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
305                 310                 315                 320

Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys
                325                 330                 335

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
            340                 345                 350

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
        355                 360                 365

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
    370                 375                 380

Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
385                 390                 395                 400

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
                405                 410                 415

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
            420                 425                 430
```

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
435 440 445

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
450 455 460

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
465 470 475 480

Ala Leu Pro Pro Arg
485

<210> 339
<211> 1455
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 339
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aactcgtcca gtccggtgca gaagtcaaga aacccggtgc ttccgtgaaa 120

gtgtcctgca aggcctcagg ttacaccttc acctcctact acatgcattg ggtccgccaa 180

gcccccggac aaggcctgga gtggatggga attatcaacc cgtccggcgg cagcacaagc 240

tacgcccaga agttccaggg acgcgtgact atgaccagag atacctccac ctccaccgtg 300

tacatggaac tgtcctcact ccggtcggaa gataccgccg tgtactactg tgcccgggga 360

gactactata tggacgtctg gggaaagggc accaccgtga ctgtgtcgtc gggcggcggg 420

ggttcgggag gaggaggaag cggtggcggg ggaagccagt ccgcactgac tcagcccgcg 480

tcggccagcg ggagccctgg ccagagcgtg accatttcgt gcaccggaac ttcctctgac 540

gtcggcggat acaactacgt gtcctggtac cagcagcacc ctggaaaggc cccgaagctg 600

atgatctacg aggtgtccaa gaggccatcc ggcgtgccgg accggttttc gggatcaaag 660

tccgggaaca cggccagcct gaccatcagc gggcttcagg ctgaggacga agcggattac 720

tactgctcct cctatacttc atccggcacc ttggtgttcg gcggagggac taagctgact 780

gtgctcacca ctaccccagc accgaggcca cccaccccgg ctcctaccat cgcctcccag 840

cctctgtccc tgcgtccgga ggcatgtaga cccgcagctg gtggggccgt gcatacccgg 900

ggtcttgact tcgcctgcga tatctacatt tgggcccctc tggctggtac ttgcggggtc 960

ctgctgcttt cactcgtgat cactctttac tgtaagcgcg gtcggaagaa gctgctgtac 1020

atctttaagc aacccttcat gaggcctgtg cagactactc aagaggagga cggctgttca 1080

tgccggttcc cagaggagga ggaaggcggc tgcgaactgc gcgtgaaatt cagccgcagc 1140

gcagatgctc cagcctacaa gcaggggcag aaccagctct acaacgaact caatcttggt 1200

cggagagagg agtacgacgt gctggacaag cggagaggac gggacccaga aatgggcggg 1260

aagccgcgca gaaagaatcc ccaagagggc ctgtacaacg agctccaaaa ggataagatg 1320

gcagaagcct atagcgagat tggtatgaaa ggggaacgca gaagaggcaa aggccacgac 1380

ggactgtacc agggactcag caccgccacc aaggacacct atgacgctct tcacatgcag 1440

gccctgccgc ctcgg 1455

<210> 340
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 340
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

```
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Pro Ile Arg Tyr Phe Asp His Ser Lys Ala Phe Asp
            100                 105                 110

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Ser Glu Leu Thr
    130                 135                 140

Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr
145                 150                 155                 160

Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln
                165                 170                 175

Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg
            180                 185                 190

Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr
        195                 200                 205

Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr
```

210 215 220

Tyr Arg Asn Ser Arg Asp Ser Ser Gly Asn Pro Tyr Val Phe Gly Thr
225 230 235 240

Gly Thr Lys Val Thr Val Leu
245

<210> 341
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 341
gaagtgcaat tggtggaatc aggaggagga cttgtgcaac ctggaggatc tctgagactg 60

tcatgcgccg cgtcgggatt cactttctcc tcctacgcaa tgtcgtgggt cagacaggcc 120

cccggaaagg gcctggaatg ggtgtcatac atcagctcct cctcctccac gatctactac 180

gccgactctg tgaaggggcg gttcaccatt agccgggaca acgcaaagaa ctccctgtat 240

ctgcaaatga acagcctcag ggcggaagat accgccgtgt actactgtgc gcgcgatggt 300

ccgattcgct atttcgacca ctccaaggcc ttcgatatct ggggccaggg aaccatggtc 360

accgtgtcgt ccggtggagg cggcagcggg gggggcggaa gcggcggcgg gggttcatcc 420

tcggagctga ctcaggaccc cgccgtgtcc gtggctctgg gacagaccgt gcgcatcaca 480

tgccagggag attccctgcg gtcgtactac gcctcctggt accagcagaa accgggccag 540

gcccccgtcc tcgtgatcta cggaaagaac aacaggcctt cgggtatccc agaccggttc 600

agcggcagct ccagcggaaa caccgcaagc ctcactatta ccggggccca ggctgaggac 660

gaggccgact actaccggaa ctcccgcgac tcctcgggca atccgtacgt ctttggtact 720

gggaccaagg tcaccgtgct g 741

<210> 342
<211> 834
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 342
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aattggtgga atcaggagga ggacttgtgc aacctggagg atctctgaga 120

ctgtcatgcg ccgcgtcggg attcactttc tcctcctacg caatgtcgtg ggtcagacag 180

gcccccggaa agggcctgga atgggtgtca tacatcagct cctcctcctc cacgatctac 240

tacgccgact ctgtgaaggg gcggttcacc attagccggg acaacgcaaa gaactccctg 300

tatctgcaaa tgaacagcct cagggcggaa gataccgccg tgtactactg tgcgcgcgat 360

ggtccgattc gctatttcga ccactccaag gccttcgata tctggggcca gggaaccatg 420

gtcaccgtgt cgtccggtgg aggcggcagc gggggggggcg gaagcggcgg cgggggttca 480

tcctcggagc tgactcagga ccccgccgtg tccgtggctc tgggacagac cgtgcgcatc 540

acatgccagg gagattccct gcggtcgtac tacgcctcct ggtaccagca gaaaccgggc 600

caggcccccg tcctcgtgat ctacggaaag aacaacaggc cttcgggtat cccagaccgg 660

ttcagcggca gctccagcgg aaacaccgca agcctcacta ttaccggggc ccaggctgag 720

gacgaggccg actactaccg gaactcccgc gactcctcgg gcaatccgta cgtctttggt 780

actgggacca aggtcaccgt gctgggatcg caccaccatc accatcatca tcac 834

<210> 343
<211> 278
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 343
```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15


His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30


Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45


Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60


Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr
65                  70                  75                  80


Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
                85                  90                  95


Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110


Ala Val Tyr Tyr Cys Ala Arg Asp Gly Pro Ile Arg Tyr Phe Asp His
        115                 120                 125


Ser Lys Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser
    130                 135                 140


Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145                 150                 155                 160


Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
                165                 170                 175
```

```
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
            180                 185                 190


Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        195                 200                 205


Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    210                 215                 220


Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
225                 230                 235                 240


Asp Glu Ala Asp Tyr Tyr Arg Asn Ser Arg Asp Ser Ser Gly Asn Pro
                245                 250                 255


Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Ser His His
            260                 265                 270


His His His His His His
        275


<210> 344
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 344
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30


Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
```

```
        35                  40                  45

Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
                85                  90                  95

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Asp Gly Pro Ile Arg Tyr Phe Asp His
        115                 120                 125

Ser Lys Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145                 150                 155                 160

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
                165                 170                 175

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
            180                 185                 190

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        195                 200                 205

Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    210                 215                 220

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
```

225 230 235 240

Asp Glu Ala Asp Tyr Tyr Arg Asn Ser Arg Asp Ser Ser Gly Asn Pro
245 250 255

Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Thr Thr Thr Pro
260 265 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
275 280 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
290 295 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305 310 315 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
325 330 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
340 345 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
355 360 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn

420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 345
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 345
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc aattggtgga atcaggagga ggacttgtgc aacctggagg atctctgaga 120

ctgtcatgcg ccgcgtcggg attcactttc tcctcctacg caatgtcgtg ggtcagacag 180

gcccccggaa agggcctgga atgggtgtca tacatcagct cctcctcctc cacgatctac 240

tacgccgact ctgtgaaggg gcggttcacc attagccggg acaacgcaaa gaactccctg 300

tatctgcaaa tgaacagcct cagggcggaa gataccgccg tgtactactg tgcgcgcgat 360

ggtccgattc gctatttcga ccactccaag gccttcgata tctggggcca gggaaccatg 420

gtcaccgtgt cgtccggtgg aggcggcagc ggggggggcg gaagcggcgg cgggggttca 480

tcctcggagc tgactcagga ccccgccgtg tccgtggctc tgggacagac cgtgcgcatc 540

acatgccagg gagattccct gcggtcgtac tacgcctcct ggtaccagca gaaaccgggc 600

caggcccccg tcctcgtgat ctacggaaag aacaacaggc cttcgggtat cccagaccgg 660

ttcagcggca gctccagcgg aaacaccgca agcctcacta ttaccggggc ccaggctgag 720

gacgaggccg actactaccg gaactcccgc gactcctcgg gcaatccgta cgtctttggt 780

actgggacca aggtcaccgt gctgaccact accccagcac cgaggccacc caccccggct 840

cctaccatcg cctcccagcc tctgtccctg cgtccggagg catgtagacc cgcagctggt 900

ggggccgtgc atacccgggg tcttgacttc gcctgcgata tctacatttg ggcccctctg 960

gctggtactt gcggggtcct gctgctttca ctcgtgatca ctctttactg taagcgcggt 1020

cggaagaagc tgctgtacat ctttaagcaa cccttcatga ggcctgtgca gactactcaa 1080

gaggaggacg gctgttcatg ccggttccca gaggaggagg aaggcggctg cgaactgcgc 1140

gtgaaattca gccgcagcgc agatgctcca gcctacaagc aggggcagaa ccagctctac 1200

aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

gacccagaaa tgggcgggaa gccgcgcaga aagaatcccc aagagggcct gtacaacgag 1320

ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 346
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 346
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Met Asp Asp Ser Ser Gly Pro Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val
    130                 135                 140

Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser
145                 150                 155                 160

Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro
                165                 170                 175

Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Val Ser Asn Arg Pro Ser
            180                 185                 190

Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser
        195                 200                 205
```

Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
210 215 220

Ser Ser Tyr Thr Ser Ser Ser Thr Leu Val Phe Gly Thr Gly Thr Lys
225 230 235 240

Leu Thr Val Leu

<210> 347
<211> 732
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 347
caagtgcagc tcgtccagtc cggtgcagaa gtcaagaaac ccggtgcttc cgtgaaagtg 60

tcctgcaagg catccggcta cacgttcacc tcctactaca tgcattgggt ccgccaagcc 120

cccggccaag gcctggagtg gatggggatc attaacccaa gcggaggaag cactagctac 180

gcgcagaagt ttcagggccg cgtgaccatg accagggata cttccatctc caccgcttac 240

atggaactgt cgcggctgag aagcgacgac acagccgtgt actactgtgc ccgggaaatg 300

gacgactcct ccgggcctga ttactgggga caggggactc tggtcaccgt gtcgtccggt 360

ggaggcggat cgggggcgg aggttccggc ggaggggct cacagtccgc gctgacccag 420

ccggccagcg tgtcaggatc accgggccag agcatcacca tttcctgcac cggaacctca 480

tcggacgtcg gcggatataa ctacgtgtcg tggtaccagc agcaccctgg aaaggccccg 540

aagctcatga tctacgaggt gtccaataga cccagcggag tgtcgaaccg gttcagcggg 600

tccaagtcgg gaaacaccgc cagcttgacc atctctggac tgcaagccga ggacgaagcc 660

gattactact gctcctcgta tacttcctcc tcaacccttg tgttcggaac tggcactaag 720

ctgaccgtgc tc 732

<210> 348
<211> 825
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 348
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agctcgtcca gtccggtgca gaagtcaaga aacccggtgc ttccgtgaaa 120

gtgtcctgca aggcatccgg ctacacgttc acctcctact acatgcattg ggtccgccaa 180

gcccccggcc aaggcctgga gtggatgggg atcattaacc caagcggagg aagcactagc 240

tacgcgcaga agtttcaggg ccgcgtgacc atgaccaggg atacttccat ctccaccgct 300

tacatggaac tgtcgcggct gagaagcgac gacacagccg tgtactactg tgcccgggaa 360

atggacgact cctccgggcc tgattactgg ggacagggga ctctggtcac cgtgtcgtcc 420

ggtggaggcg gatcgggggg cggaggttcc ggcggagggg gctcacagtc cgcgctgacc 480

cagccggcca gcgtgtcagg atcaccgggc cagagcatca ccatttcctg caccggaacc 540

tcatcggacg tcggcggata taactacgtg tcgtggtacc agcagcaccc tggaaaggcc 600

ccgaagctca tgatctacga ggtgtccaat agacccagcg gagtgtcgaa ccggttcagc 660

gggtccaagt cgggaaacac cgccagcttg accatctctg gactgcaagc cgaggacgaa 720

gccgattact actgctcctc gtatacttcc tcctcaaccc ttgtgttcgg aactggcact 780

aagctgaccg tgctcggatc gcaccaccat caccatcatc atcac 825

<210> 349
<211> 275
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 349

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Glu Met Asp Asp Ser Ser Gly Pro Asp
        115                 120                 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr
145                 150                 155                 160

Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser
                165                 170                 175
```

```
Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp
            180                 185                 190


Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Val
        195                 200                 205


Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser
    210                 215                 220


Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu
225                 230                 235                 240


Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Val Phe
                245                 250                 255


Gly Thr Gly Thr Lys Leu Thr Val Leu Gly Ser His His His His His
            260                 265                 270


His His His
        275
```

<210> 350
<211> 488
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 350

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30
```

```
Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Glu Met Asp Asp Ser Ser Gly Pro Asp
        115                 120                 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr
145                 150                 155                 160

Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser
                165                 170                 175

Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp
            180                 185                 190

Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Val
        195                 200                 205

Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser
    210                 215                 220
```

```
Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu
225                 230                 235                 240


Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Val Phe
                245                 250                 255


Gly Thr Gly Thr Lys Leu Thr Val Leu Thr Thr Thr Pro Ala Pro Arg
            260                 265                 270


Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg
        275                 280                 285


Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly
    290                 295                 300


Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr
305                 310                 315                 320


Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg
                325                 330                 335


Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro
            340                 345                 350


Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu
        355                 360                 365


Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala
    370                 375                 380


Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu
385                 390                 395                 400


Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly
                405                 410                 415
```

Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu
420 425 430

Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser
435 440 445

Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly
450 455 460

Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu
465 470 475 480

His Met Gln Ala Leu Pro Pro Arg
485

<210> 351
<211> 1464
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 351
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agctcgtcca gtccggtgca gaagtcaaga aacccggtgc ttccgtgaaa 120

gtgtcctgca aggcatccgg ctacacgttc acctcctact acatgcattg ggtccgccaa 180

gcccccggcc aaggcctgga gtggatgggg atcattaacc caagcggagg aagcactagc 240

tacgcgcaga agtttcaggg ccgcgtgacc atgaccaggg atacttccat ctccaccgct 300

tacatggaac tgtcgcggct gagaagcgac gacacagccg tgtactactg tgcccgggaa 360

atggacgact cctccgggcc tgattactgg ggacagggga ctctggtcac cgtgtcgtcc 420

ggtggaggcg gatcgggggg cggaggttcc ggcggagggg gctcacagtc cgcgctgacc 480

cagccggcca gcgtgtcagg atcaccgggc cagagcatca ccatttcctg caccggaacc 540

tcatcggacg tcggcggata taactacgtg tcgtggtacc agcagcaccc tggaaaggcc 600

ccgaagctca tgatctacga ggtgtccaat agacccagcg gagtgtcgaa ccggttcagc 660

gggtccaagt cgggaaacac cgccagcttg accatctctg gactgcaagc cgaggacgaa 720

gccgattact actgctcctc gtatacttcc tcctcaaccc ttgtgttcgg aactggcact 780

aagctgaccg tgctcaccac taccccagca ccgaggccac ccaccccggc tcctaccatc 840

gcctcccagc ctctgtccct gcgtccggag gcatgtagac ccgcagctgg tggggccgtg 900

catacccggg gtcttgactt cgcctgcgat atctacattt gggcccctct ggctggtact 960

tgcggggtcc tgctgctttc actcgtgatc actctttact gtaagcgcgg tcggaagaag 1020

ctgctgtaca tctttaagca acccttcatg aggcctgtgc agactactca agaggaggac 1080

ggctgttcat gccggttccc agaggaggag gaaggcggct gcgaactgcg cgtgaaattc 1140

agccgcagcg cagatgctcc agcctacaag caggggcaga accagctcta caacgaactc 1200

aatcttggtc ggagagagga gtacgacgtg ctggacaagc ggagaggacg ggacccagaa 1260

atgggcggga agccgcgcag aaagaatccc caagagggcc tgtacaacga gctccaaaag 1320

gataagatgg cagaagccta tagcgagatt ggtatgaaag gggaacgcag aagaggcaaa 1380

ggccacgacg gactgtacca gggactcagc accgccacca aggacaccta tgacgctctt 1440

cacatgcagg ccctgccgcc tcgg 1464

<210> 352
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 352
Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

```
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Ser
            20                  25                  30

Trp Ile Gly Trp Gly Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Phe Leu Arg Gly Gly Asp Cys Cys Gly Ala Leu Asp Ile
            100                 105                 110

Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln
    130                 135                 140

Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser
145                 150                 155                 160

Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu
                165                 170                 175

Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr
            180                 185                 190

Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
        195                 200                 205
```

Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu
210 215 220

Asp Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln Thr Pro Pro Trp
225 230 235 240

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
245 250

<210> 353
<211> 756
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 353
gaagtgcagt tggtggaatc aggagcagaa gtcaagaaac ccggagaaag cctgaagatc 60

tcgtgcaaag ggagcggata ctcgttcacc ggatcatgga ttggatgggg ccgccagatg 120

cctggaaagg gtctggaatg gatgggaatc atctacccgg gggactccga tactcggtac 180

tccccgagct ttcagggcca ggtcaccatc tccgccgaca agtccatctc cactgcgtat 240

ttgcagtgga gctcactgaa ggcctcggac accgctatgt actactgcgc ccgcggtttc 300

ctgaggggcg gagattgttg cggcgccctt gatatctggg gccaggggac catggtgacc 360

gtgtcctccg gtggtggcgg ctccggcgga ggagggtccg ggggaggagg ctccgacatt 420

gtgatgaccc agagccccct gtccctgccc gtgactcctg gggagccagc ctcgatcagc 480

tgccggtcgt cccagtccct tctgcactcc aacggctaca actatctcga ttggtacctc 540

cagaagcctg gtcaaagccc gcagctgctg atctacctcg gttcaaacag agcttccggg 600

gtgccggaca gattcagcgg atctggatcg ggcacagact tcacgctcaa gatttcccgc 660

gtggaggccg aggacgtcgg cgtgtactac tgtatgcaag cgctgcagac cccgccctgg 720

actttcggac aaggaaccaa gctggagatt aagcgg 756

<210> 354
<211> 849
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 354
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agttggtgga atcaggagca gaagtcaaga aacccggaga aagcctgaag 120

atctcgtgca aagggagcgg atactcgttc accggatcat ggattggatg gggccgccag 180

atgcctggaa agggtctgga atggatggga atcatctacc cgggggactc cgatactcgg 240

tactccccga gctttcaggg ccaggtcacc atctccgccg acaagtccat ctccactgcg 300

tatttgcagt ggagctcact gaaggcctcg gacaccgcta tgtactactg cgcccgcggt 360

ttcctgaggg gcggagattg ttgcggcgcc cttgatatct ggggccaggg gaccatggtg 420

accgtgtcct ccggtggtgg cggctccggc ggaggagggt ccgggggagg aggctccgac 480

attgtgatga cccagagccc cctgtccctg cccgtgactc ctggggagcc agcctcgatc 540

agctgccggt cgtcccagtc ccttctgcac tccaacggct acaactatct cgattggtac 600

ctccagaagc ctggtcaaag cccgcagctg ctgatctacc tcggttcaaa cagagcttcc 660

ggggtgccgg acagattcag cggatctgga tcgggcacag acttcacgct caagatttcc 720

cgcgtggagg ccgaggacgt cggcgtgtac tactgtatgc aagcgctgca gaccccgccc 780

tggactttcg gacaaggaac caagctggag attaagcggg gatcgcacca ccatcaccat 840

catcatcac 849

<210> 355
<211> 283
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 355

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr
        35                  40                  45

Ser Phe Thr Gly Ser Trp Ile Gly Trp Gly Arg Gln Met Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg
65                  70                  75                  80

Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser
                85                  90                  95

Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr
            100                 105                 110

Ala Met Tyr Tyr Cys Ala Arg Gly Phe Leu Arg Gly Gly Asp Cys Cys
        115                 120                 125

Gly Ala Leu Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
145                 150                 155                 160
```

```
Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu
                165                 170                 175


Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn
            180                 185                 190


Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro
        195                 200                 205


Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp
    210                 215                 220


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser
225                 230                 235                 240


Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala Leu
                245                 250                 255


Gln Thr Pro Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            260                 265                 270


Arg Gly Ser His His His His His His His His
        275                 280


<210> 356
<211> 496
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 356
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val
```

```
            20                  25                  30

Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr
        35                  40                  45

Ser Phe Thr Gly Ser Trp Ile Gly Trp Gly Arg Gln Met Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg
65                  70                  75                  80

Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser
                85                  90                  95

Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr
            100                 105                 110

Ala Met Tyr Tyr Cys Ala Arg Gly Phe Leu Arg Gly Gly Asp Cys Cys
        115                 120                 125

Gly Ala Leu Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
145                 150                 155                 160

Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu
                165                 170                 175

Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn
            180                 185                 190

Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro
        195                 200                 205

Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp
```

210 215 220

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser
225 230 235 240

Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala Leu
245 250 255

Gln Thr Pro Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
260 265 270

Arg Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
275 280 285

Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
290 295 300

Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr
305 310 315 320

Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu
325 330 335

Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile
340 345 350

Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp
355 360 365

Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
370 375 380

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly
385 390 395 400

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr

405 410 415

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
420 425 430

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
435 440 445

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
450 455 460

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
465 470 475 480

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 357
<211> 1488
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 357
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agttggtgga atcaggagca gaagtcaaga aacccggaga aagcctgaag 120

atctcgtgca aagggagcgg atactcgttc accggatcat ggattggatg gggccgccag 180

atgcctggaa agggtctgga atggatggga atcatctacc cgggggactc cgatactcgg 240

tactccccga gctttcaggg ccaggtcacc atctccgccg acaagtccat ctccactgcg 300

tatttgcagt ggagctcact gaaggcctcg gacaccgcta tgtactactg cgcccgcggt 360

ttcctgaggg gcggagattg ttgcggcgcc cttgatatct ggggccaggg gaccatggtg 420

accgtgtcct ccggtggtgg cggctccggc ggaggagggt ccgggggagg aggctccgac 480

attgtgatga cccagagccc cctgtccctg cccgtgactc ctggggagcc agcctcgatc 540

agctgccggt cgtcccagtc ccttctgcac tccaacggct acaactatct cgattggtac 600

ctccagaagc ctggtcaaag cccgcagctg ctgatctacc tcggttcaaa cagagcttcc 660

ggggtgccgg acagattcag cggatctgga tcgggcacag acttcacgct caagatttcc 720

cgcgtggagg ccgaggacgt cggcgtgtac tactgtatgc aagcgctgca gaccccgccc 780

tggactttcg gacaaggaac caagctggag attaagcgga ccactacccc agcaccgagg 840

ccacccaccc cggctcctac catcgcctcc cagcctctgt ccctgcgtcc ggaggcatgt 900

agacccgcag ctggtggggc cgtgcatacc cggggtcttg acttcgcctg cgatatctac 960

atttgggccc ctctggctgg tacttgcggg gtcctgctgc tttcactcgt gatcactctt 1020

tactgtaagc gcggtcggaa gaagctgctg tacatcttta agcaaccctt catgaggcct 1080

gtgcagacta ctcaagagga ggacggctgt tcatgccggt tcccagagga ggaggaaggc 1140

ggctgcgaac tgcgcgtgaa attcagccgc agcgcagatg ctccagccta caagcagggg 1200

cagaaccagc tctacaacga actcaatctt ggtcggagag aggagtacga cgtgctggac 1260

aagcggagag gacgggaccc agaaatgggc gggaagccgc gcagaaagaa tccccaagag 1320

ggcctgtaca acgagctcca aaaggataag atggcagaag cctatagcga gattggtatg 1380

aaaggggaac gcagaagagg caaaggccac gacggactgt accagggact cagcaccgcc 1440

accaaggaca cctatgacgc tcttcacatg caggccctgc cgcctcgg 1488

<210> 358
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 358

N2067-7072WO_SL (1)

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                  10                  15

Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser Ile Asn Ser Tyr
            20                  25                  30

Tyr Trp Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Ala Phe Thr Ser His Ser Gly Asn Val Lys Tyr Asn Pro Ser Leu Thr
    50                  55                  60

Gly Arg Val Thr Ile Ala Val Asp Thr Ser Lys Asn Gln Phe Tyr Leu
65                  70                  75                  80

Glu Val Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala
                85                  90                  95

Arg Gly Leu Asp Pro Leu Phe Ala Tyr Asp Ala Phe Glu Ile Trp Gly
            100                 105                 110

Leu Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro
    130                 135                 140

Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg
145                 150                 155                 160

Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp Trp
                165                 170                 175

Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly
            180                 185                 190
```

Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
195 200 205

Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val
210 215 220

Gly Val Tyr Tyr Cys Met Gln Val Leu Gln Thr Pro Pro Leu Thr Phe
225 230 235 240

Gly Gly Gly Thr Lys Val Asp Ile Lys Arg
245 250

<210> 359
<211> 750
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 359
caagtgcaac ttcaggaatc aggccccgga cttgtgaaac catcagaaac tctctccctc 60

acttgctccg tgagcggggg gtccatcaac tcctactact ggtcgtggat tagacaggcc 120

cctggaaagg ggctggagtg gatcgcgttc acttcgcact ccggcaacgt caagtacaac 180

ccgtccctga ccggaagagt gaccattgcc gtggatacct ccaagaacca gttctacctg 240

gaagtcacgt cggtgaccgc tgctgacacc gccgtgtact tctgcgcacg ggggctggac 300

ccattgtttg cctacgatgc gttcgaaatc tgggggctcg gaaccatggt cactgtgtcc 360

tccggcggag gcggcagcgg tggaggaggc agcggaggag gaggttccga gatcgtgctg 420

acccagagcc ccctgtccct ccccgtgacc cctggagaac cggccagcat ttcctgccgg 480

tcgagccagt ccctgttgca ttcaaatggc tacaactacc tggattggta tctgcagaag 540

cccggccagt caccgcaact gctcatctac ctgggaagca accgcgcctc gggtgtcccg 600

gaccgcttct ccggctcggg gtctggcact gacttcacac tgaagatctc cagggtggag 660

gccgaggacg tgggagtgta ttactgtatg caagtgctgc agaccccgcc tctgaccttc 720

ggcggtggaa ctaaggtcga catcaagcgg 750

<210> 360
<211> 843
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 360
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aacttcagga atcaggcccc ggacttgtga aaccatcaga aactctctcc 120

ctcacttgct ccgtgagcgg ggggtccatc aactcctact actggtcgtg gattagacag 180

gcccctggaa aggggctgga gtggatcgcg ttcacttcgc actccggcaa cgtcaagtac 240

aacccgtccc tgaccggaag agtgaccatt gccgtggata cctccaagaa ccagttctac 300

ctggaagtca cgtcggtgac cgctgctgac accgccgtgt acttctgcgc acgggggctg 360

gacccattgt ttgcctacga tgcgttcgaa atctgggggc tcggaaccat ggtcactgtg 420

tcctccggcg gaggcggcag cggtggagga ggcagcggag gaggaggttc cgagatcgtg 480

ctgacccaga gccccctgtc cctccccgtg acccctggag aaccggccag catttcctgc 540

cggtcgagcc agtccctgtt gcattcaaat ggctacaact acctggattg gtatctgcag 600

aagcccggcc agtcaccgca actgctcatc tacctgggaa gcaaccgcgc ctcgggtgtc 660

ccggaccgct tctccggctc ggggtctggc actgacttca cactgaagat ctccagggtg 720

gaggccgagg acgtgggagt gtattactgt atgcaagtgc tgcagacccc gcctctgacc 780

ttcggcggtg gaactaaggt cgacatcaag cggggatcgc accaccatca ccatcatcat 840

cac 843

<210> 361
<211> 281
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 361

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly
        35                  40                  45

Ser Ile Asn Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Ala Phe Thr Ser His Ser Gly Asn Val Lys Tyr
65                  70                  75                  80

Asn Pro Ser Leu Thr Gly Arg Val Thr Ile Ala Val Asp Thr Ser Lys
                85                  90                  95

Asn Gln Phe Tyr Leu Glu Val Thr Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Phe Cys Ala Arg Gly Leu Asp Pro Leu Phe Ala Tyr Asp Ala
        115                 120                 125

Phe Glu Ile Trp Gly Leu Gly Thr Met Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val
```

```
145                 150                 155                 160

Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala
                165                 170                 175

Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr
            180                 185                 190

Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu
        195                 200                 205

Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val
225                 230                 235                 240

Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Val Leu Gln Thr
                245                 250                 255

Pro Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Asp Ile Lys Arg Gly
            260                 265                 270

Ser His His His His His His His His
        275                 280
```

<210> 362
<211> 494
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 362

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15
```

```
His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20                  25                  30

Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly
        35                  40                  45

Ser Ile Asn Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Ala Phe Thr Ser His Ser Gly Asn Val Lys Tyr
65                  70                  75                  80

Asn Pro Ser Leu Thr Gly Arg Val Thr Ile Ala Val Asp Thr Ser Lys
                85                  90                  95

Asn Gln Phe Tyr Leu Glu Val Thr Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Phe Cys Ala Arg Gly Leu Asp Pro Leu Phe Ala Tyr Asp Ala
        115                 120                 125

Phe Glu Ile Trp Gly Leu Gly Thr Met Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val
145                 150                 155                 160

Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala
                165                 170                 175

Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr
            180                 185                 190

Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu
        195                 200                 205
```

```
Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe
    210                 215                 220

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val
225                 230                 235                 240

Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Val Leu Gln Thr
                245                 250                 255

Pro Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Asp Ile Lys Arg Thr
            260                 265                 270

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
        275                 280                 285

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
    290                 295                 300

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
305                 310                 315                 320

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
                325                 330                 335

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
            340                 345                 350

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
        355                 360                 365

Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
    370                 375                 380

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn
385                 390                 395                 400
```

```
Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
                405                 410                 415

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
            420                 425                 430

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        435                 440                 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    450                 455                 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465                 470                 475                 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 363
<211> 1482
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 363
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aacttcagga atcaggcccc ggacttgtga aaccatcaga aactctctcc 120

ctcacttgct ccgtgagcgg ggggtccatc aactcctact actggtcgtg gattagacag 180

gcccctggaa aggggctgga gtggatcgcg ttcacttcgc actccggcaa cgtcaagtac 240

aacccgtccc tgaccggaag agtgaccatt gccgtggata cctccaagaa ccagttctac 300

ctggaagtca cgtcggtgac cgctgctgac accgccgtgt acttctgcgc acgggggctg 360

gacccattgt ttgcctacga tgcgttcgaa atctgggggc tcggaaccat ggtcactgtg 420

tcctccggcg gaggcggcag cggtggagga ggcagcggag gaggaggttc cgagatcgtg 480

ctgacccaga gccccctgtc cctccccgtg acccctggag aaccggccag catttcctgc 540

cggtcgagcc agtccctgtt gcattcaaat ggctacaact acctggattg gtatctgcag 600

aagcccggcc agtcaccgca actgctcatc tacctgggaa gcaaccgcgc ctcgggtgtc 660

ccggaccgct tctccggctc ggggtctggc actgacttca cactgaagat ctccagggtg 720

gaggccgagg acgtgggagt gtattactgt atgcaagtgc tgcagacccc gcctctgacc 780

ttcggcggtg gaactaaggt cgacatcaag cggaccacta ccccagcacc gaggccaccc 840

accccggctc ctaccatcgc ctcccagcct ctgtccctgc gtccggaggc atgtagaccc 900

gcagctggtg gggccgtgca tacccggggt cttgacttcg cctgcgatat ctacatttgg 960

gcccctctgg ctggtacttg cggggtcctg ctgctttcac tcgtgatcac tctttactgt 1020

aagcgcggtc ggaagaagct gctgtacatc tttaagcaac ccttcatgag gcctgtgcag 1080

actactcaag aggaggacgg ctgttcatgc cggttcccag aggaggagga aggcggctgc 1140

gaactgcgcg tgaaattcag ccgcagcgca gatgctccag cctacaagca ggggcagaac 1200

cagctctaca acgaactcaa tcttggtcgg agagaggagt acgacgtgct ggacaagcgg 1260

agaggacggg acccagaaat gggcgggaag ccgcgcagaa agaatcccca agagggcctg 1320

tacaacgagc tccaaaagga taagatggca gaagcctata gcgagattgg tatgaaaggg 1380

gaacgcagaa gaggcaaagg ccacgacgga ctgtaccagg gactcagcac cgccaccaag 1440

gacacctatg acgctcttca catgcaggcc ctgccgcctc gg 1482

<210> 364
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polypeptide"

<400> 364

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Asp Phe Trp Ser Gly Ser Val Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu Thr
    130                 135                 140

Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys Thr Ala Thr Ile Thr
145                 150                 155                 160

Cys Gly Gly Thr Asn Ile Gly Ser Lys Asn Val His Trp Tyr Gln Gln
                165                 170                 175

Lys Pro Gly Gln Ala Pro Val Leu Ala Ile Tyr Tyr Asp Ser Asp Arg
```

180 185 190

Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr
195 200 205

Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly Asp Glu Ala Asp Tyr
210 215 220

Phe Cys Gln Val Trp Asp Ser Ser Ser Asp His Trp Val Phe Gly Gly
225 230 235 240

Gly Thr Lys Leu Thr Val Leu
245

<210> 365
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 365
gaagtgcagt tggtggaatc tggtggtgga ctcgtgaaac ctggaggaag cttgcgcctg 60

tcttgcgcgg cctccggctt cactttctcg gattactaca tgtcctggat tagacaggct 120

ccggggaagg gactcgaatg ggtgtcctac atttcatcaa gcggcagcac catctactat 180

gcggactccg tgaaggggcg gttcactatt tcccgggata acgcaaagaa cagcctgtac 240

cttcaaatga attcactgcg cgccgaggac accgccgtgt actattgcgc ccgggatgac 300

ttctggtcgg ggtccgtgga ctactggggc caggggaccc tggtcaccgt gtcctcggga 360

ggaggaggaa gcgggggagg cggttccggg ggcggcggct cgggcggcgg tggctccagc 420

tacgtgctca cccagccgcc ctccgtgtcc gtggccccgg gaaagaccgc caccatcacc 480

tgtggaggaa cgaacatcgg ctccaagaac gtccattggt accagcagaa gcccggacag 540

gcccccgtgc tggcaatcta ctacgactcc gaccgcccaa gcggtatccc tgaaaggttc 600

tccggctcca acagcggaaa cactgcgact ctgaccatct caagagtgga ggctggcgat 660

gaggccgact acttctgcca agtctgggac tcgtcctcgg accactgggt gtttggggga 720

ggcaccaagc tgactgtcct g 741

<210> 366
<211> 834
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 366
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agttggtgga atctggtggt ggactcgtga aacctggagg aagcttgcgc 120

ctgtcttgcg cggcctccgg cttcactttc tcggattact acatgtcctg gattagacag 180

gctccgggga agggactcga atgggtgtcc tacatttcat caagcggcag caccatctac 240

tatgcggact ccgtgaaggg gcggttcact atttcccggg ataacgcaaa gaacagcctg 300

taccttcaaa tgaattcact gcgcgccgag gacaccgccg tgtactattg cgcccgggat 360

gacttctggt cggggtccgt ggactactgg ggccagggga ccctggtcac cgtgtcctcg 420

ggaggaggag gaagcggggg aggcggttcc gggggcggcg gctcgggcgg cggtggctcc 480

agctacgtgc tcacccagcc gccctccgtg tccgtggccc cgggaaagac cgccaccatc 540

acctgtggag gaacgaacat cggctccaag aacgtccatt ggtaccagca gaagcccgga 600

caggcccccg tgctggcaat ctactacgac tccgaccgcc caagcggtat ccctgaaagg 660

ttctccggct ccaacagcgg aaacactgcg actctgacca tctcaagagt ggaggctggc 720

gatgaggccg actacttctg ccaagtctgg gactcgtcct cggaccactg ggtgtttggg 780

ggaggcacca agctgactgt cctgggatcg caccaccatc accatcatca tcac 834

<210> 367
<211> 278
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 367

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15


His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30


Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
        35                  40                  45


Thr Phe Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys
    50                  55                  60


Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr
65                  70                  75                  80


Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
                85                  90                  95


Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110


Ala Val Tyr Tyr Cys Ala Arg Asp Asp Phe Trp Ser Gly Ser Val Asp
        115                 120                 125


Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
    130                 135                 140
```

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145 150 155 160

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
165 170 175

Thr Ala Thr Ile Thr Cys Gly Gly Thr Asn Ile Gly Ser Lys Asn Val
180 185 190

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Ala Ile Tyr
195 200 205

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
210 215 220

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
225 230 235 240

Asp Glu Ala Asp Tyr Phe Cys Gln Val Trp Asp Ser Ser Ser Asp His
245 250 255

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser His His
260 265 270

His His His His His His
275

<210> 368
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 368
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu

1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

Thr Phe Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr
65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala
85 90 95

Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Asp Phe Trp Ser Gly Ser Val Asp
115 120 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145 150 155 160

Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
165 170 175

Thr Ala Thr Ile Thr Cys Gly Gly Thr Asn Ile Gly Ser Lys Asn Val
180 185 190

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Ala Ile Tyr

195 200 205

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
210 215 220

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
225 230 235 240

Asp Glu Ala Asp Tyr Phe Cys Gln Val Trp Asp Ser Ser Ser Asp His
245 250 255

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Thr Thr Thr Pro
260 265 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
275 280 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
290 295 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305 310 315 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
325 330 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
340 345 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
355 360 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
370 375 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr

385 390 395 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
405 410 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
420 425 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
435 440 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
450 455 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465 470 475 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 369
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 369
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agttggtgga atctggtggt ggactcgtga aacctggagg aagcttgcgc 120

ctgtcttgcg cggcctccgg cttcactttc tcggattact acatgtcctg gattagacag 180

gctccgggga agggactcga atgggtgtcc tacatttcat caagcggcag caccatctac 240

tatgcggact ccgtgaaggg gcggttcact atttcccggg ataacgcaaa gaacagcctg 300

taccttcaaa tgaattcact gcgcgccgag gacaccgccg tgtactattg cgcccgggat 360

gacttctggt cggggtccgt ggactactgg ggccagggga ccctggtcac cgtgtcctcg 420

ggaggaggag gaagcggggg aggcggttcc gggggcggcg gctcgggcgg cggtggctcc 480

agctacgtgc tcacccagcc gccctccgtg tccgtggccc cgggaaagac cgccaccatc 540

acctgtggag gaacgaacat cggctccaag aacgtccatt ggtaccagca gaagcccgga 600

caggcccccg tgctggcaat ctactacgac tccgaccgcc caagcggtat ccctgaaagg 660

ttctccggct ccaacagcgg aaacactgcg actctgacca tctcaagagt ggaggctggc 720

gatgaggccg actacttctg ccaagtctgg gactcgtcct cggaccactg ggtgtttggg 780

ggaggcacca agctgactgt cctgaccact accccagcac cgaggccacc caccccggct 840

cctaccatcg cctcccagcc tctgtccctg cgtccggagg catgtagacc cgcagctggt 900

ggggccgtgc atacccgggg tcttgacttc gcctgcgata tctacatttg ggcccctctg 960

gctggtactt gcggggtcct gctgctttca ctcgtgatca ctctttactg taagcgcggt 1020

cggaagaagc tgctgtacat ctttaagcaa cccttcatga ggcctgtgca gactactcaa 1080

gaggaggacg gctgttcatg ccggttccca gaggaggagg aaggcggctg cgaactgcgc 1140

gtgaaattca gccgcagcgc agatgctcca gcctacaagc aggggcagaa ccagctctac 1200

aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

gacccagaaa tgggcgggaa gccgcgcaga aagaatcccc aagagggcct gtacaacgag 1320

ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 370
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 370
```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Glu Asp Asp Ser Ser Gly Tyr Thr Ser Pro Phe Asp Tyr Trp
            100                 105                 110


Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Arg Ser Ser Tyr
    130                 135                 140


Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Glu Thr Ala
145                 150                 155                 160


Ser Ile Ala Cys Gly Gly His Asn Ile Arg Ser Lys Asn Val His Trp
                165                 170                 175
```

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Ser Tyr Asp
180 185 190

Gly Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Leu
195 200 205

Gly Ser Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly Asp Glu
210 215 220

Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Asp Ser Asp His Tyr Val
225 230 235 240

Phe Gly Thr Gly Thr Lys Val Thr Val Leu
245 250

<210> 371
<211> 750
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 371
caagtccaac tcgtccagtc cggtgcagaa gtcaagaaac ccggagcttc cgtgaaagtg 60

tcctgcaagg cctcggggta cacattcacc tcctactaca tgcactgggt gcgccaggcc 120

ccgggccagg gactggaatg gatgggaatc attaacccgt ccggcggatc gaccagctac 180

gcccagaagt ttcagggacg cgtgaccatg acccgggaca ctagcaccag cactgtgtac 240

atggaactga gctcactgcg gtccgaggac actgcggtgt actattgcgc ccgggaggac 300

gattcctccg ggtacacttc gcccttcgac tattggggac agggaacctt ggtcaccgtg 360

tcatcgggtg gtggaggaag cggaggaggc ggctccggcg gcgggggttc aggcggtggc 420

agaagctcct acgaactgac ccagcctccg tccgtgtccg tggcccccgg cgaaaccgcc 480

tcgatcgcgt gtggagggca caatattcgg agcaagaacg tgcattggta ccagcagaag 540

ccgggacagg caccagtgct cgtgatctcc tacgatgggg acaggccttc tggcatccct 600

gagagattca gcgggtccaa cctgggctcc actgctaccc tgaccatctc gcgcgtggaa 660

gccggggatg aggccgacta ctactgccaa gtctgggact ccgacagcga tcactacgtg 720

ttcggaactg gaaccaaggt cacggtgctt 750

<210> 372
<211> 843
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 372
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca gtccggtgca gaagtcaaga aacccggagc ttccgtgaaa 120

gtgtcctgca aggcctcggg gtacacattc acctcctact acatgcactg ggtgcgccag 180

gccccgggcc agggactgga atggatggga atcattaacc cgtccggcgg atcgaccagc 240

tacgcccaga agtttcaggg acgcgtgacc atgacccggg acactagcac cagcactgtg 300

tacatggaac tgagctcact gcggtccgag gacactgcgg tgtactattg cgcccgggag 360

gacgattcct ccgggtacac ttcgcccttc gactattggg gacagggaac cttggtcacc 420

gtgtcatcgg gtggtggagg aagcggagga ggcggctccg gcggcggggg ttcaggcggt 480

ggcagaagct cctacgaact gacccagcct ccgtccgtgt ccgtggcccc cggcgaaacc 540

gcctcgatcg cgtgtggagg gcacaatatt cggagcaaga acgtgcattg gtaccagcag 600

aagccgggac aggcaccagt gctcgtgatc tcctacgatg gggacaggcc ttctggcatc 660

cctgagagat tcagcgggtc caacctgggc tccactgcta ccctgaccat ctcgcgcgtg 720

gaagccgggg atgaggccga ctactactgc caagtctggg actccgacag cgatcactac 780

gtgttcggaa ctggaaccaa ggtcacggtg cttggatcgc accaccatca ccatcatcat 840

cac 843

<210> 373
<211> 281
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 373
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Glu Asp Asp Ser Ser Gly Tyr Thr Ser
115 120 125

Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly

```
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Arg Ser Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala
                165                 170                 175

Pro Gly Glu Thr Ala Ser Ile Ala Cys Gly Gly His Asn Ile Arg Ser
            180                 185                 190

Lys Asn Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu
        195                 200                 205

Val Ile Ser Tyr Asp Gly Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe
    210                 215                 220

Ser Gly Ser Asn Leu Gly Ser Thr Ala Thr Leu Thr Ile Ser Arg Val
225                 230                 235                 240

Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Asp
                245                 250                 255

Ser Asp His Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
            260                 265                 270

Ser His His His His His His His His
        275                 280


<210> 374
<211> 494
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"
```

<400> 374
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1   5   10   15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20   25   30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35   40   45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50   55   60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65   70   75   80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85   90   95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100   105   110

Ala Val Tyr Tyr Cys Ala Arg Glu Asp Asp Ser Ser Gly Tyr Thr Ser
        115   120   125

Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
    130   135   140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145   150   155   160

Gly Arg Ser Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala
                165   170   175

Pro Gly Glu Thr Ala Ser Ile Ala Cys Gly Gly His Asn Ile Arg Ser
            180   185   190

```
Lys Asn Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu
        195                 200                 205

Val Ile Ser Tyr Asp Gly Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe
    210                 215                 220

Ser Gly Ser Asn Leu Gly Ser Thr Ala Thr Leu Thr Ile Ser Arg Val
225                 230                 235                 240

Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Asp
                245                 250                 255

Ser Asp His Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Thr
            260                 265                 270

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
        275                 280                 285

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
    290                 295                 300

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
305                 310                 315                 320

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
                325                 330                 335

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
            340                 345                 350

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
        355                 360                 365

Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
    370                 375                 380
```

```
Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn
385                 390                 395                 400


Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
                405                 410                 415


Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
            420                 425                 430


Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
        435                 440                 445


Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
    450                 455                 460


Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465                 470                 475                 480


Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 375
<211> 1482
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"

<400> 375
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg       60

ccccaagtcc aactcgtcca gtccggtgca gaagtcaaga aacccggagc ttccgtgaaa      120

gtgtcctgca aggcctcggg gtacacattc acctcctact acatgcactg ggtgcgccag      180

gccccgggcc agggactgga atggatggga atcattaacc cgtccggcgg atcgaccagc      240
```

tacgcccaga agtttcaggg acgcgtgacc atgacccggg acactagcac cagcactgtg 300

tacatggaac tgagctcact gcggtccgag gacactgcgg tgtactattg cgcccgggag 360

gacgattcct ccgggtacac ttcgcccttc gactattggg gacagggaac cttggtcacc 420

gtgtcatcgg gtggtggagg aagcggagga ggcggctccg gcggcggggg ttcaggcggt 480

ggcagaagct cctacgaact gacccagcct ccgtccgtgt ccgtggcccc cggcgaaacc 540

gcctcgatcg cgtgtggagg gcacaatatt cggagcaaga acgtgcattg gtaccagcag 600

aagccgggac aggcaccagt gctcgtgatc tcctacgatg gggacaggcc ttctggcatc 660

cctgagagat tcagcgggtc caacctgggc tccactgcta ccctgaccat ctcgcgcgtg 720

gaagccgggg atgaggccga ctactactgc caagtctggg actccgacag cgatcactac 780

gtgttcggaa ctggaaccaa ggtcacggtg cttaccacta ccccagcacc gaggccaccc 840

accccggctc ctaccatcgc ctcccagcct ctgtccctgc gtccggaggc atgtagaccc 900

gcagctggtg gggccgtgca tacccggggt cttgacttcg cctgcgatat ctacatttgg 960

gcccctctgg ctggtacttg cggggtcctg ctgctttcac tcgtgatcac tctttactgt 1020

aagcgcggtc ggaagaagct gctgtacatc tttaagcaac ccttcatgag gcctgtgcag 1080

actactcaag aggaggacgg ctgttcatgc cggttcccag aggaggagga aggcggctgc 1140

gaactgcgcg tgaaattcag ccgcagcgca gatgctccag cctacaagca ggggcagaac 1200

cagctctaca acgaactcaa tcttggtcgg agagaggagt acgacgtgct ggacaagcgg 1260

agaggacggg acccagaaat gggcgggaag ccgcgcagaa agaatcccca agagggcctg 1320

tacaacgagc tccaaaagga taagatggca gaagcctata gcgagattgg tatgaaaggg 1380

gaacgcagaa gaggcaaagg ccacgacgga ctgtaccagg gactcagcac cgccaccaag 1440

gacacctatg acgctcttca catgcaggcc ctgccgcctc gg 1482

<210> 376
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 376
Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Pro Ala Ser Ser Ser Trp Tyr Gly Tyr Tyr Tyr Tyr Met
100 105 110

Asp Val Trp Gly Lys Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
130 135 140

Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
145 150 155 160

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Thr

165 170 175

Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Pro Pro Lys Leu Leu
180 185 190

Ile Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
195 200 205

Gly Ser Gly Ser Gly Thr His Phe Thr Leu Thr Ile Ser Ser Leu Gln
210 215 220

Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ser Leu
225 230 235 240

Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
245 250

<210> 377
<211> 756
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 377
gaagtgcagt tggtggaatc aggagcagaa gtcaagaaac ccggagcatc agtcaaagtg 60

tcctgcaagg cctccgggta cactttcact ggttactaca tgcattgggt gcgccaggcg 120

cccggacaag gactcgagtg gatgggctgg attaacccca actccggcgg aaccaactac 180

gcccagaagt tccagggtag agtgacgatg actcgggaca ccagcatctc caccgcgtac 240

atggagctgt cgagactgag gtccgacgat accgccgtgt actactgcgc ccgggaaccg 300

gcttcctcgt cttggtacgg atattactat tacatggatg tctggggaaa gggaacactt 360

gtcactgtgt ccagcggtgg cggaggcagc ggcggtggag ggtccggcgg cggcggatcg 420

ggaggggggag gcagcgacat ccagatgact cagtccccat cctcgctgtc ggctagcgtg 480

ggcgaccgcg tgaccattac ctgtcgggcc agccaatcca tcaacaccta cctgaactgg 540

taccagcaga agccggggaa gcctccaaag ctgctcatct acgcggcctc aaatctgcaa 600

tccggggtgc cttcccggtt ctccggttcc ggttcgggga cccacttcac tctgaccatt 660

agctcactgc aaccggacga ctttgccacc tactactgcc agcagagcta ctcctccctc 720

ctgaccttcg gcggaggaac caagctcgag atcaag 756

<210> 378
<211> 849
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 378
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agttggtgga atcaggagca gaagtcaaga aacccggagc atcagtcaaa 120

gtgtcctgca aggcctccgg gtacactttc actggttact acatgcattg ggtgcgccag 180

gcgcccggac aaggactcga gtggatgggc tggattaacc ccaactccgg cggaaccaac 240

tacgcccaga agttccaggg tagagtgacg atgactcggg acaccagcat ctccaccgcg 300

tacatggagc tgtcgagact gaggtccgac gataccgccg tgtactactg cgcccgggaa 360

ccggcttcct cgtcttggta cggatattac tattacatgg atgtctgggg aaagggaaca 420

cttgtcactg tgtccagcgg tggcggaggc agcggcggtg gagggtccgg cggcggcgga 480

tcgggagggg gaggcagcga catccagatg actcagtccc catcctcgct gtcggctagc 540

gtgggcgacc gcgtgaccat tacctgtcgg gccagccaat ccatcaacac ctacctgaac 600

tggtaccagc agaagccggg gaagcctcca aagctgctca tctacgcggc ctcaaatctg 660

caatccgggg tgccttcccg gttctccggt tccggttcgg ggacccactt cactctgacc 720

attagctcac tgcaaccgga cgactttgcc acctactact gccagcagag ctactcctcc 780

ctcctgacct tcggcggagg aaccaagctc gagatcaagg gatcgcacca ccatcaccat 840

catcatcac 849

<210> 379
<211> 283
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 379

Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Glu Pro Ala Ser Ser Ser Trp Tyr Gly
115 120 125

```
Tyr Tyr Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr Leu Val Thr Val
    130                 135                 140

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
                165                 170                 175

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
            180                 185                 190

Gln Ser Ile Asn Thr Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
        195                 200                 205

Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val
    210                 215                 220

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr His Phe Thr Leu Thr
225                 230                 235                 240

Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
                245                 250                 255

Ser Tyr Ser Ser Leu Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
            260                 265                 270

Lys Gly Ser His His His His His His His His
        275                 280
```

<210> 380
<211> 496
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 380

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Glu Pro Ala Ser Ser Ser Trp Tyr Gly
        115                 120                 125

Tyr Tyr Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr Leu Val Thr Val
    130                 135                 140

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
145                 150                 155                 160

Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
                165                 170                 175
```

```
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
            180                 185                 190


Gln Ser Ile Asn Thr Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
        195                 200                 205


Pro Pro Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val
    210                 215                 220


Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr His Phe Thr Leu Thr
225                 230                 235                 240


Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
                245                 250                 255


Ser Tyr Ser Ser Leu Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
            260                 265                 270


Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
        275                 280                 285


Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
    290                 295                 300


Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr
305                 310                 315                 320


Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu
                325                 330                 335


Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile
            340                 345                 350


Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp
        355                 360                 365
```

```
Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
    370                 375                 380


Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly
385                 390                 395                 400


Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
                405                 410                 415


Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
            420                 425                 430


Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
        435                 440                 445


Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
    450                 455                 460


Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
465                 470                 475                 480


Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490                 495
```

<210> 381
<211> 1488
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 381
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agttggtgga atcaggagca gaagtcaaga aacccggagc atcagtcaaa 120

gtgtcctgca aggcctccgg gtacactttc actggttact acatgcattg ggtgcgccag 180

gcgcccggac aaggactcga gtggatgggc tggattaacc ccaactccgg cggaaccaac 240

tacgcccaga agttccaggg tagagtgacg atgactcggg acaccagcat ctccaccgcg 300

tacatggagc tgtcgagact gaggtccgac gataccgccg tgtactactg cgcccgggaa 360

ccggcttcct cgtcttggta cggatattac tattacatgg atgtctgggg aaagggaaca 420

cttgtcactg tgtccagcgg tggcggaggc agcggcggtg gagggtccgg cggcggcgga 480

tcgggagggg gaggcagcga catccagatg actcagtccc catcctcgct gtcggctagc 540

gtgggcgacc gcgtgaccat tacctgtcgg gccagccaat ccatcaacac ctacctgaac 600

tggtaccagc agaagccggg gaagcctcca aagctgctca tctacgcggc ctcaaatctg 660

caatccgggg tgccttcccg gttctccggt tccggttcgg ggacccactt cactctgacc 720

attagctcac tgcaaccgga cgactttgcc acctactact gccagcagag ctactcctcc 780

ctcctgacct tcggcggagg aaccaagctc gagatcaaga ccactacccc agcaccgagg 840

ccacccaccc cggctcctac catcgcctcc cagcctctgt ccctgcgtcc ggaggcatgt 900

agacccgcag ctggtggggc cgtgcatacc cggggtcttg acttcgcctg cgatatctac 960

atttgggccc ctctggctgg tacttgcggg gtcctgctgc tttcactcgt gatcactctt 1020

tactgtaagc gcggtcggaa gaagctgctg tacatcttta agcaaccctt catgaggcct 1080

gtgcagacta ctcaagagga ggacggctgt tcatgccggt tcccagagga ggaggaaggc 1140

ggctgcgaac tgcgcgtgaa attcagccgc agcgcagatg ctccagccta caagcagggg 1200

cagaaccagc tctacaacga actcaatctt ggtcggagag aggagtacga cgtgctggac 1260

aagcggagag gacgggaccc agaaatgggc gggaagccgc gcagaaagaa tccccaagag 1320

ggcctgtaca acgagctcca aaaggataag atggcagaag cctatagcga gattggtatg 1380

aaaggggaac gcagaagagg caaaggccac gacggactgt accagggact cagcaccgcc 1440

accaaggaca cctatgacgc tcttcacatg caggccctgc cgcctcgg 1488

<210> 382

<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 382

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asp Ser Asn Tyr Trp Ser Tyr Tyr Gly Met Asp Val Trp
            100                 105                 110


Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser
    130                 135                 140


Val Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln Ser Val
145                 150                 155                 160
```

```
Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr
                165                 170                 175


Val Ser Trp Tyr Gln Gln His Pro Gly Glu Ala Pro Lys Leu Ile Ile
            180                 185                 190


Tyr Asp Ala Asp Lys Arg Pro Ser Gly Ile Ser Asn Arg Phe Ser Ser
        195                 200                 205


Gly Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Val
    210                 215                 220


Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Gly Ser Thr
225                 230                 235                 240


Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
                245                 250


<210> 383
<211> 756
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"

<400> 383
caagtccaac tcgtccagtc cggtgcagaa gtcaagaaac ccggagcttc cgtgaaagtg       60

tcctgcaagg cctcgggtta caccttcacc tcctacgaca ttaactgggt gcgccaggcc      120

actgggcagg gactggaatg gatgggctgg atgaacccta actcgggcaa caccggctat      180

gcccagaagt ttcagggacg cgtgacgatg acccggaata cctccatctc aaccgcctac      240

atggaactga gcagcctgag gtccgaggat actgcagtgt actactgcgc tcggggagac      300

tccaactatt ggtcctacta cggaatggac gtgtggggcc agggaaccct cgtcactgtg      360
```

tcgagcgggg gaggcggttc agggggcggc ggaagcggag gcggagggtc cggcggagga 420

ggttctcaga gcgtgctgac tcaaccgaga tccgtgtccg ggagcccggg ccagtcagtg 480

actatctcgt gcaccgggac cagctccgac gtgggagggt acaactacgt gtcgtggtac 540

cagcagcacc ccggagaggc gccaaagttg attatctacg acgccgataa gcgcccttcg 600

ggaatctcca accggttctc ctccgggaag tccggcaaca ctgcctccct gaccatcagc 660

ggacttcaag tggaggacga agcggattac tactgctgtt catacgccgg cggatcgacc 720

tgggtgttcg gcggtggtac caaggtcaca gtgctg 756

<210> 384
<211> 849
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 384
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca gtccggtgca gaagtcaaga aacccggagc ttccgtgaaa 120

gtgtcctgca aggcctcggg ttacaccttc acctcctacg acattaactg ggtgcgccag 180

gccactgggc agggactgga atggatgggc tggatgaacc ctaactcggg caacaccggc 240

tatgcccaga agtttcaggg acgcgtgacg atgacccgga atacctccat ctcaaccgcc 300

tacatggaac tgagcagcct gaggtccgag gatactgcag tgtactactg cgctcgggga 360

gactccaact attggtccta ctacggaatg gacgtgtggg gccagggaac cctcgtcact 420

gtgtcgagcg ggggaggcgg ttcaggggggc ggcggaagcg gaggcggagg gtccggcgga 480

ggaggttctc agagcgtgct gactcaaccg agatccgtgt ccgggagccc gggccagtca 540

gtgactatct cgtgcaccgg gaccagctcc gacgtgggag ggtacaacta cgtgtcgtgg 600

taccagcagc accccggaga ggcgccaaag ttgattatct acgacgccga taagcgccct 660

tcgggaatct ccaaccggtt ctcctccggg aagtccggca acactgcctc cctgaccatc 720

agcggacttc aagtggagga cgaagcggat tactactgct gttcatacgc cggcggatcg 780

acctgggtgt tcggcggtgg taccaaggtc acagtgctgg gatcgcacca ccatcaccat 840

catcatcac 849

<210> 385
<211> 283
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 385
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly
65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser
85 90 95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

```
Ala Val Tyr Tyr Cys Ala Arg Gly Asp Ser Asn Tyr Trp Ser Tyr Tyr
        115                 120                 125


Gly Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
    130                 135                 140


Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160


Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Arg Ser Val Ser Gly Ser
                165                 170                 175


Pro Gly Gln Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val
            180                 185                 190


Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Glu Ala
        195                 200                 205


Pro Lys Leu Ile Ile Tyr Asp Ala Asp Lys Arg Pro Ser Gly Ile Ser
    210                 215                 220


Asn Arg Phe Ser Ser Gly Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile
225                 230                 235                 240


Ser Gly Leu Gln Val Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr
                245                 250                 255


Ala Gly Gly Ser Thr Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val
            260                 265                 270


Leu Gly Ser His His His His His His His His
        275                 280
```

<210> 386
<211> 496
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 386

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser
                85                  90                  95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asp Ser Asn Tyr Trp Ser Tyr Tyr
        115                 120                 125

Gly Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160
```

```
Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Arg Ser Val Ser Gly Ser
                165                 170                 175

Pro Gly Gln Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val
            180                 185                 190

Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Glu Ala
        195                 200                 205

Pro Lys Leu Ile Ile Tyr Asp Ala Asp Lys Arg Pro Ser Gly Ile Ser
    210                 215                 220

Asn Arg Phe Ser Ser Gly Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile
225                 230                 235                 240

Ser Gly Leu Gln Val Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr
                245                 250                 255

Ala Gly Gly Ser Thr Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val
            260                 265                 270

Leu Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile
        275                 280                 285

Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala
    290                 295                 300

Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr
305                 310                 315                 320

Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu
                325                 330                 335

Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile
            340                 345                 350
```

Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp
355 360 365

Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
370 375 380

Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly
385 390 395 400

Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
405 410 415

Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
420 425 430

Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
435 440 445

Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
450 455 460

Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
465 470 475 480

Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 387
<211> 1488
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 387
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca gtccggtgca gaagtcaaga aacccggagc ttccgtgaaa 120

gtgtcctgca aggcctcggg ttacaccttc acctcctacg acattaactg ggtgcgccag 180

gccactgggc agggactgga atggatgggc tggatgaacc ctaactcggg caacaccggc 240

tatgcccaga agtttcaggg acgcgtgacg atgacccgga atacctccat ctcaaccgcc 300

tacatggaac tgagcagcct gaggtccgag gatactgcag tgtactactg cgctcgggga 360

gactccaact attggtccta ctacggaatg gacgtgtggg gccagggaac cctcgtcact 420

gtgtcgagcg ggggaggcgg ttcagggggc ggcggaagcg gaggcggagg gtccggcgga 480

ggaggttctc agagcgtgct gactcaaccg agatccgtgt ccgggagccc gggccagtca 540

gtgactatct cgtgcaccgg gaccagctcc gacgtgggag ggtacaacta cgtgtcgtgg 600

taccagcagc accccggaga ggcgccaaag ttgattatct acgacgccga taagcgccct 660

tcgggaatct ccaaccggtt ctcctccggg aagtccggca acactgcctc cctgaccatc 720

agcggacttc aagtggagga cgaagcggat tactactgct gttcatacgc cggcggatcg 780

acctgggtgt tcggcggtgg taccaaggtc acagtgctga ccactacccc agcaccgagg 840

ccacccaccc cggctcctac catcgcctcc cagcctctgt ccctgcgtcc ggaggcatgt 900

agacccgcag ctggtggggc cgtgcatacc cggggtcttg acttcgcctg cgatatctac 960

atttgggccc ctctggctgg tacttgcggg gtcctgctgc tttcactcgt gatcactctt 1020

tactgtaagc gcggtcggaa gaagctgctg tacatcttta agcaaccctt catgaggcct 1080

gtgcagacta ctcaagagga ggacggctgt tcatgccggt tcccagagga ggaggaaggc 1140

ggctgcgaac tgcgcgtgaa attcagccgc agcgcagatg ctccagccta caagcagggg 1200

cagaaccagc tctacaacga actcaatctt ggtcggagag aggagtacga cgtgctggac 1260

aagcggagag gacgggaccc agaaatgggc gggaagccgc gcagaaagaa tccccaagag 1320

ggcctgtaca acgagctcca aaaggataag atggcagaag cctatagcga gattggtatg 1380

aaaggggaac gcagaagagg caaaggccac gacggactgt accagggact cagcaccgcc 1440

accaaggaca cctatgacgc tcttcacatg caggccctgc cgcctcgg 1488

<210> 388
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 388
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ser Phe Ser Ser Ser Asp Ser Tyr Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln
130 135 140

```
Ser Pro Ala Thr Leu Ser Val Ser Pro Gly Glu Arg Ala Thr Leu Ser
145                 150                 155                 160


Cys Arg Ala Ser Gln Ser Val Thr Ser Asn Leu Ala Trp Tyr Gln Gln
                165                 170                 175


Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ala Ala Ser Thr Arg
            180                 185                 190


Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu
        195                 200                 205


Phe Thr Leu Thr Ile Ser Ser Met Gln Ser Glu Asp Phe Ala Val Tyr
    210                 215                 220


Phe Cys Gln Gln Tyr His Thr Trp Pro Pro Leu Thr Phe Gly Gly Gly
225                 230                 235                 240


Thr Lys Val Glu Ile Lys Thr
                245
```

<210> 389
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 389
caagtccaac tcgtccagtc cggtgcagaa gtcaagaaac caggagcttc agtgaaagtg 60

tcgtgcaagg cctccgggta taccttcact tcctacggca ttagctgggt gcggcaggcc 120

cccggccaag ggctggagtg gatgggctgg atcagcgcct acaacggaaa caccaactac 180

gcccagaagc tgcagggacg cgtgaccatg accactgaca cctccacttc gaccgcgtac 240

atggagctca gatcactgcg ctccgacgat accgccgtgt actactgcgc ctccttctcc 300

tcctccgact cctacgacta ctggggacag gggactctgg tcactgtgtc gtccggcggc 360

ggcggaagcg gtggcggagg cagcggtgga ggcggttcgg gaggaggagg gtccgaaatc 420

gtgctgaccc agtcccccgc tacccctttcc gtgagcccgg gggaacgggc caccctgtct 480

tgccgcgcgt cacaaagcgt gacttcgaac ctggcctggt accagcagaa gccggggcag 540

gccccgagat tgctcatcta tgccgcgagc accagggcaa ccggaattcc tgcccggttt 600

tccggttccg ggtcgggcac tgagttcacc ctgacaatca gctcaatgca gtccgaggat 660

ttcgctgtgt acttctgtca acagtaccac acctggcctc ccctgacgtt cggaggcgga 720

accaaggtcg aaatcaagac c 741

<210> 390
<211> 834
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 390
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca gtccggtgca gaagtcaaga aaccaggagc ttcagtgaaa 120

gtgtcgtgca aggcctccgg gtataccttc acttcctacg gcattagctg ggtgcggcag 180

gcccccggcc aagggctgga gtggatgggc tggatcagcg cctacaacgg aaacaccaac 240

tacgcccaga agctgcaggg acgcgtgacc atgaccactg acacctccac ttcgaccgcg 300

tacatggagc tcagatcact gcgctccgac gataccgccg tgtactactg cgcctccttc 360

tcctcctccg actcctacga ctactgggga caggggactc tggtcactgt gtcgtccggc 420

ggcggcggaa gcggtggcgg aggcagcggt ggaggcggtt cgggaggagg agggtccgaa 480

atcgtgctga cccagtcccc cgctaccctt tccgtgagcc cgggggaacg ggccaccctg 540

tcttgccgcg cgtcacaaag cgtgacttcg aacctggcct ggtaccagca gaagccgggg 600

caggccccga gattgctcat ctatgccgcg agcaccaggg caaccggaat tcctgcccgg 660

ttttccggtt ccgggtcggg cactgagttc accctgacaa tcagctcaat gcagtccgag 720

gatttcgctg tgtacttctg tcaacagtac cacacctggc ctcccctgac gttcggaggc 780

ggaaccaagg tcgaaatcaa gaccggatcg caccaccatc accatcatca tcac 834

<210> 391
<211> 278
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 391
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn
65 70 75 80

Tyr Ala Gln Lys Leu Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser
85 90 95

Thr Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr
100 105 110

```
Ala Val Tyr Tyr Cys Ala Ser Phe Ser Ser Ser Asp Ser Tyr Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
145                 150                 155                 160

Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly Glu
                165                 170                 175

Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Thr Ser Asn Leu
            180                 185                 190

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
        195                 200                 205

Ala Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Met Gln Ser Glu
225                 230                 235                 240

Asp Phe Ala Val Tyr Phe Cys Gln Gln Tyr His Thr Trp Pro Pro Leu
                245                 250                 255

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Thr Gly Ser His His
            260                 265                 270

His His His His His His
        275
```

<210> 392
<211> 490

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 392

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn
65                  70                  75                  80

Tyr Ala Gln Lys Leu Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser
                85                  90                  95

Thr Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Ser Phe Ser Ser Ser Asp Ser Tyr Asp Tyr
        115                 120                 125

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
145                 150                 155                 160
```

```
Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly Glu
                165                 170                 175

Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Thr Ser Asn Leu
            180                 185                 190

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
        195                 200                 205

Ala Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Met Gln Ser Glu
225                 230                 235                 240

Asp Phe Ala Val Tyr Phe Cys Gln Gln Tyr His Thr Trp Pro Pro Leu
                245                 250                 255

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350
```

```
Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365


Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380


Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400


Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415


Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430


Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445


Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
    450                 455                 460


Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465                 470                 475                 480


Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 393
<211> 1470
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 393

atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca gtccggtgca gaagtcaaga aaccaggagc ttcagtgaaa 120

gtgtcgtgca aggcctccgg gtataccttc acttcctacg gcattagctg ggtgcggcag 180

gcccccggcc aagggctgga gtggatgggc tggatcagcg cctacaacgg aaacaccaac 240

tacgcccaga agctgcaggg acgcgtgacc atgaccactg acacctccac ttcgaccgcg 300

tacatggagc tcagatcact gcgctccgac gataccgccg tgtactactg cgcctccttc 360

tcctcctccg actcctacga ctactgggga caggggactc tggtcactgt gtcgtccggc 420

ggcggcggaa gcggtggcgg aggcagcggt ggaggcggtt cgggaggagg agggtccgaa 480

atcgtgctga cccagtcccc cgctaccctt tccgtgagcc cgggggaacg ggccaccctg 540

tcttgccgcg cgtcacaaag cgtgacttcg aacctggcct ggtaccagca gaagccgggg 600

caggccccga gattgctcat ctatgccgcg agcaccaggg caaccggaat tcctgcccgg 660

ttttccggtt ccgggtcggg cactgagttc accctgacaa tcagctcaat gcagtccgag 720

gatttcgctg tgtacttctg tcaacagtac cacacctggc ctcccctgac gttcggaggc 780

ggaaccaagg tcgaaatcaa gaccactacc ccagcaccga ggccacccac cccggctcct 840

accatcgcct cccagcctct gtccctgcgt ccggaggcat gtagacccgc agctggtggg 900

gccgtgcata cccggggtct tgacttcgcc tgcgatatct acatttgggc ccctctggct 960

ggtacttgcg gggtcctgct gctttcactc gtgatcactc tttactgtaa gcgcggtcgg 1020

aagaagctgc tgtacatctt taagcaaccc ttcatgaggc ctgtgcagac tactcaagag 1080

gaggacggct gttcatgccg gttcccagag gaggaggaag gcggctgcga actgcgcgtg 1140

aaattcagcc gcagcgcaga tgctccagcc tacaagcagg ggcagaacca gctctacaac 1200

gaactcaatc ttggtcggag agaggagtac gacgtgctgg acaagcggag aggacgggac 1260

ccagaaatgg gcgggaagcc gcgcagaaag aatccccaag agggcctgta caacgagctc 1320

caaaaggata agatggcaga agcctatagc gagattggta tgaaaggggа acgcagaaga 1380

ggcaaaggcc acgacggact gtaccaggga ctcagcaccg ccaccaagga cacctatgac 1440

gctcttcaca tgcaggccct gccgcctcgg 1470

<210> 394
<211> 254
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 394
Gln Val Asn Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Asn Thr Phe
20 25 30

Gly Met Ser Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35 40 45

Trp Leu Ala Leu Ile Asp Trp Asp Asp Asp Lys Tyr Tyr Ser Thr Ser
50 55 60

Leu Arg Thr Arg Leu Thr Ile Ser Lys Asp Thr Ala Lys Asn Gln Val
65 70 75 80

Val Leu Arg Met Thr Asn Met Asp Pro Met Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Ile Tyr Gly Gly Asp Arg Thr Asn Thr Gln Ala Pro Tyr
100 105 110

Phe Phe Asp Leu Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val
130 135 140

```
Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro
145                 150                 155                 160


Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly
                165                 170                 175


Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln
            180                 185                 190


Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg
        195                 200                 205


Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg
    210                 215                 220


Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln
225                 230                 235                 240


Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
                245                 250


<210> 395
<211> 762
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"

<400> 395
caagtcaacc tcagagaatc aggtcctgcc ctcgtcaaac ctacccagac cctcaccttg       60

acctgtacct tctccgggtt ctcgctgaac accttcggga tgtccgtgag ctggattagg      120

cagcccccgg gaaaggccct ggagtggctg gccctgatcg attgggatga cgacaagtac      180

tactccacct cactccgcac tcgcctgacc atctcaaagg acactgccaa gaaccaagtg      240
```

gtgctgcgga tgactaacat ggacccgatg gacaccgcca cctattactg cgcccggatc 300

tacggaggcg acagaaccaa cactcaggcc ccctacttct tcgatctgtg gggacagggc 360

actcttgtga ccgtgtcctc gggcggagga ggctccggtg gaggggatc aggaggaggc 420

ggcagcgacg tcgtgatgac tcaatccccg ctgtccttgc ctgtgacccc tggcgaaccc 480

gcgtccatta gctgccggag cagccagtcc ctcctgcact cgaacggata caactacctg 540

gattggtatc tgcagaagcc cggccagtcc ccacaactcc tgatctacct gggctctaat 600

cgggcatccg gggtcccgga tcgcttcagc ggttcgggct cgggtaccga cttcacgctg 660

aagatttcca gggtggaagc tgaggacgtg ggagtgtact actgcatgca ggcgcttcag 720

actccatgga catttggaca ggggaccaag ctggagatca ag 762

<210> 396
<211> 855
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 396
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtca acctcagaga atcaggtcct gccctcgtca aacctaccca gaccctcacc 120

ttgacctgta ccttctccgg gttctcgctg aacaccttcg ggatgtccgt gagctggatt 180

aggcagcccc cgggaaaggc cctggagtgg ctggccctga tcgattggga tgacgacaag 240

tactactcca cctcactccg cactcgcctg accatctcaa aggacactgc caagaaccaa 300

gtggtgctgc ggatgactaa catggacccg atggacaccg ccacctatta ctgcgcccgg 360

atctacggag gcgacagaac caacactcag gccccctact tcttcgatct gtggggacag 420

ggcactcttg tgaccgtgtc ctcgggcgga ggaggctccg gtggaggggg atcaggagga 480

ggcggcagcg acgtcgtgat gactcaatcc ccgctgtcct tgcctgtgac ccctggcgaa 540

cccgcgtcca ttagctgccg gagcagccag tccctcctgc actcgaacgg atacaactac 600

ctggattggt atctgcagaa gcccggccag tccccacaac tcctgatcta cctgggctct 660

aatcgggcat ccggggtccc ggatcgcttc agcggttcgg gctcgggtac cgacttcacg 720

ctgaagattt ccagggtgga agctgaggac gtgggagtgt actactgcat gcaggcgctt 780

cagactccat ggacatttgg acaggggacc aagctggaga tcaagggatc gcaccaccat 840

caccatcatc atcac 855

<210> 397
<211> 285
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 397
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Asn Leu Arg Glu Ser Gly Pro Ala Leu
20 25 30

Val Lys Pro Thr Gln Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe
35 40 45

Ser Leu Asn Thr Phe Gly Met Ser Val Ser Trp Ile Arg Gln Pro Pro
50 55 60

Gly Lys Ala Leu Glu Trp Leu Ala Leu Ile Asp Trp Asp Asp Asp Lys
65 70 75 80

Tyr Tyr Ser Thr Ser Leu Arg Thr Arg Leu Thr Ile Ser Lys Asp Thr
85 90 95

```
Ala Lys Asn Gln Val Val Leu Arg Met Thr Asn Met Asp Pro Met Asp
            100                 105                 110

Thr Ala Thr Tyr Tyr Cys Ala Arg Ile Tyr Gly Gly Asp Arg Thr Asn
        115                 120                 125

Thr Gln Ala Pro Tyr Phe Phe Asp Leu Trp Gly Gln Gly Thr Leu Val
    130                 135                 140

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val
                165                 170                 175

Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
            180                 185                 190

Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro
        195                 200                 205

Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser
    210                 215                 220

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
225                 230                 235                 240

Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys
                245                 250                 255

Met Gln Ala Leu Gln Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu
            260                 265                 270

Glu Ile Lys Gly Ser His His His His His His His His
        275                 280                 285
```

<210> 398
<211> 498
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 398
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Asn Leu Arg Glu Ser Gly Pro Ala Leu
20 25 30

Val Lys Pro Thr Gln Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe
35 40 45

Ser Leu Asn Thr Phe Gly Met Ser Val Ser Trp Ile Arg Gln Pro Pro
50 55 60

Gly Lys Ala Leu Glu Trp Leu Ala Leu Ile Asp Trp Asp Asp Asp Lys
65 70 75 80

Tyr Tyr Ser Thr Ser Leu Arg Thr Arg Leu Thr Ile Ser Lys Asp Thr
85 90 95

Ala Lys Asn Gln Val Val Leu Arg Met Thr Asn Met Asp Pro Met Asp
100 105 110

Thr Ala Thr Tyr Tyr Cys Ala Arg Ile Tyr Gly Gly Asp Arg Thr Asn
115 120 125

Thr Gln Ala Pro Tyr Phe Phe Asp Leu Trp Gly Gln Gly Thr Leu Val
130 135 140

```
Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160


Gly Gly Ser Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val
                165                 170                 175


Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
            180                 185                 190


Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro
        195                 200                 205


Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser
    210                 215                 220


Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
225                 230                 235                 240


Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys
                245                 250                 255


Met Gln Ala Leu Gln Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu
            260                 265                 270


Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
        275                 280                 285


Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
    290                 295                 300


Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
305                 310                 315                 320


Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
                325                 330                 335
```

Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
340 345 350

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
355 360 365

Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
370 375 380

Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys
385 390 395 400

Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
405 410 415

Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
420 425 430

Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
435 440 445

Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
450 455 460

Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
465 470 475 480

Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
485 490 495

Pro Arg

<210> 399
<211> 1494
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 399
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtca acctcagaga atcaggtcct gccctcgtca aacctaccca gaccctcacc 120

ttgacctgta ccttctccgg gttctcgctg aacaccttcg ggatgtccgt gagctggatt 180

aggcagcccc cgggaaaggc cctggagtgg ctggccctga tcgattggga tgacgacaag 240

tactactcca cctcactccg cactcgcctg accatctcaa aggacactgc caagaaccaa 300

gtggtgctgc ggatgactaa catggacccg atggacaccg ccacctatta ctgcgcccgg 360

atctacggag gcgacagaac caacactcag gccccctact tcttcgatct gtggggacag 420

ggcactcttg tgaccgtgtc ctcgggcgga ggaggctccg gtggaggggg atcaggagga 480

ggcggcagcg acgtcgtgat gactcaatcc ccgctgtcct tgcctgtgac ccctggcgaa 540

cccgcgtcca ttagctgccg gagcagccag tccctcctgc actcgaacgg atacaactac 600

ctggattggt atctgcagaa gcccggccag tccccacaac tcctgatcta cctgggctct 660

aatcgggcat ccggggtccc ggatcgcttc agcggttcgg gctcgggtac cgacttcacg 720

ctgaagattt ccagggtgga agctgaggac gtgggagtgt actactgcat gcaggcgctt 780

cagactccat ggacatttgg acaggggacc aagctggaga tcaagaccac taccccagca 840

ccgaggccac ccaccccggc tcctaccatc gcctcccagc ctctgtccct gcgtccggag 900

gcatgtagac ccgcagctgg tggggccgtg catacccggg gtcttgactt cgcctgcgat 960

atctacattt gggcccctct ggctggtact tgcggggtcc tgctgctttc actcgtgatc 1020

actctttact gtaagcgcgg tcggaagaag ctgctgtaca tctttaagca acccttcatg 1080

aggcctgtgc agactactca agaggaggac ggctgttcat gccggttccc agaggaggag 1140

gaaggcggct gcgaactgcg cgtgaaattc agccgcagcg cagatgctcc agcctacaag 1200

caggggcaga accagctcta caacgaactc aatcttggtc ggagagagga gtacgacgtg 1260

ctggacaagc ggagaggacg ggacccagaa atgggcggga agccgcgcag aaagaatccc 1320

caagagggcc tgtacaacga gctccaaaag gataagatgg cagaagccta tagcgagatt 1380

ggtatgaaag gggaacgcag aagaggcaaa ggccacgacg gactgtacca gggactcagc 1440

accgccacca aggacaccta tgacgctctt cacatgcagg ccctgccgcc tcgg 1494

<210> 400
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 400
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Ala Ser Ile Thr Ser Arg
20 25 30

His Trp Trp Asn Trp Val Arg His Ser Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Gln Ile Tyr His Ser Gly Thr Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Gly Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Ile Ser
65 70 75 80

Leu Glu Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Val Arg Asp Tyr Leu Glu Leu Ala Thr Tyr Tyr Gly Met Asp Val Trp
100 105 110

```
Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
    130                 135                 140


Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys
145                 150                 155                 160


Arg Ser Ser Gln Ser Leu Leu Tyr Ser Asp Gly Tyr Asn Tyr Leu Asp
                165                 170                 175


Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu
            180                 185                 190


Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
        195                 200                 205


Ser Gly Thr Asp Phe Thr Leu Gln Ile Ser Gly Val Glu Thr Glu Asp
    210                 215                 220


Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln Thr Gln Ser Phe Gly
225                 230                 235                 240


Gln Gly Thr Lys Leu Glu Ile Lys
                245
```

<210> 401
<211> 744
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 401

caagtgcagc ttcaagaatc aggacctggc ctcgtcaaac cctccggtac cctctccctc 60

acctgtgccg tgtccggggc atctatcacc tcccgccact ggtggaactg ggtcagacac 120

tccccgggaa agggattgga gtggattggc cagatctacc attccggcac cactacttac 180

aacccgtccc tgggctcccg cgtcactatc tccgtggaca agtccaagaa tcagattagc 240

ctggagctgc ggtccgtgac cgctgccgat accgcgacct attactgcgt gcgggactac 300

ctggagctcg ccacgtacta cggaatggac gtctggggcc agggcactac cgtgaccgtg 360

tcaagcgggg ggggcggatc gggtggtgga ggatcgggag gaggagggtc ggaaatcgtg 420

ctgactcagt ccccctgtc gctgcctgtg actcctgggg aaccagcctc aattagctgc 480

cgctcgagcc agtccctgct gtattccgac ggatacaact acctggattg gtaccttcaa 540

aagcccggcc agagcccgca gctgctgatc tacctgggtt caaacagggc ctccggcgtg 600

ccggatcggt tctcgggaag cggtagcggg acagacttca ccctgcaaat cagcggagtg 660

gaaactgagg acgtgggcgt gtactactgc atgcaggcgt tgcagaccca gtcctttgga 720

caaggcacca agctcgaaat caag 744

<210> 402
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 402
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agcttcaaga atcaggacct ggcctcgtca aaccctccgg taccctctcc 120

ctcacctgtg ccgtgtccgg ggcatctatc acctcccgcc actggtggaa ctgggtcaga 180

cactccccgg gaaagggatt ggagtggatt ggccagatct accattccgg caccactact 240

tacaacccgt ccctgggctc ccgcgtcact atctccgtgg acaagtccaa gaatcagatt 300

agcctggagc tgcggtccgt gaccgctgcc gataccgcga cctattactg cgtgcgggac 360

tacctggagc tcgccacgta ctacggaatg gacgtctggg gccagggcac taccgtgacc 420

gtgtcaagcg gggggggcgg atcgggtggt ggaggatcgg gaggaggagg gtcggaaatc 480

gtgctgactc agtccccct gtcgctgcct gtgactcctg gggaaccagc ctcaattagc 540

tgccgctcga gccagtccct gctgtattcc gacggataca actacctgga ttggtacctt 600

caaaagcccg gccagagccc gcagctgctg atctacctgg gttcaaacag ggcctccggc 660

gtgccggatc ggttctcggg aagcggtagc gggacagact tcaccctgca aatcagcgga 720

gtggaaactg aggacgtggg cgtgtactac tgcatgcagg cgttgcagac ccagtccttt 780

ggacaaggca ccaagctcga aatcaaggga tcgcaccacc atcaccatca tcatcac 837

<210> 403
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 403
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
20 25 30

Val Lys Pro Ser Gly Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Ala
35 40 45

Ser Ile Thr Ser Arg His Trp Trp Asn Trp Val Arg His Ser Pro Gly
50 55 60

Lys Gly Leu Glu Trp Ile Gly Gln Ile Tyr His Ser Gly Thr Thr Thr
65 70 75 80

```
Tyr Asn Pro Ser Leu Gly Ser Arg Val Thr Ile Ser Val Asp Lys Ser
                85                  90                  95

Lys Asn Gln Ile Ser Leu Glu Leu Arg Ser Val Thr Ala Ala Asp Thr
            100                 105                 110

Ala Thr Tyr Tyr Cys Val Arg Asp Tyr Leu Glu Leu Ala Thr Tyr Tyr
        115                 120                 125

Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro
                165                 170                 175

Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Tyr Ser Asp Gly
            180                 185                 190

Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln
        195                 200                 205

Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg
    210                 215                 220

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Gln Ile Ser Gly
225                 230                 235                 240

Val Glu Thr Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln
                245                 250                 255

Thr Gln Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Ser His
            260                 265                 270
```

His His His His His His His
        275

<210> 404
<211> 492
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 404
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1   5   10   15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu
            20   25   30

Val Lys Pro Ser Gly Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Ala
        35   40   45

Ser Ile Thr Ser Arg His Trp Trp Asn Trp Val Arg His Ser Pro Gly
    50   55   60

Lys Gly Leu Glu Trp Ile Gly Gln Ile Tyr His Ser Gly Thr Thr Thr
65   70   75   80

Tyr Asn Pro Ser Leu Gly Ser Arg Val Thr Ile Ser Val Asp Lys Ser
                85   90   95

Lys Asn Gln Ile Ser Leu Glu Leu Arg Ser Val Thr Ala Ala Asp Thr
            100   105   110

Ala Thr Tyr Tyr Cys Val Arg Asp Tyr Leu Glu Leu Ala Thr Tyr Tyr
        115   120   125

```
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile
145                 150                 155                 160

Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro
                165                 170                 175

Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Tyr Ser Asp Gly
            180                 185                 190

Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln
        195                 200                 205

Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg
    210                 215                 220

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Gln Ile Ser Gly
225                 230                 235                 240

Val Glu Thr Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln
                245                 250                 255

Thr Gln Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr
            260                 265                 270

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        275                 280                 285

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    290                 295                 300

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
305                 310                 315                 320
```

```
Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
                325                 330                 335

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
            340                 345                 350

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
        355                 360                 365

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
    370                 375                 380

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
385                 390                 395                 400

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                405                 410                 415

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            420                 425                 430

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        435                 440                 445

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    450                 455                 460

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
465                 470                 475                 480

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 405
<211> 1476
<212> DNA

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 405
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agcttcaaga atcaggacct ggcctcgtca aaccctccgg taccctctcc 120

ctcacctgtg ccgtgtccgg ggcatctatc acctcccgcc actggtggaa ctgggtcaga 180

cactccccgg gaaagggatt ggagtggatt ggccagatct accattccgg caccactact 240

tacaacccgt ccctgggctc ccgcgtcact atctccgtgg acaagtccaa gaatcagatt 300

agcctggagc tgcggtccgt gaccgctgcc gataccgcga cctattactg cgtgcgggac 360

tacctggagc tcgccacgta ctacggaatg gacgtctggg gccagggcac taccgtgacc 420

gtgtcaagcg gggggggcgg atcgggtggt ggaggatcgg gaggaggagg gtcggaaatc 480

gtgctgactc agtcccccct gtcgctgcct gtgactcctg gggaaccagc ctcaattagc 540

tgccgctcga gccagtccct gctgtattcc gacggataca actacctgga ttggtacctt 600

caaaagcccg gccagagccc gcagctgctg atctacctgg gttcaaacag ggcctccggc 660

gtgccggatc ggttctcggg aagcggtagc gggacagact tcaccctgca aatcagcgga 720

gtggaaactg aggacgtggg cgtgtactac tgcatgcagg cgttgcagac ccagtccttt 780

ggacaaggca ccaagctcga aatcaagacc actaccccag caccgaggcc acccaccccg 840

gctcctacca tcgcctccca gcctctgtcc ctgcgtccgg aggcatgtag acccgcagct 900

ggtggggccg tgcatacccg gggtcttgac ttcgcctgcg atatctacat ttgggccct 960

ctggctggta cttgcggggt cctgctgctt tcactcgtga tcactcttta ctgtaagcgc 1020

ggtcggaaga agctgctgta catctttaag caacccttca tgaggcctgt gcagactact 1080

caagaggagg acggctgttc atgccggttc ccagaggagg aggaaggcgg ctgcgaactg 1140

cgcgtgaaat tcagccgcag cgcagatgct ccagcctaca agcaggggca gaaccagctc 1200

tacaacgaac tcaatcttgg tcggagagag gagtacgacg tgctggacaa gcggagagga 1260

cgggacccag aaatgggcgg gaagccgcgc agaaagaatc cccaagaggg cctgtacaac 1320

gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggtatgaa aggggaacgc 1380

agaagaggca aaggccacga cggactgtac cagggactca gcaccgccac caaggacacc 1440

tatgacgctc ttcacatgca ggccctgccg cctcgg 1476

<210> 406
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 406

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1				5				10					15		
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
			20					25					30		
Tyr	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Ile	Ile	Asn	Pro	Ser	Gly	Gly	Ser	Thr	Ser	Tyr	Ala	Gln	Lys	Phe
	50					55					60				
Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr
65					70					75					80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Asp	Leu	Ala	Ala	Ala	Gly	Asn	Tyr	Tyr	Tyr	Tyr	Gly	Met	Asp
			100					105					110		

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Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly
        115                 120                 125


Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Ser Glu Leu Thr
    130                 135                 140


Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Ala Arg Ile Thr
145                 150                 155                 160


Cys Gln Gly Asp Ser Leu Arg Ser Tyr Phe Thr Ser Trp Tyr His Gln
                165                 170                 175


Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Asn Asn Asn Arg
            180                 185                 190


Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr
        195                 200                 205


Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Gly Asp Tyr
    210                 215                 220


Tyr Cys Asp Ser Arg Asp Ser Ser Gly Asp His Leu Val Phe Gly Gly
225                 230                 235                 240


Gly Thr Lys Leu Thr Val Leu
                245
```

<210> 407
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 407
caagtccaac tcgtccagtc cggtgcagaa gtcaagaaac caggagcttc agtgaaagtg 60

tcgtgcaagg cctccggcta taccttcacc tcctactaca tgcactgggt gcgccaggcc 120

ccgggccagg gactggagtg gatgggaatt atcaaccctt cgggcggctc cactagctac 180

gcccaaaagt ttcaggggag agtgaccatg actcgggaca cctcaacctc gaccgtgtac 240

atggaactgt cgtcactgcg gtccgaggac accgccgtgt actactgcgc gcgcgacttg 300

gccgccgcgg ggaattacta ctactacgga atggatgtct ggggacaggg aaccactgtg 360

actgtgtcgt ctggtggtgg tggaagcggg ggaggaggtt cgggcggcgg cggaagctcc 420

tccgaactga cccaggaccc tgcggtgtcc gtggccctgg gacagaccgc aaggatcacg 480

tgtcagggag acagcctccg ctcctacttc acatcctggt atcatcagaa gcccggccag 540

gctccggtgc tggtcatcta cggaaacaac aacagaccgt ccgggattcc cgaccggttc 600

agcggctcct catccggcaa caccgcctcc ctgaccatca ccggcgccca ggccgaggac 660

gagggagatt actactgcga ctcccgggat agcagcggcg atcacctcgt gttcggggga 720

gggactaagc ttactgtgct g 741

<210> 408
<211> 834
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 408
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca gtccggtgca gaagtcaaga aaccaggagc ttcagtgaaa 120

gtgtcgtgca aggcctccgg ctataccttc acctcctact acatgcactg ggtgcgccag 180

gccccgggcc agggactgga gtggatggga attatcaacc cttcgggcgg ctccactagc 240

tacgcccaaa agtttcaggg gagagtgacc atgactcggg acacctcaac ctcgaccgtg 300

tacatggaac tgtcgtcact gcggtccgag gacaccgccg tgtactactg cgcgcgcgac 360

ttggccgccg cggggaatta ctactactac ggaatggatg tctggggaca gggaaccact 420

gtgactgtgt cgtctggtgg tggtggaagc gggggaggag gttcgggcgg cggcggaagc 480

tcctccgaac tgacccagga ccctgcggtg tccgtggccc tgggacagac cgcaaggatc 540

acgtgtcagg gagacagcct ccgctcctac ttcacatcct ggtatcatca gaagcccggc 600

caggctccgg tgctggtcat ctacggaaac aacaacagac cgtccgggat tcccgaccgg 660

ttcagcggct cctcatccgg caacaccgcc tccctgacca tcaccggcgc ccaggccgag 720

gacgagggag attactactg cgactcccgg gatagcagcg gcgatcacct cgtgttcggg 780

ggagggacta agcttactgt gctgggatcg caccaccatc accatcatca tcac 834

<210> 409
<211> 278
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 409
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser

65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Leu Ala Ala Ala Gly Asn Tyr Tyr
115 120 125

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145 150 155 160

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
165 170 175

Thr Ala Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Phe Thr
180 185 190

Ser Trp Tyr His Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
195 200 205

Gly Asn Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
210 215 220

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
225 230 235 240

Asp Glu Gly Asp Tyr Tyr Cys Asp Ser Arg Asp Ser Ser Gly Asp His
245 250 255

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser His His

260 265 270

His His His His His His
275

<210> 410
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 410
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Leu Ala Ala Ala Gly Asn Tyr Tyr
115 120 125

```
Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145                 150                 155                 160

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
                165                 170                 175

Thr Ala Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Phe Thr
            180                 185                 190

Ser Trp Tyr His Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        195                 200                 205

Gly Asn Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    210                 215                 220

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
225                 230                 235                 240

Asp Glu Gly Asp Tyr Tyr Cys Asp Ser Arg Asp Ser Ser Gly Asp His
                245                 250                 255

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320
```

```
Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 411
<211> 1473

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 411
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca gtccggtgca gaagtcaaga aaccaggagc ttcagtgaaa 120

gtgtcgtgca aggcctccgg ctataccttc acctcctact acatgcactg ggtgcgccag 180

gccccgggcc agggactgga gtggatggga attatcaacc cttcgggcgg ctccactagc 240

tacgcccaaa agtttcaggg gagagtgacc atgactcggg acacctcaac ctcgaccgtg 300

tacatggaac tgtcgtcact gcggtccgag gacaccgccg tgtactactg cgcgcgcgac 360

ttggccgccg cggggaatta ctactactac ggaatggatg tctggggaca gggaaccact 420

gtgactgtgt cgtctggtgg tggtggaagc gggggaggag gttcgggcgg cggcggaagc 480

tcctccgaac tgacccagga ccctgcggtg tccgtggccc tgggacagac cgcaaggatc 540

acgtgtcagg gagacagcct ccgctcctac ttcacatcct ggtatcatca gaagcccggc 600

caggctccgg tgctggtcat ctacggaaac aacaacagac cgtccgggat tcccgaccgg 660

ttcagcggct cctcatccgg caacaccgcc tccctgacca tcaccggcgc ccaggccgag 720

gacgagggag attactactg cgactcccgg gatagcagcg gcgatcacct cgtgttcggg 780

ggagggacta agcttactgt gctgaccact accccagcac cgaggccacc caccccggct 840

cctaccatcg cctcccagcc tctgtccctg cgtccggagg catgtagacc cgcagctggt 900

ggggccgtgc atacccgggg tcttgacttc gcctgcgata tctacatttg ggcccctctg 960

gctggtactt gcggggtcct gctgctttca ctcgtgatca ctctttactg taagcgcggt 1020

cggaagaagc tgctgtacat ctttaagcaa cccttcatga ggcctgtgca gactactcaa 1080

gaggaggacg gctgttcatg ccggttccca gaggaggagg aaggcggctg cgaactgcgc 1140

gtgaaattca gccgcagcgc agatgctcca gcctacaagc aggggcagaa ccagctctac 1200

aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

gacccagaaa tgggcgggaa gccgcgcaga aagaatcccc aagagggcct gtacaacgag 1320

ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 412
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 412
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Asp Asp Phe Trp Ser Gly Ser Gly Ala Phe Asp Ile Trp

100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Ser Glu Leu Thr Gln Asp
130 135 140

Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr Cys Gln
145 150 155 160

Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg Pro Ser
180 185 190

Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr Ala Ser
195 200 205

Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
210 215 220

Asn Ser Arg Asp Ser Ser Gly Asn His Pro Val Val Phe Gly Gly Gly
225 230 235 240

Thr Lys Leu Thr Val Leu
245

<210> 413
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 413
caagtccaac tcgtccaatc cggtgcagaa gtcaagaaac ctggagcttc cgtgaaagtg 60

tcctgcaagg cgtcaggcta cacctttacg tcctactaca tgcactgggt ccgccaggcc 120

ccgggccagg gcttggagtg gatgggaatc attaacccca gcggcggcag cactagctat 180

gcccagaagt tccagggtcg ggtcaccatg actagagaca catccacctc caccgtgtac 240

atggaactga gctccctgcg gtccgaggat accgcggtgt actactgcgc ccgcgatgac 300

gacttctggt ccggctcggg ggcattcgac atctggggac agggcaccac cgtgactgtg 360

tcctccggcg gtggaggatc gggtggcgga ggaagcggtg gaggcggatc ttcgtccgaa 420

ctgactcagg accctgccgt gtcggtggcc ctgggacaga ctgtgcgcat cacctgtcaa 480

ggagatagcc tgaggtcgta ctatgcctcc tggtaccagc agaagcccgg acaggccccg 540

gtgcttgtga tctacgggaa gaacaacaga ccgtcaggga ttccagaccg gttcagcggg 600

tcatccagcg ggaataccgc ttccctcact atcaccggag cccaggcgga ggacgaggcc 660

gattactact gcaactcgcg ggactcatcc ggcaaccatc ccgtggtgtt cggaggggggc 720

actaagctga ccgtgctg 738

<210> 414
<211> 831
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 414
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca atccggtgca gaagtcaaga aacctggagc ttccgtgaaa 120

gtgtcctgca aggcgtcagg ctacaccttt acgtcctact acatgcactg ggtccgccag 180

gccccgggcc agggcttgga gtggatggga atcattaacc ccagcggcgg cagcactagc 240

tatgcccaga agttccaggg tcgggtcacc atgactagag acacatccac ctccaccgtg 300

tacatggaac tgagctccct gcggtccgag gataccgcgg tgtactactg cgcccgcgat 360

gacgacttct ggtccggctc gggggcattc gacatctggg gacagggcac caccgtgact 420

gtgtcctccg gcggtggagg atcgggtggc ggaggaagcg gtggaggcgg atcttcgtcc 480

gaactgactc aggaccctgc cgtgtcggtg gccctgggac agactgtgcg catcacctgt 540

caaggagata gcctgaggtc gtactatgcc tcctggtacc agcagaagcc cggacaggcc 600

ccggtgcttg tgatctacgg gaagaacaac agaccgtcag ggattccaga ccggttcagc 660

gggtcatcca gcgggaatac cgcttccctc actatcaccg gagcccaggc ggaggacgag 720

gccgattact actgcaactc gcgggactca tccggcaacc atcccgtggt gttcggaggg 780

ggcactaagc tgaccgtgct gggatcgcac caccatcacc atcatcatca c 831

<210> 415
<211> 277
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 415
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

```
Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80


Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95


Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110


Ala Val Tyr Tyr Cys Ala Arg Asp Asp Asp Phe Trp Ser Gly Ser Gly
        115                 120                 125


Ala Phe Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly
    130                 135                 140


Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Ser
145                 150                 155                 160


Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val
                165                 170                 175


Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp
            180                 185                 190


Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys
        195                 200                 205


Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser
    210                 215                 220


Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu
225                 230                 235                 240


Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His Pro Val
                245                 250                 255
```

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser His His His
260 265 270

His His His His His
275

<210> 416
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 416
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Asp Asp Phe Trp Ser Gly Ser Gly

```
        115                 120                 125

Ala Phe Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Ser
145                 150                 155                 160

Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val
                165                 170                 175

Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys
        195                 200                 205

Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser
    210                 215                 220

Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu
225                 230                 235                 240

Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His Pro Val
                245                 250                 255

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Thr Thr Thr Pro Ala
            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
```

305 310 315 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
325 330 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
340 345 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
355 360 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
370 375 380

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385 390 395 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
405 410 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
420 425 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
435 440 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
450 455 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465 470 475 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 417

<211> 1470
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 417
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca atccggtgca gaagtcaaga aacctggagc ttccgtgaaa 120

gtgtcctgca aggcgtcagg ctacaccttt acgtcctact acatgcactg ggtccgccag 180

gccccgggcc agggcttgga gtggatggga atcattaacc ccagcggcgg cagcactagc 240

tatgcccaga agttccaggg tcgggtcacc atgactagag acacatccac ctccaccgtg 300

tacatggaac tgagctccct gcggtccgag gataccgcgg tgtactactg cgcccgcgat 360

gacgacttct ggtccggctc gggggcattc gacatctggg gacagggcac caccgtgact 420

gtgtcctccg gcggtggagg atcgggtggc ggaggaagcg gtggaggcgg atcttcgtcc 480

gaactgactc aggaccctgc cgtgtcggtg gccctgggac agactgtgcg catcacctgt 540

caaggagata gcctgaggtc gtactatgcc tcctggtacc agcagaagcc cggacaggcc 600

ccggtgcttg tgatctacgg gaagaacaac agaccgtcag ggattccaga ccggttcagc 660

gggtcatcca gcgggaatac cgcttccctc actatcaccg gagcccaggc ggaggacgag 720

gccgattact actgcaactc gcgggactca tccggcaacc atcccgtggt gttcggaggg 780

ggcactaagc tgaccgtgct gaccactacc ccagcaccga ggccacccac cccggctcct 840

accatcgcct cccagcctct gtccctgcgt ccggaggcat gtagacccgc agctggtggg 900

gccgtgcata cccggggtct tgacttcgcc tgcgatatct acatttgggc ccctctggct 960

ggtacttgcg gggtcctgct gctttcactc gtgatcactc tttactgtaa gcgcggtcgg 1020

aagaagctgc tgtacatctt taagcaaccc ttcatgaggc ctgtgcagac tactcaagag 1080

gaggacggct gttcatgccg gttcccagag gaggaggaag gcggctgcga actgcgcgtg 1140

aaattcagcc gcagcgcaga tgctccagcc tacaagcagg ggcagaacca gctctacaac 1200

gaactcaatc ttggtcggag agaggagtac gacgtgctgg acaagcggag aggacgggac 1260

ccagaaatgg gcgggaagcc gcgcagaaag aatccccaag agggcctgta caacgagctc 1320

caaaaggata agatggcaga agcctatagc gagattggta tgaaagggga acgcagaaga 1380

ggcaaaggcc acgacggact gtaccaggga ctcagcaccg ccaccaagga cacctatgac 1440

gctcttcaca tgcaggccct gccgcctcgg 1470

<210> 418
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 418
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

```
Ala Arg Pro Glu Gly Val Ser Tyr Tyr Asp Ser Ser Val Leu Asp Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
        115                 120                 125


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln
    130                 135                 140


Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys
145                 150                 155                 160


Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Lys His Val Ser Trp Tyr
                165                 170                 175


Gln His His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp Val Ser
            180                 185                 190


Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly
        195                 200                 205


Asn Thr Ala Ser Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala
    210                 215                 220


His Tyr Tyr Cys Val Ser Tyr Arg Asn Phe Asn Ser Leu Val Phe Gly
225                 230                 235                 240


Thr Gly Thr Lys Val Thr Val Leu
                245
```

<210> 419
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<400> 419
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca gtccggtgca gaagtcaaga aacccggagc ttccgtgaaa 120

gtgtcctgca aggcctcggg gtataccttc acttcctact acatgcactg ggtccggcag 180

gcgccgggac agggactgga atggatgggt atcatcaacc cctcgggcgg ttccactagc 240

tacgcccaga agttccaggg aagagtgacc atgacccggg acacttccac ttcgaccgtg 300

tacatggaac tgagcagcct gaggagcgag gacaccgccg tgtactactg tgcccggccc 360

gagggagtgt cctactacga ttcctccgtg ctggattact ggggacaggg aacacttgtg 420

accgtgtcct cgggaggagg cggaagcggg ggcggagggt ctgggggagg cggctcccag 480

tccgctctga cgcagcctgc gtccgtgtcc gggagccctg gccagagcat tactatttca 540

tgcaccggta ccagctccga cgtgggcgga tataagcacg tgtcatggta ccagcatcac 600

ccgggaaagg ccccaaagct gatgatctac gacgtgtcga acagaccgag cggggtgtca 660

aatcgctttt ccggttcaaa gtcgggcaac actgcctcac tcaccgtgtc gggcctccaa 720

gcggaggacg aagcccacta ctactgcgtg tcctaccgca acttcaactc cttggtgttc 780

ggcaccggca ccaaggtcac cgtcctggga tcgcaccacc atcaccatca tcatcac 837

<210> 420
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 420
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val

```
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Pro Glu Gly Val Ser Tyr Tyr Asp Ser
        115                 120                 125

Ser Val Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
145                 150                 155                 160

Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser
                165                 170                 175

Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Lys
            180                 185                 190

His Val Ser Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Leu Met
        195                 200                 205

Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser
```

210 215 220

Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Val Ser Gly Leu Gln
225 230 235 240

Ala Glu Asp Glu Ala His Tyr Tyr Cys Val Ser Tyr Arg Asn Phe Asn
245 250 255

Ser Leu Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Ser His
260 265 270

His His His His His His His
275

<210> 421
<211> 492
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 421
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65 70 75 80

```
Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Pro Glu Gly Val Ser Tyr Tyr Asp Ser
        115                 120                 125

Ser Val Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
145                 150                 155                 160

Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser
                165                 170                 175

Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Lys
            180                 185                 190

His Val Ser Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Leu Met
        195                 200                 205

Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser
    210                 215                 220

Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Val Ser Gly Leu Gln
225                 230                 235                 240

Ala Glu Asp Glu Ala His Tyr Tyr Cys Val Ser Tyr Arg Asn Phe Asn
                245                 250                 255

Ser Leu Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Thr Thr Thr
            260                 265                 270
```

```
Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        275                 280                 285

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    290                 295                 300

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
305                 310                 315                 320

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
                325                 330                 335

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
            340                 345                 350

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
        355                 360                 365

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
    370                 375                 380

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
385                 390                 395                 400

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                405                 410                 415

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            420                 425                 430

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        435                 440                 445

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    450                 455                 460
```

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
465 470 475 480

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 422
<211> 1476
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 422
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca gtccggtgca gaagtcaaga aacccggagc ttccgtgaaa 120

gtgtcctgca aggcctcggg gtataccttc acttcctact acatgcactg ggtccggcag 180

gcgccgggac agggactgga atggatgggt atcatcaacc cctcgggcgg ttccactagc 240

tacgcccaga agttccaggg aagagtgacc atgacccggg acacttccac ttcgaccgtg 300

tacatggaac tgagcagcct gaggagcgag gacaccgccg tgtactactg tgcccggccc 360

gagggagtgt cctactacga ttcctccgtg ctggattact ggggacaggg aacacttgtg 420

accgtgtcct cgggaggagg cggaagcggg ggcggagggt ctgggggagg cggctcccag 480

tccgctctga cgcagcctgc gtccgtgtcc gggagccctg gccagagcat tactatttca 540

tgcaccggta ccagctccga cgtgggcgga tataagcacg tgtcatggta ccagcatcac 600

ccgggaaagg ccccaaagct gatgatctac gacgtgtcga acagaccgag cggggtgtca 660

aatcgctttt ccggttcaaa gtcgggcaac actgcctcac tcaccgtgtc gggcctccaa 720

gcggaggacg aagcccacta ctactgcgtg tcctaccgca acttcaactc cttggtgttc 780

ggcaccggca ccaaggtcac cgtcctgacc actaccccag caccgaggcc acccaccccg 840

gctcctacca tcgcctccca gcctctgtcc ctgcgtccgg aggcatgtag acccgcagct 900

ggtggggccg tgcatacccg gggtcttgac ttcgcctgcg atatctacat ttgggcccct 960

ctggctggta cttgcggggt cctgctgctt tcactcgtga tcactcttta ctgtaagcgc 1020

ggtcggaaga agctgctgta catctttaag caacccttca tgaggcctgt gcagactact 1080

caagaggagg acggctgttc atgccggttc ccagaggagg aggaaggcgg ctgcgaactg 1140

cgcgtgaaat tcagccgcag cgcagatgct ccagcctaca agcaggggca gaaccagctc 1200

tacaacgaac tcaatcttgg tcggagagag gagtacgacg tgctggacaa gcggagagga 1260

cgggacccag aaatgggcgg gaagccgcgc agaaagaatc cccaagaggg cctgtacaac 1320

gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggtatgaa aggggaacgc 1380

agaagaggca aaggccacga cggactgtac cagggactca gcaccgccac caaggacacc 1440

tatgacgctc ttcacatgca ggccctgccg cctcgg 1476

<210> 423
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 423
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe

```
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Gly Tyr Gly Asp Tyr Leu Asp Ala Phe Asp Ile Trp Gly
            100                 105                 110

Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Ser Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala
    130                 135                 140

Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly
145                 150                 155                 160

Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln
                165                 170                 175

His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Val Ser Asn Arg
            180                 185                 190

Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr
        195                 200                 205

Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr
    210                 215                 220

Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu Val Phe Gly Thr Gly
225                 230                 235                 240

Thr Gln Leu Thr Val Leu
```

<210> 424
<211> 738
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 424
caagtccaac tcgtccaatc cggtgcagaa gtcaagaaac ctggagcatc cgtgaaagtg 60

tcctgcaagg cgtccgggta tacgttcacc tcctactaca tgcactgggt gcgccaggcc 120

ccgggacagg gactggaatg gatgggaatc atcaatccta gcggcggcag caccagctac 180

gcccagaagt ttcagggccg cgtgaccatg accagggaca ctagcacctc caccgtgtac 240

atggaattgt ccagcctgag agccgaggat actgctgtgt actactgcgc ccggggcgga 300

tacggagatt atctggacgc cttcgacatt tggggacagg gcactactgt gaccgtgtcc 360

tcgggggggag gcggctcggg gggcggcgga tcaggatcag gcggttccca gtccgcgctg 420

acacagcccg cttccgtgag cggttcgccc gggcagtcca tcaccatttc gtgtaccgga 480

acttcctccg acgtcggtgg ctacaactac gtgtcgtggt accagcaaca tccgggaaag 540

gccccaaagc tcatgatcta cgaggtgtcc aaccggccgt ccggggtgtc aaaccggttc 600

agcggctcaa agagcggaaa caccgcctcc ctcaccatct cgggactgca ggccgaggat 660

gaagcggact actactgctc gagctacact tcctcatcta ccctggtgtt cgggactggt 720

acccagctta ccgtgctg 738

<210> 425
<211> 831
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 425
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca atccggtgca gaagtcaaga aacctggagc atccgtgaaa 120

gtgtcctgca aggcgtccgg gtatacgttc acctcctact acatgcactg ggtgcgccag 180

gccccgggac agggactgga atggatggga atcatcaatc ctagcggcgg cagcaccagc 240

tacgcccaga agtttcaggg ccgcgtgacc atgaccaggg acactagcac ctccaccgtg 300

tacatggaat tgtccagcct gagagccgag gatactgctg tgtactactg cgcccggggc 360

ggatacggag attatctgga cgccttcgac atttggggac agggcactac tgtgaccgtg 420

tcctcggggg gaggcggctc gggggggcggc ggatcaggat caggcggttc ccagtccgcg 480

ctgacacagc ccgcttccgt gagcggttcg cccgggcagt ccatcaccat ttcgtgtacc 540

ggaacttcct ccgacgtcgg tggctacaac tacgtgtcgt ggtaccagca acatccggga 600

aaggccccaa agctcatgat ctacgaggtg tccaaccggc cgtccggggt gtcaaaccgg 660

ttcagcggct caaagagcgg aaacaccgcc tccctcacca tctcgggact gcaggccgag 720

gatgaagcgg actactactg ctcgagctac acttcctcat ctaccctggt gttcgggact 780

ggtacccagc ttaccgtgct gggatcgcac caccatcacc atcatcatca c 831

<210> 426
<211> 277
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 426
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Gly Tyr Gly Asp Tyr Leu Asp Ala
        115                 120                 125

Phe Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Ser Gly Gly Ser Gln Ser Ala
145                 150                 155                 160

Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr
                165                 170                 175

Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val
            180                 185                 190

Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr
        195                 200                 205
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Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser
210 215 220

Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu
225 230 235 240

Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu
245 250 255

Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu Gly Ser His His His
260 265 270

His His His His His
275

<210> 427
<211> 490
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 427
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser

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65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Gly Tyr Gly Asp Tyr Leu Asp Ala
        115                 120                 125

Phe Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Ser Gly Gly Ser Gln Ser Ala
145                 150                 155                 160

Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr
                165                 170                 175

Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val
            180                 185                 190

Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr
        195                 200                 205

Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser
    210                 215                 220

Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu
225                 230                 235                 240

Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Thr Leu
                245                 250                 255

Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu Thr Thr Thr Pro Ala
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            260                 265                 270

Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser
        275                 280                 285

Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr
    290                 295                 300

Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala
305                 310                 315                 320

Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys
                325                 330                 335

Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
            340                 345                 350

Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
        355                 360                 365

Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg
    370                 375                 380

Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn
385                 390                 395                 400

Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg
                405                 410                 415

Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro
            420                 425                 430

Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala
        435                 440                 445

Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His
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450 455 460

Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp
465 470 475 480

Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 428
<211> 1470
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 428
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca atccggtgca gaagtcaaga aacctggagc atccgtgaaa 120

gtgtcctgca aggcgtccgg gtatacgttc acctcctact acatgcactg ggtgcgccag 180

gccccgggac agggactgga atggatggga atcatcaatc ctagcggcgg cagcaccagc 240

tacgcccaga agtttcaggg ccgcgtgacc atgaccaggg acactagcac ctccaccgtg 300

tacatggaat tgtccagcct gagagccgag gatactgctg tgtactactg cgccccgggc 360

ggatacggag attatctgga cgccttcgac atttggggac agggcactac tgtgaccgtg 420

tcctcggggg gaggcggctc gggggggcggc ggatcaggat caggcggttc ccagtccgcg 480

ctgacacagc ccgcttccgt gagcggttcg cccgggcagt ccatcaccat ttcgtgtacc 540

ggaacttcct ccgacgtcgg tggctacaac tacgtgtcgt ggtaccagca acatccggga 600

aaggccccaa agctcatgat ctacgaggtg tccaaccggc cgtccggggt gtcaaaccgg 660

ttcagcggct caaagagcgg aaacaccgcc tccctcacca tctcgggact gcaggccgag 720

gatgaagcgg actactactg ctcgagctac acttcctcat ctaccctggt gttcgggact 780

ggtacccagc ttaccgtgct gaccactacc ccagcaccga ggccacccac cccggctcct 840

accatcgcct cccagcctct gtccctgcgt ccggaggcat gtagacccgc agctggtggg 900

gccgtgcata cccggggtct tgacttcgcc tgcgatatct acatttgggc ccctctggct 960

ggtacttgcg gggtcctgct gctttcactc gtgatcactc tttactgtaa gcgcggtcgg 1020

aagaagctgc tgtacatctt taagcaaccc ttcatgaggc ctgtgcagac tactcaagag 1080

gaggacggct gttcatgccg gttcccagag gaggaggaag gcggctgcga actgcgcgtg 1140

aaattcagcc gcagcgcaga tgctccagcc tacaagcagg ggcagaacca gctctacaac 1200

gaactcaatc ttggtcggag agaggagtac gacgtgctgg acaagcggag aggacgggac 1260

ccagaaatgg gcgggaagcc gcgcagaaag aatccccaag agggcctgta caacgagctc 1320

caaaaggata agatggcaga agcctatagc gagattggta tgaaaggggа acgcagaaga 1380

ggcaaaggcc acgacggact gtaccaggga ctcagcaccg ccaccaagga cacctatgac 1440

gctcttcaca tgcaggccct gccgcctcgg 1470

<210> 429
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 429
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 430
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 430
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 431
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 431
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 432
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 432
Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 433
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 433
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 434
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 434
Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 435
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 435
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 436
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 436
Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 437
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 437
Phe Thr Ser His Ser Gly Asn Val Lys Tyr Asn Pro Ser Leu Thr Gly
1 5 10 15

<210> 438
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 438
Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 439
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 439
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 440
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 440
Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 441
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 441
Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 442
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 442
Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> 443

<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 443
Leu Ile Asp Trp Asp Asp Asp Lys Tyr Tyr Ser Thr Ser Leu Arg Thr
1 5 10 15

<210> 444
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 444
Gln Ile Tyr His Ser Gly Thr Thr Thr Tyr Asn Pro Ser Leu Gly Ser
1 5 10 15

<210> 445
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 445
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 446
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 446
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 447
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 447
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 448
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 448
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 449
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 449
Glu Val Thr Gly Asp Leu Glu Asp Ala Phe Asp Ile
1   5   10

<210> 450
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 450
Gln Ser Thr Pro Tyr Asp Ser Ser Gly Tyr Tyr Ser Gly Asp Ala Phe
1   5   10   15

Asp Ile

<210> 451
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 451
Asp Leu Gly Trp Ile Ala Val Ala Gly Thr Phe Asp Tyr
1 5 10

<210> 452
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 452
Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp Ala Phe Asp Val
1 5 10 15

<210> 453
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 453
Gly Leu Ser Ser Trp His Phe His Asp Ala Leu Asp Ile
1 5 10

<210> 454
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 454
Asp Lys Gly Gly Gly Tyr Tyr Asp Phe Trp Ser Gly Ser Asp Tyr
1 5 10 15

<210> 455
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 455
Glu Gly Ser Gly Ser Tyr Tyr Ala Tyr
1 5

<210> 456
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 456
Asp Tyr Trp Gly Tyr Tyr Gly Ser Gly Thr Leu Asp Tyr
1 5 10

<210> 457
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 457

Ala Gly Leu Ala Leu Tyr Ser Asn Tyr Val Pro Tyr Tyr Tyr Tyr Gly
1 5 10 15

Met Asp Val

<210> 458
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 458
Gly Ala Thr Asp Val
1 5

<210> 459
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 459
Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp Ala Phe Asp Val
1 5 10 15

<210> 460
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 460
Glu Glu Ser Ser Ser Gly Trp Tyr Glu Gly Asn Trp Phe Asp Pro
1 5 10 15

<210> 461
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 461
Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp Ala Phe Asp Val
1 5 10 15

<210> 462
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 462
Gly Arg Met Asp Thr Ala Met Ala Gln Ile
1 5 10

<210> 463
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 463
Asp Leu Asp Val Ser Leu Asp Ile
1 5

<210> 464
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 464
Val His Ser Ser Gly Tyr Tyr His Pro Gly Pro Asn Asp Tyr
1 5 10

<210> 465
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 465
Glu Ala Gly Val Val Ala Val Asp Tyr
1 5

<210> 466
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 466
Glu Pro Leu Phe Gly Val Val Glu Glu Asp Val Asp Tyr
1 5 10

<210> 467

<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 467
Gly Ser Gly Ser Leu Gly Asp Ala Phe Asp Ile
1 5 10

<210> 468
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 468
Asp Gly Phe Gly Glu Leu Ser Gly Ala Phe Asp Ile
1 5 10

<210> 469
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 469
Gly Pro Ile Gly Cys Ser Gly Gly Ser Cys Leu Asp Tyr
1 5 10

<210> 470
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 470
Gly Ser Tyr Gly Asp Tyr Gly Asp Ala Phe Asp Ile
1   5   10

<210> 471
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 471
Asp His Lys Val Val Arg Phe Gly Tyr
1   5

<210> 472
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 472
Gly Asp Tyr Tyr Met Asp Val
1   5

<210> 473
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 473
Asp Gly Pro Ile Arg Tyr Phe Asp His Ser Lys Ala Phe Asp Ile
1   5   10   15

<210> 474
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 474
Glu Met Asp Asp Ser Ser Gly Pro Asp Tyr
1   5   10

<210> 475
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 475
Gly Phe Leu Arg Gly Gly Asp Cys Cys Gly Ala Leu Asp Ile
1   5   10

<210> 476
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 476
Gly Leu Asp Pro Leu Phe Ala Tyr Asp Ala Phe Glu Ile
1 5 10

<210> 477
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 477
Asp Asp Phe Trp Ser Gly Ser Val Asp Tyr
1 5 10

<210> 478
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 478
Glu Asp Asp Ser Ser Gly Tyr Thr Ser Pro Phe Asp Tyr
1 5 10

<210> 479
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 479
Glu Pro Ala Ser Ser Ser Trp Tyr Gly Tyr Tyr Tyr Tyr Met Asp Val
1 5 10 15

<210> 480
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 480
Gly Asp Ser Asn Tyr Trp Ser Tyr Tyr Gly Met Asp Val
1 5 10

<210> 481
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 481
Phe Ser Ser Ser Asp Ser Tyr Asp Tyr
1 5

<210> 482
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 482
Ile Tyr Gly Gly Asp Arg Thr Asn Thr Gln Ala Pro Tyr Phe Phe Asp
1 5 10 15

Leu

<210> 483
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 483
Asp Tyr Leu Glu Leu Ala Thr Tyr Tyr Gly Met Asp Val
1 5 10

<210> 484
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 484
Asp Leu Ala Ala Ala Gly Asn Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 485
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 485
Asp Asp Asp Phe Trp Ser Gly Ser Gly Ala Phe Asp Ile
1 5 10

<210> 486
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 486
Pro Glu Gly Val Ser Tyr Tyr Asp Ser Ser Val Leu Asp Tyr
1   5   10

<210> 487
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 487
Gly Gly Tyr Gly Asp Tyr Leu Asp Ala Phe Asp Ile
1   5   10

<210> 488
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 488
Ser Asn Ser Ala Ala Trp Asn
1   5

<210> 489
<211> 9
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 489
Gly Asp Ser Val Ser Ser Asn Ser Ala
1 5

<210> 490
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 490
Gly Asp Ser Val Ser Asn Asn Asn Ala Ala Trp Asn
1 5 10

<210> 491
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 491
Gly Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn
1 5 10

<210> 492
<211> 12
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 492
Gly Asp Ser Val Leu Ser Asn Ser Asp Thr Trp Asn
1 5 10

<210> 493
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 493
Gly Asp Ser Val Leu Ser Asn Ser Asp Thr Trp Asn
1 5 10

<210> 494
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 494
Gly Asp Ser Val Leu Ser Asn Ser Asp Thr Trp Asn
1 5 10

<210> 495
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 495
Gly Asp Ser Val Leu Ser Asn Ser Asp Thr Trp Asn
1 5 10

<210> 496
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 496
Gly Asp Ser Val Leu Ser Asn Ser Asp Thr Trp Asn
1 5 10

<210> 497
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
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1 5

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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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1 5

<210> 597
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<220>
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1 5

<210> 598
<211> 7
<212> PRT
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<223> /note="Description of Artificial Sequence: Synthetic

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<400> 598
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1 5

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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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Gln Gln Ser Tyr Ser Ile Pro Gln Thr
1 5

<210> 600
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<212> PRT
<213> Artificial Sequence

<220>
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Ala Ala Trp Asp Asp Ser Leu Ser Gly Tyr Val
1 5 10

<210> 601
<211> 11
<212> PRT
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<220>
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<400> 601

Ser Ser Tyr Thr Ser Ser Ser Leu Asn His Val
1 5 10

<210> 602
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<220>
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<400> 602
Ser Ser Tyr Thr Ser Ser Ser Thr Pro Tyr Val
1 5 10

<210> 603
<211> 12
<212> PRT
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<220>
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1 5 10

<210> 604
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<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

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1 5

<210> 605
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<220>
<221> source
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<400> 605
Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr Val
1 5 10

<210> 606
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<220>
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1 5 10

<210> 607
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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1 5 10

<210> 608
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<212> PRT
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Ala Ala Trp Asp Asp Ser Leu Ser Gly Pro Val
1 5 10

<210> 609
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Ser Ser Tyr Thr Ser Ser Ser Thr Leu Val Tyr Val
1 5 10

<210> 610
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<213> Artificial Sequence

<220>
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His Ser Arg Asp Ser Ser Gly Asn His Leu
1 5 10

<210> 611
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Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr Val
1 5 10

<210> 612
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<400> 612
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1 5

<210> 613
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<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

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Ser Ser Tyr Thr Ser Ser Ser Thr Leu Phe
1 5 10

<210> 614
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<220>
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peptide"

<400> 614
Ser Ser Arg Asp Ser Ser Gly Asn Pro Ser Cys Val
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<210> 615
<211> 10
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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1 5 10

<210> 616
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

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1 5

<210> 617
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 617

Ser Ser Tyr Thr Ser Ser Ser Thr Leu Val
1 5 10

<210> 618
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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 618
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1 5 10

<210> 619
<211> 10
<212> PRT
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<220>
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<400> 619
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1 5 10

<210> 620
<211> 10
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 620
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1 5 10

<210> 621
<211> 9
<212> PRT
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<220>
<221> source
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<400> 621
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1 5

<210> 622
<211> 10
<212> PRT
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<220>
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<400> 622
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1 5 10

<210> 623
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<220>
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<400> 623
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1 5 10

<210> 624
<211> 10

<212> PRT
<213> Artificial Sequence

<220>
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<400> 624
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1 5 10

<210> 625
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<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 625
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1 5 10

<210> 626
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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 626
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1 5 10

<210> 627
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<212> PRT
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<400> 627
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1 5 10

<210> 628
<211> 11
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 628
Gln Val Trp Asp Ser Asp Ser Asp His Tyr Val
1 5 10

<210> 629
<211> 9
<212> PRT
<213> Artificial Sequence

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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 629
Gln Gln Ser Tyr Ser Ser Leu Leu Thr
1 5

<210> 630
<211> 10
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 630
Cys Ser Tyr Ala Gly Gly Ser Thr Trp Val
1 5 10

<210> 631
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 631
Gln Gln Tyr His Thr Trp Pro Pro Leu Thr
1 5 10

<210> 632
<211> 9
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 632
Met Gln Ala Leu Gln Thr Pro Trp Thr
1 5

<210> 633
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<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 633

Met Gln Ala Leu Gln Thr Gln Ser
1 5

<210> 634
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 634
Asp Ser Arg Asp Ser Ser Gly Asp His Leu Val
1 5 10

<210> 635
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 635
Asn Ser Arg Asp Ser Ser Gly Asn His Pro Val Val
1 5 10

<210> 636
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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Val Ser Tyr Arg Asn Phe Asn Ser Leu Val
1 5 10

<210> 637
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 637
Ser Ser Tyr Thr Ser Ser Ser Thr Leu Val
1 5 10

<210> 638
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 638
Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 639
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 639
Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr
1 5 10

<210> 640
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<212> PRT
<213> Artificial Sequence

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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 640
Thr Gly Ser Arg Asn Asp Ile Gly Ala Tyr Glu Ser Val Ser
1 5 10

<210> 641
<211> 14
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 641
Thr Gly Ser Ser Ser Asp Val Gly Gly Tyr Asn Ser Val Ser
1 5 10

<210> 642
<211> 14
<212> PRT
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<220>
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<400> 642
Thr Gly Ser Ser Ser Asp Ile Gly Gly Phe Asn Tyr Val Ser
1 5 10

<210> 643
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
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<400> 643
Thr Gly Thr Ser Ser Asp Ile Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 644
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<220>
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<400> 644
Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 645
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<220>
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<400> 645
Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 646
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 646
Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 647
<211> 14
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<220>
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<400> 647
Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 648
<211> 14
<212> PRT
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<220>
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<400> 648
Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 649
<211> 7
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 649

Glu Val Asn Asn Arg Pro Ser
1 5

<210> 650
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<210> 651
<211> 7
<212> PRT
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<220>
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<400> 651
Gly Val Asn Asn Arg Pro Ser
1 5

<210> 652
<211> 7
<212> PRT
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<220>
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<400> 652
Glu Val Ile Asn Arg Pro Ser
1 5

<210> 653
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<212> PRT
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<220>
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<400> 653
Glu Val Thr Asn Arg Pro Ser
1 5

<210> 654
<211> 7
<212> PRT
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<220>
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<400> 654
Glu Val Ser Asn Arg Pro Ser
1 5

<210> 655
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<400> 655
Glu Val Ser Asn Arg Pro Ser
1 5

<210> 656
<211> 7

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 656
Asp Val Ser Asn Arg Pro Ser
1 5

<210> 657
<211> 7
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 657
Glu Val Ser Asn Arg Pro Ser
1 5

<210> 658
<211> 7
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 658
Asp Val Ser Asn Arg Pro Ser
1 5

<210> 659
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 659
Asp Val Ser Asn Arg Pro Ser
1 5

<210> 660
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 660
Ser Ser Tyr Thr Ser Gly Arg Thr Leu Tyr Val
1 5 10

<210> 661
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 661
Tyr Thr Ser Gly Arg Thr Leu Tyr
1 5

<210> 662
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 662
Ser Ser His Thr Thr Thr Ser Thr Leu Tyr Val
1 5 10

<210> 663
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 663
Ser Ser Tyr Thr Ser Ser Ser Thr Tyr Val
1 5 10

<210> 664
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 664
Ser Ser Tyr Ala Ser Gly Ser Pro Leu Tyr Val
1 5 10

<210> 665
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 665

Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr Val
1 5 10

<210> 666
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 666
Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr Val
1 5 10

<210> 667
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 667
Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr Val
1 5 10

<210> 668
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 668
Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr Ile
1 5 10

<210> 669
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 669
Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr Val
1 5 10

<210> 670
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 670
Ser Ser Tyr Thr Ser Ser Ser Thr Leu Tyr Val
1 5 10

<210> 671
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 671
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Ser Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Asp Pro Tyr Asp Phe Trp Ser Gly Tyr Pro Asp
100 105 110

Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120 125

<210> 672
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 672
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Asn Asn
20 25 30

Asn Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asn Asp Tyr Val
50 55 60

Gly Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Glu Thr Asp Tyr Gly Asp Tyr Gly Ala Phe Asp
100 105 110

Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 673
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 673
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Asn Pro Ser Gln
1 5 10 15

Thr Leu Ser Ile Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Phe Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Gly Arg Ile Thr Ile Ser Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Gly Gly Asp Tyr Tyr Tyr Gly Leu Asp Val Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 674
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 674
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
20 25 30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
50 55 60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65 70 75 80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val

85 90 95

Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
100 105 110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120 125

<210> 675
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 675
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
20 25 30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
50 55 60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65 70 75 80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
85 90 95

Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
100 105 110

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Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120                 125


<210> 676
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 676
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
            20                  25                  30


Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45


Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
    50                  55                  60


Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65                  70                  75                  80


Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
                85                  90                  95


Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
            100                 105                 110


Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120                 125
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<210> 677
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 677
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
            20   25   30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35   40   45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
    50   55   60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65   70   75   80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
                85   90   95

Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
            100   105   110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115   120   125

<210> 678
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 678
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
20 25 30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
50 55 60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65 70 75 80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
85 90 95

Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
100 105 110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120 125

<210> 679
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 679
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Pro Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
            20   25   30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35   40   45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
    50   55   60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65   70   75   80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
                85   90   95

Tyr Tyr Cys Ala Arg Val Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
            100   105   110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115   120   125

<210> 680
<211> 127
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 680
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

```
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Met Leu Ser Asn
            20                  25                  30


Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45


Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
    50                  55                  60


Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65                  70                  75                  80


Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
                85                  90                  95


Tyr Tyr Cys Ala Arg Val Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
            100                 105                 110


Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120                 125


<210> 681
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 681
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
```

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Val
35 40 45

Ile Ile Ser Glu Val Asn Asn Arg Pro Ser Gly Val Ser His Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Phe Cys Ser Ser Tyr Thr Ser Gly
85 90 95

Arg Thr Leu Tyr Val Phe Gly Thr Gly Ser Lys Val Thr Val Leu Gly
100 105 110

<210> 682
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 682
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Ser Arg Asn Asp Ile Gly Ala Tyr
20 25 30

Glu Ser Val Ser Trp Tyr Gln Gln His Pro Gly Asn Ala Pro Lys Leu
35 40 45

Ile Ile His Gly Val Asn Asn Arg Pro Ser Gly Val Phe Asp Arg Phe
50 55 60

Ser Val Ser Gln Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser His Thr Thr Thr
85 90 95

Ser Thr Leu Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
100 105 110

<210> 683
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 683
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Ser Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Ser Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Ile Asn Arg Pro Ser Gly Val Ser His Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
100 105 110

<210> 684
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 684
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Ser Ser Ser Asp Ile Gly Gly Phe
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Ala Gly Glu Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Thr Asn Arg Pro Ser Gly Val Ser Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Asp Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Ser Gly
85 90 95

Ser Pro Leu Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
100 105 110

<210> 685
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 685
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Phe Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Thr Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Leu Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 686
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 686
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr

20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Leu Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
100 105 110

<210> 687
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 687
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

```
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80


Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
                85                  90                  95


Ser Thr Leu Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
            100                 105                 110


<210> 688
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 688
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30


Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60


Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80


Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
                85                  90                  95
```

Ser Thr Leu Tyr Ile Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
100 105 110

<210> 689
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 689
Gln Ser Ala Leu Thr Gln Pro Ala Ser Ala Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Leu Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu
100 105 110

<210> 690
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 690
Gln Ser Ala Leu Thr Gln Pro Ala Ser Ala Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Leu Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu
100 105 110

<210> 691
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 691
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Asp Tyr
            20                  25                  30

Tyr Met Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys
    50                  55                  60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr Leu
65                  70                  75                  80

Gln Met Ser Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg His Asp His Asn Asn Val Asp Trp Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr
    130                 135                 140

Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly Gln Pro Val Ser Met
145                 150                 155                 160

Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn
                165                 170                 175

Tyr Leu Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu
            180                 185                 190

Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser
        195                 200                 205
```

```
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu
    210                 215                 220

Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Tyr Tyr Asn Phe Pro
225                 230                 235                 240

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
                245                 250
```

<210> 692
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 692

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Arg Asp Tyr
            20                  25                  30

Tyr Met Ala Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
        35                  40                  45

Gly Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys
    50                  55                  60

Gly Arg Val Thr Ile Thr Arg Asp Asn Ser Ala Ser Thr Leu Tyr Met
65                  70                  75                  80

Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95
```

```
Arg His Asp His Asn Asn Val Asp Trp Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125


Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr
    130                 135                 140


Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
145                 150                 155                 160


Thr Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn
                165                 170                 175


Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu
            180                 185                 190


Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Ser Arg Phe Ser
        195                 200                 205


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
    210                 215                 220


Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Asn Phe Pro
225                 230                 235                 240


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
                245                 250
```

<210> 693
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 693
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1   5   10   15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Phe Thr Phe Arg Asp Tyr
            20   25   30

Tyr Met Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35   40   45

Gly Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys
    50   55   60

Gly Gln Val Thr Ile Ser Arg Asp Asn Ser Ile Ser Thr Leu Tyr Leu
65   70   75   80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
                85   90   95

Arg His Asp His Asn Asn Val Asp Trp Phe Ala Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115   120   125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr
    130   135   140

Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu
145   150   155   160

Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn
                165   170   175

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
180 185 190

Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Ala Arg Phe Ser
195 200 205

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
210 215 220

Pro Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asn Phe Pro
225 230 235 240

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
245 250

<210> 694
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 694
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Phe Thr Phe Arg Asp Tyr
20 25 30

Tyr Met Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys
50 55 60

Gly Gln Val Thr Ile Ser Arg Asp Asn Ser Ile Ser Thr Leu Tyr Leu

65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg His Asp His Asn Asn Val Asp Trp Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr
130 135 140

Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
145 150 155 160

Thr Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn
165 170 175

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu
180 185 190

Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Ser Arg Phe Ser
195 200 205

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
210 215 220

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Asn Phe Pro
225 230 235 240

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
245 250

<210> 695

<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 695

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Arg Asp Tyr
            20                  25                  30


Tyr Met Ala Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys
    50                  55                  60


Gly Arg Val Thr Met Thr Arg Asp Asn Ser Thr Ser Thr Leu Tyr Met
65                  70                  75                  80


Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Arg His Asp His Asn Asn Val Asp Trp Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125


Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr
    130                 135                 140


Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu
145                 150                 155                 160
```

```
Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn
                165                 170                 175


Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
            180                 185                 190


Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Ile Pro Ala Arg Phe Ser
        195                 200                 205


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
    210                 215                 220


Pro Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asn Phe Pro
225                 230                 235                 240


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
                245                 250


<210> 696
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 696
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Arg Asp Tyr
            20                  25                  30


Tyr Met Ala Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
```

```
Gly Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys
    50                  55                  60

Gly Arg Val Thr Met Thr Arg Asp Asn Ser Thr Ser Thr Leu Tyr Met
65                  70                  75                  80

Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg His Asp His Asn Asn Val Asp Trp Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr
    130                 135                 140

Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
145                 150                 155                 160

Thr Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn
                165                 170                 175

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu
            180                 185                 190

Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Ser Arg Phe Ser
        195                 200                 205

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
    210                 215                 220

Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Asn Phe Pro
225                 230                 235                 240
```

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
245 250

<210> 697
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 697
Glu Tyr Thr Phe Thr Asp Tyr Ala Phe His
1 5 10

<210> 698
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 698
Gly Phe Thr Phe Ser Lys Tyr Gly Met Asn
1 5 10

<210> 699
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 699
Gly Phe Thr Phe Arg Asp Tyr Tyr Met Ala
1 5 10

<210> 700
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 700
Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Glu Val Thr Gly Asp Leu Glu Asp Ala Phe Asp
100 105 110

Ile Trp Gly Gln Gly Thr Met Val Thr Val
115 120

<210> 701
<211> 124
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 701

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Gly	Gly	Leu	Ile	Gln	Pro	Gly	Gly
1				5				10					15		

Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Val	Ser	Ser	Asn
			20					25					30		

Tyr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			

Ser	Val	Ile	Tyr	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys
	50					55					60				

Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	Leu
65					70					75					80

Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala
				85					90					95	

Ser	Gln	Ser	Thr	Pro	Tyr	Asp	Ser	Ser	Gly	Tyr	Tyr	Ser	Gly	Asp	Ala
			100					105					110		

Phe	Asp	Ile	Trp	Gly	Gln	Gly	Thr	Met	Val	Thr	Val				
		115					120								

<210> 702
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polypeptide"

<400> 702
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Asp Leu Gly Trp Ile Ala Val Ala Gly Thr Phe
100 105 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
115 120

<210> 703
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 703
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

```
Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
            20                  25                  30


Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45


Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
    50                  55                  60


Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65                  70                  75                  80


Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Ala
                85                  90                  95


Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
            100                 105                 110


Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val
        115                 120                 125


<210> 704
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 704
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
```

```
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95


Ala Lys Gly Leu Ser Ser Trp His Phe His Asp Ala Leu Asp Ile Trp
            100                 105                 110


Gly Gln Gly Thr Met Val Thr Val
        115                 120


<210> 705
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 705
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30


Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
```

Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Lys Asp Lys Gly Gly Gly Tyr Tyr Asp Phe Trp Ser Gly Ser Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
115 120

<210> 706
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 706
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Leu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Thr Trp Thr Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Thr Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn

65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Glu Gly Ser Gly Ser Tyr Tyr Ala Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val
115

<210> 707
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 707
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

```
Ala Arg Asp Tyr Trp Gly Tyr Tyr Gly Ser Gly Thr Leu Asp Tyr Trp
            100                 105                 110


Gly Gln Gly Thr Leu Val Thr Val
        115                 120


<210> 708
<211> 126
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 708
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Ala Gly Leu Ala Leu Tyr Ser Asn Tyr Val Pro Tyr Tyr Tyr
            100                 105                 110
```

```
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val
        115                 120                 125


<210> 709
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 709
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asn Ala
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Gly Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr Ala Asp Tyr Ala Ala
    50                  55                  60


Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80


Met Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Gly Val Tyr
                85                  90                  95


Tyr Cys Ile Thr Gly Ala Thr Asp Val Trp Gly Gln Gly Thr Thr Val
            100                 105                 110


Thr Val
```

<210> 710
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 710
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
            20   25   30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35   40   45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
    50   55   60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65   70   75   80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
                85   90   95

Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
            100   105   110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val
        115   120   125

<210> 711
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 711
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65 70 75 80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Glu Glu Ser Ser Ser Gly Trp Tyr Glu Gly Asn
100 105 110

Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val
115 120 125

<210> 712
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 712
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1   5   10   15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Leu Ser Asn
            20   25   30

Ser Asp Thr Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35   40   45

Trp Leu Gly Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala
    50   55   60

Ser Ser Val Arg Gly Arg Val Ser Ile Asn Val Asp Thr Ser Lys Asn
65   70   75   80

Gln Tyr Ser Leu Gln Leu Asn Ala Val Thr Pro Glu Asp Thr Gly Val
                85   90   95

Tyr Tyr Cys Ala Arg Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp
            100   105   110

Ala Phe Asp Val Trp Gly Gln Gly Thr Met Val Thr Val
        115   120   125

<210> 713
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 713
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1   5   10   15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
20 25 30

Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Gly Arg Met Asp Thr Ala Met Ala Gln Ile Trp Gly Gln
100 105 110

Gly Thr Met Val Thr Val
115

<210> 714
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 714
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Leu Asp Val Ser Leu Asp Ile Trp Gly Gln Gly Thr Met
100 105 110

Val Thr Val
115

<210> 715
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 715
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Tyr Val
35 40 45

Ser Ala Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asn Ser Val
50 55 60

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Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Gly Ser Leu Arg Ala Glu Asp Met Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Val His Ser Ser Gly Tyr Tyr His Pro Gly Pro Asn Asp Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Leu Val Thr Val
        115                 120


<210> 716
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 716
Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
```

```
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Glu Ala Gly Val Val Ala Val Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val
        115


<210> 717
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 717
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30


Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

Ala Lys Glu Pro Leu Phe Gly Val Val Glu Glu Asp Val Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val
115 120

<210> 718
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 718
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Ser Gly Ser Leu Gly Asp Ala Phe Asp Ile Trp Gly Gln
100 105 110

Gly Thr Met Val Thr Val

115

<210> 719
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 719
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Phe Gly Glu Leu Ser Gly Ala Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val
115

<210> 720
<211> 120

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 720
Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Pro Ile Gly Cys Ser Gly Gly Ser Cys Leu Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val
115 120

<210> 721
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 721
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Ser Tyr Gly Asp Tyr Gly Asp Ala Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val
115

<210> 722
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 722
Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp His Lys Val Val Arg Phe Gly Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val
115

<210> 723
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 723
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asp Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val
100 105 110

Thr Val

<210> 724
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 724
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Pro Ile Arg Tyr Phe Asp His Ser Lys Ala Phe Asp
100 105 110

Ile Trp Gly Gln Gly Thr Met Val Thr Val
115 120

<210> 725
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 725
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Met Asp Asp Ser Ser Gly Pro Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val
115

<210> 726
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 726
Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Ser
20 25 30

Trp Ile Gly Trp Gly Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Ala Arg Gly Phe Leu Arg Gly Gly Asp Cys Cys Gly Ala Leu Asp Ile
100 105 110

Trp Gly Gln Gly Thr Met Val Thr Val
115 120

<210> 727
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 727
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Val Ser Gly Gly Ser Ile Asn Ser Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Ala Phe Thr Ser His Ser Gly Asn Val Lys Tyr Asn Pro Ser Leu Thr
50 55 60

Gly Arg Val Thr Ile Ala Val Asp Thr Ser Lys Asn Gln Phe Tyr Leu
65 70 75 80

Glu Val Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala
85 90 95

Arg Gly Leu Asp Pro Leu Phe Ala Tyr Asp Ala Phe Glu Ile Trp Gly
100 105 110

Leu Gly Thr Met Val Thr Val
        115

<210> 728
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 728
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20   25   30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Asp Asp Phe Trp Ser Gly Ser Val Asp Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val
        115

<210> 729
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 729
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Glu Asp Asp Ser Ser Gly Tyr Thr Ser Pro Phe Asp Tyr Trp
            100   105   110

Gly Gln Gly Thr Leu Val Thr Val
        115   120

<210> 730
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 730
Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Pro Ala Ser Ser Ser Trp Tyr Gly Tyr Tyr Tyr Tyr Met
100 105 110

Asp Val Trp Gly Lys Gly Thr Leu Val Thr Val
115 120

<210> 731
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 731
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gly Asp Ser Asn Tyr Trp Ser Tyr Tyr Gly Met Asp Val Trp
            100   105   110

Gly Gln Gly Thr Leu Val Thr Val
        115   120

<210> 732
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 732
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

```
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Ser Phe Ser Ser Ser Asp Ser Tyr Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val
        115


<210> 733
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 733
Gln Val Asn Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1               5                   10                  15


Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Asn Thr Phe
            20                  25                  30
```

Gly Met Ser Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35 40 45

Trp Leu Ala Leu Ile Asp Trp Asp Asp Asp Lys Tyr Tyr Ser Thr Ser
50 55 60

Leu Arg Thr Arg Leu Thr Ile Ser Lys Asp Thr Ala Lys Asn Gln Val
65 70 75 80

Val Leu Arg Met Thr Asn Met Asp Pro Met Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Ile Tyr Gly Gly Asp Arg Thr Asn Thr Gln Ala Pro Tyr
100 105 110

Phe Phe Asp Leu Trp Gly Gln Gly Thr Leu Val Thr Val
115 120 125

<210> 734
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 734
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Ala Ser Ile Thr Ser Arg
20 25 30

His Trp Trp Asn Trp Val Arg His Ser Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Gln Ile Tyr His Ser Gly Thr Thr Thr Tyr Asn Pro Ser Leu

50 55 60

Gly Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Ile Ser
65 70 75 80

Leu Glu Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Val Arg Asp Tyr Leu Glu Leu Ala Thr Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val
115 120

<210> 735
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 735
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Leu Ala Ala Ala Gly Asn Tyr Tyr Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val
115 120

<210> 736
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 736
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

```
Ala Arg Asp Asp Asp Phe Trp Ser Gly Ser Gly Ala Phe Asp Ile Trp
            100                 105                 110


Gly Gln Gly Thr Thr Val Thr Val
        115                 120


<210> 737
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 737
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Pro Glu Gly Val Ser Tyr Tyr Asp Ser Ser Val Leu Asp Tyr
            100                 105                 110
```

Trp Gly Gln Gly Thr Leu Val Thr Val
        115   120

<210> 738
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 738
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gly Gly Tyr Gly Asp Tyr Leu Asp Ala Phe Asp Ile Trp Gly
            100   105   110

Gln Gly Thr Thr Val Thr Val
        115

<210> 739

<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 739
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Trp Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Arg Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Arg Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ile Pro Gln
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 740
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 740
Ser Tyr Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Tyr Val Tyr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 741
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 741
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Leu Asn His Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 742
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 742
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Pro Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu
100 105 110

<210> 743
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 743
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His
85 90 95

Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 744
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 744
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Trp Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 745
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 745
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Leu Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 746
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 746
Gln Ser Ala Leu Thr Gln Pro Gly Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr

20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Ile Ile Tyr Asp Val Ser Ser Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Gln Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Ser Cys Ser Ser Tyr Ala Gly Ser
85 90 95

Asn Thr Leu Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 747
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 747
Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1 5 10 15

Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Asn
20 25 30

Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr Val
35 40 45

Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

```
Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65                  70                  75                  80


Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser
                85                  90                  95


Ser Asn Pro Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210> 748
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 748
Ser Tyr Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1               5                   10                  15


Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30


Tyr Val Tyr Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45


Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60


Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
65                  70                  75                  80


Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
                85                  90                  95
```

Ser Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 749
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 749
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Leu Val Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 750
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 750
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Lys Asn His Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asp Thr Asp Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys His Ser Arg Asp Ser Ser Gly Asn His
85 90 95

Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 751
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 751
Gln Ser Ala Leu Thr Gln Pro Ala Ser Ala Ser Gly Ser Pro Gly Gln
1 5 10 15

```
Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30


Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60


Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80


Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
                85                  90                  95


Ser Thr Leu Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu
            100                 105                 110


<210> 752
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 752
Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1               5                   10                  15


Thr Val Thr Ile Pro Cys Thr Gly Ser Ser Gly Ser Phe Ala Ser Ser
            20                  25                  30


Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ala Pro Ala Thr Val
        35                  40                  45
```

Ile Tyr Glu Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50   55   60

Gly Ser Val Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65   70   75   80

Leu Lys Thr Glu Asp Glu Ala Val Tyr Tyr Cys Gln Ser Tyr Asp Gly
                85   90   95

Ala Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100   105   110

<210> 753
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 753
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1   5   10   15

Ser Ile Thr Ile Ser Cys Ser Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20   25   30

Asn Ser Val Ser Trp Tyr Gln Gln Tyr Pro Gly Lys Ala Pro Lys Leu
        35   40   45

Met Ile Tyr Asp Val Asn Asn Arg Pro Ser Gly Val Ser Ser Arg Phe
    50   55   60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65   70   75   80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Leu Phe Phe Gly Ala Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 754
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 754
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Thr Tyr Tyr Ala
20 25 30

Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Phe Tyr
35 40 45

Asp Glu Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Arg Asp Ser Ser Gly Asn Pro
85 90 95

Ser Cys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 755

<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 755
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 756
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 756
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Ala Gly
20 25 30

Asn Gly His Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Asn Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg

<210> 757
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 757
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Ser Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Leu Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 758
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 758
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe

50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Ser Ser
85 90 95

Ser Thr Leu Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 759
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 759
Gln Ser Ala Leu Thr Gln Pro Ala Tyr Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Asn Ser Asp Val Gly Arg Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Ser Tyr Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Thr Ser
85 90 95

Ser Thr Leu Asp Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 760
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 760
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Lys Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 761
<211> 111
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 761
His Val Ile Leu Thr Gln Pro Pro Ser Ala Ser Ala Ser Leu Gly Ala
1 5 10 15

Ser Val Lys Leu Thr Cys Thr Leu Ser Ser Gly His Ser Ser Tyr Ala
20 25 30

Ile Ala Trp His Gln Gln Gln Pro Glu Lys Gly Pro Arg Tyr Leu Met
35 40 45

Lys Val Asn Ser Asp Gly Ser Leu Ser Lys Gly Asp Gly Ile Pro Asp
50 55 60

Arg Phe Ser Gly Ser Thr Ser Gly Ala Glu Arg Tyr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Gly
85 90 95

Ser Gly Met Ala Ile Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 762
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 762
Gln Ser Ala Leu Thr Gln Pro Ala Ser Ala Ser Gly Ser Pro Gly Gln

1 5 10 15

Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Gly Thr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 763
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 763
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

```
Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    50                  55                  60

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Arg Asn Ser Arg Asp Ser Ser Gly Asn Pro
                85                  90                  95

Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
            100                 105
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<210> 764
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 764

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Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45

Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
```

```
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
                85                  90                  95


Ser Thr Leu Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210> 765
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 765
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
                85                  90                  95


Leu Gln Thr Pro Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
            100                 105                 110
```

Lys Arg

<210> 766
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 766
Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1   5   10   15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20   25   30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35   40   45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
    50   55   60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65   70   75   80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Val
                85   90   95

Leu Gln Thr Pro Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Asp Ile
            100   105   110

Lys Arg

<210> 767

<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 767
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1 5 10 15

Thr Ala Thr Ile Thr Cys Gly Gly Thr Asn Ile Gly Ser Lys Asn Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Ala Ile Tyr
35 40 45

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Phe Cys Gln Val Trp Asp Ser Ser Ser Asp His
85 90 95

Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 768
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 768
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Glu
1 5 10 15

Thr Ala Ser Ile Ala Cys Gly Gly His Asn Ile Arg Ser Lys Asn Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Ser
35 40 45

Tyr Asp Gly Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Leu Gly Ser Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Asp Ser Asp His
85 90 95

Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105

<210> 769
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 769
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Thr Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Pro Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr His Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ser Leu Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 770
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 770
Gln Ser Val Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Glu Ala Pro Lys Leu
35 40 45

Ile Ile Tyr Asp Ala Asp Lys Arg Pro Ser Gly Ile Ser Asn Arg Phe
50 55 60

Ser Ser Gly Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

65 70 75 80

Gln Val Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Gly
85 90 95

Ser Thr Trp Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 771
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 771
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Thr Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Met Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Tyr His Thr Trp Pro Pro
85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Thr
100 105

<210> 772
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 772
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 773
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 773
Glu Ile Val Leu Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

Asp Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Gln Ile
65 70 75 80

Ser Gly Val Glu Thr Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Gln Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 774
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 774
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Ala Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Phe Thr

20 25 30

Ser Trp Tyr His Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Asn Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Gly Asp Tyr Tyr Cys Asp Ser Arg Asp Ser Ser Gly Asp His
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 775
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 775
Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

```
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65                  70                  75                  80


Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His
                85                  90                  95


Pro Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210> 776
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 776
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30


Lys His Val Ser Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60


Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Val Ser Gly Leu
65                  70                  75                  80


Gln Ala Glu Asp Glu Ala His Tyr Tyr Cys Val Ser Tyr Arg Asn Phe
                85                  90                  95
```

Asn Ser Leu Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> 777
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 777
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser
85 90 95

Ser Thr Leu Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu
100 105 110

<210> 778
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 778
Arg Phe Ser Leu Ser Thr Tyr Gly Met Ser Val Gly
1 5 10

<210> 779
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 779
Gly Phe Thr Phe Ser Ser Ser Gly Met Gln
1 5 10

<210> 780
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 780
Gly Phe Ser Leu Asn Thr His Gly Met Gly Val Gly
1 5 10

<210> 781
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 781
Gly Phe Ser Leu Ser Thr Ser Gly Met Val Val Ser
1   5   10

<210> 782
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 782
Gly Asn Thr Val Thr Gly Tyr Ala Met His
1   5   10

<210> 783
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 783
Gly Phe Thr Phe Arg Asp Tyr Tyr Met Ala
1   5   10

<210> 784
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 784
Gly Phe Thr Phe Ser Ser Ser Gly Met Gln
1 5 10

<210> 785
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 785
Glu Tyr Thr Phe Thr Asp Tyr Ala Phe His
1 5 10

<210> 786
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 786
Gly Phe Thr Phe Ser Lys Tyr Gly Met Asn
1 5 10

<210> 787
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 787
Arg Phe Ser Leu Ser Thr Tyr Gly Met Ser Val Gly
1 5 10

<210> 788
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 788
Gly Phe Ser Leu Asn Thr His Gly Met Gly Val Gly
1 5 10

<210> 789
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 789
Gly Phe Ser Leu Ser Thr Ser Gly Met Val Val Ser
1 5 10

<210> 790
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 790
Gly Asn Thr Val Thr Gly Tyr Ala Met His
1 5 10

<210> 791

<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 791
Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gly

<210> 792
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 792
Ser Ile Ser Ser Thr Ser Ile Tyr Ile Tyr Tyr Ala Asp Thr Val Lys
1 5 10 15

Gly

<210> 793
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 793

Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys Gly
1 5 10 15

<210> 794
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 794
Asp Ile Trp Trp Asp Asp Asp Lys His Tyr Asn Pro Ser Leu Lys Asn
1 5 10 15

<210> 795
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 795
Gly Ile Tyr Tyr Asp Ser Tyr Lys Lys Ser Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 796
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 796
Asn Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Asn
1 5 10 15

<210> 797
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 797
Ala Ile Ala Trp Asp Gly Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 798
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 798
Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gly

<210> 799
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 799
Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys Gly
1 5 10 15

<210> 800
<211> 255
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 800
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Thr Ser Glu Tyr Thr Phe Thr Asp Tyr
20 25 30

Ala Phe His Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Glu Asp Ser Ala Arg Thr Ala Asn
65 70 75 80

Leu Gln Ile Ser Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Gly Ala Tyr Tyr Gly Tyr Arg Asp Trp Phe Thr Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125

```
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val
    130                 135                 140


Met Thr Gln Thr Pro Ser Ser Gln Ala Val Ser Ala Gly Glu Lys Val
145                 150                 155                 160


Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser Glu Asn Lys
                165                 170                 175


Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys
            180                 185                 190


Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg
        195                 200                 205


Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
    210                 215                 220


Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asn
225                 230                 235                 240


Phe Pro Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys
                245                 250                 255


<210> 801
<211> 765
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"

<400> 801
caaattcaac tggtccagtc cggccctgag ctgaagaagc cgggagaatc cgtgaagatc       60

tcctgcaaga cctcggagta caccttcact gactacgcct tccactgggt caagcaggca      120
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cctgggaaag gcctgaagtg gatgggctgg atcaacactt actcggggaa gccaacctac 180

gccgatgatt tcaagggaag attcgtgttt agcctggagg actccgcccg gacagctaac 240

ctccaaatct ccaaccttaa gaacgaggac actgcgacct acttctgcgc gcggggagcc 300

tattacggtt atcgcgactg gttcacctac tggggacagg gcaccctcgt gaccgtgtcc 360

tccggcggtg gaggctcagg ggggggcggc tcgggagggg gtggaagcgg aggaggaggc 420

tccgatattg tgatgaccca gaccccgtcg agccaggcag tgtccgctgg agaaaaggtc 480

accatgtcct gcaagagctc acagtccctg ttgtactccg aaaacaagaa gaattacctg 540

gcctggtacc agcagaagcc cggacagtcc cctaaactgc tgatctactg ggcctcgact 600

agggaatctg gcgtgcccga ccgctttatc ggaagcggtt cagggactga cttcaccctg 660

accattagca gcgtgcaggc cgaggacctg gcggtgtact actgtcaaca gtactacaac 720

ttcccgccct ggactttcgg cggtggaacg aagctcgaac tcaag 765

<210> 802
<211> 858
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 802
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaaattc aactggtcca gtccggccct gagctgaaga agccgggaga atccgtgaag 120

atctcctgca agacctcgga gtacaccttc actgactacg ccttccactg ggtcaagcag 180

gcacctggga aaggcctgaa gtggatgggc tggatcaaca cttactcggg gaagccaacc 240

tacgccgatg atttcaaggg aagattcgtg tttagcctgg aggactccgc ccggacagct 300

aacctccaaa tctccaacct taagaacgag gacactgcga cctacttctg cgcgcgggga 360

gcctattacg gttatcgcga ctggttcacc tactggggac agggcaccct cgtgaccgtg 420

tcctccggcg gtggaggctc agggggggggc ggctcgggag ggggtggaag cggaggagga 480

ggctccgata ttgtgatgac ccagaccccg tcgagccagg cagtgtccgc tggagaaaag 540

gtcaccatgt cctgcaagag ctcacagtcc ctgttgtact ccgaaaacaa gaagaattac 600

ctggcctggt accagcagaa gcccggacag tcccctaaac tgctgatcta ctgggcctcg 660

actagggaat ctggcgtgcc cgaccgcttt atcggaagcg gttcagggac tgacttcacc 720

ctgaccatta gcagcgtgca ggccgaggac ctggcggtgt actactgtca acagtactac 780

aacttcccgc cctggacttt cggcggtgga acgaagctcg aactcaaggg atcgcaccac 840

catcaccatc atcatcac 858

<210> 803
<211> 286
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 803
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu
20 25 30

Lys Lys Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Thr Ser Glu Tyr
35 40 45

Thr Phe Thr Asp Tyr Ala Phe His Trp Val Lys Gln Ala Pro Gly Lys
50 55 60

Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr
65 70 75 80

```
Tyr Ala Asp Asp Phe Lys Gly Arg Phe Val Phe Ser Leu Glu Asp Ser
                85                  90                  95

Ala Arg Thr Ala Asn Leu Gln Ile Ser Asn Leu Lys Asn Glu Asp Thr
            100                 105                 110

Ala Thr Tyr Phe Cys Ala Arg Gly Ala Tyr Tyr Gly Tyr Arg Asp Trp
        115                 120                 125

Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
145                 150                 155                 160

Gly Ser Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln Ala Val Ser
                165                 170                 175

Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu
            180                 185                 190

Tyr Ser Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
        195                 200                 205

Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser
    210                 215                 220

Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr
225                 230                 235                 240

Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys
                245                 250                 255

Gln Gln Tyr Tyr Asn Phe Pro Pro Trp Thr Phe Gly Gly Gly Thr Lys
            260                 265                 270
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Leu Glu Leu Lys Gly Ser His His His His His His His His
275 280 285

<210> 804
<211> 1497
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 804
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaaattc aactggtcca gtccggccct gagctgaaga agccgggaga atccgtgaag 120

atctcctgca agacctcgga gtacaccttc actgactacg ccttccactg ggtcaagcag 180

gcacctggga aaggcctgaa gtggatgggc tggatcaaca cttactcggg gaagccaacc 240

tacgccgatg atttcaaggg aagattcgtg tttagcctgg aggactccgc ccggacagct 300

aacctccaaa tctccaacct taagaacgag gacactgcga cctacttctg cgcgcgggga 360

gcctattacg gttatcgcga ctggttcacc tactggggac agggcaccct cgtgaccgtg 420

tcctccggcg gtggaggctc agggggggggc ggctcgggag ggggtggaag cggaggagga 480

ggctccgata ttgtgatgac ccagaccccg tcgagccagg cagtgtccgc tggagaaaag 540

gtcaccatgt cctgcaagag ctcacagtcc ctgttgtact ccgaaaacaa gaagaattac 600

ctggcctggt accagcagaa gcccggacag tcccctaaac tgctgatcta ctgggcctcg 660

actagggaat ctggcgtgcc cgaccgcttt atcggaagcg gttcagggac tgacttcacc 720

ctgaccatta gcagcgtgca ggccgaggac ctggcggtgt actactgtca acagtactac 780

aacttcccgc cctggacttt cggcggtgga acgaagctcg aactcaagac cactacccca 840

gcaccgaggc cacccacccc ggctcctacc atcgcctccc agcctctgtc cctgcgtccg 900

gaggcatgta gacccgcagc tggtggggcc gtgcataccc ggggtcttga cttcgcctgc 960

gatatctaca tttgggcccc tctggctggt acttgcgggg tcctgctgct ttcactcgtg 1020

atcactcttt actgtaagcg cggtcggaag aagctgctgt acatctttaa gcaacccttc 1080

atgaggcctg tgcagactac tcaagaggag gacggctgtt catgccggtt cccagaggag 1140

gaggaaggcg gctgcgaact gcgcgtgaaa ttcagccgca gcgcagatgc tccagcctac 1200

aagcaggggc agaaccagct ctacaacgaa ctcaatcttg gtcggagaga ggagtacgac 1260

gtgctggaca agcggagagg acgggaccca gaaatgggcg ggaagccgcg cagaaagaat 1320

ccccaagagg gcctgtacaa cgagctccaa aaggataaga tggcagaagc ctatagcgag 1380

attggtatga aaggggaacg cagaagaggc aaaggccacg acggactgta ccagggactc 1440

agcaccgcca ccaaggacac ctatgacgct cttcacatgc aggccctgcc gcctcgg 1497

<210> 805
<211> 499
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 805
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu
20 25 30

Lys Lys Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Thr Ser Glu Tyr
35 40 45

Thr Phe Thr Asp Tyr Ala Phe His Trp Val Lys Gln Ala Pro Gly Lys
50 55 60

Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr
65 70 75 80

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Tyr Ala Asp Asp Phe Lys Gly Arg Phe Val Phe Ser Leu Glu Asp Ser
                85                  90                  95

Ala Arg Thr Ala Asn Leu Gln Ile Ser Asn Leu Lys Asn Glu Asp Thr
            100                 105                 110

Ala Thr Tyr Phe Cys Ala Arg Gly Ala Tyr Tyr Gly Tyr Arg Asp Trp
        115                 120                 125

Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
145                 150                 155                 160

Gly Ser Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln Ala Val Ser
                165                 170                 175

Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu
            180                 185                 190

Tyr Ser Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
        195                 200                 205

Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser
    210                 215                 220

Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr
225                 230                 235                 240

Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys
                245                 250                 255

Gln Gln Tyr Tyr Asn Phe Pro Pro Trp Thr Phe Gly Gly Gly Thr Lys
            260                 265                 270
```

```
Leu Glu Leu Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
        275                 280                 285

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
    290                 295                 300

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
305                 310                 315                 320

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
                325                 330                 335

Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu
            340                 345                 350

Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
        355                 360                 365

Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly
    370                 375                 380

Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
385                 390                 395                 400

Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
                405                 410                 415

Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
            420                 425                 430

Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
        435                 440                 445

Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
    450                 455                 460
```

```
Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
465                 470                 475                 480


Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
                485                 490                 495


Pro Pro Arg



<210> 806
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 806
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Lys Leu Ser Cys Leu Ala Ser Gly Phe Thr Phe Ser Lys Tyr
            20                  25                  30


Gly Met Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Ser Ile Ser Ser Thr Ser Ile Tyr Ile Tyr Tyr Ala Asp Thr Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95
```

Ala Arg His Asp Tyr Ser Ser Tyr Ser Tyr Trp Gly Gln Gly Val Met
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Val Leu Thr Gln Pro
130 135 140

Lys Ser Val Ser Thr Ser Leu Glu Ser Thr Val Lys Leu Ser Cys Lys
145 150 155 160

Ile Asn Ser Gly Asn Ile Gly Ser Tyr Phe Ile His Trp Tyr Gln Gln
165 170 175

His Glu Gly Arg Ser Pro Thr Thr Met Ile Tyr Arg Asp Asp Lys Arg
180 185 190

Pro His Gly Val Pro Asp Arg Phe Ser Gly Ser Ile Asp Ser Ser Ser
195 200 205

Asn Ser Ala Phe Leu Thr Ile Asn Asn Val Gln Thr Glu Asp Glu Ala
210 215 220

Ile Tyr Phe Cys His Ser Tyr Asp Ser Gly Ile Asn Ile Val Phe Gly
225 230 235 240

Gly Gly Thr Lys Leu Thr Val Leu
245

<210> 807
<211> 744
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<400> 807
gaggtgcagc tcgtcgaatc cggtggagga ctggtgcagc caggaagatc cctgaagctg 60

tcctgtctcg cctcgggctt cactttctcc aaatacggca tgaattggat tcgccaggca 120

cccggaaagg ggctggaatg ggtggccagc atcagctcga ctagcatcta catctactat 180

gccgataccg tcaagggccg cttcactatc tcccgcgaga acgctaagaa caccctttac 240

ttgcaaatga cctccctgag gtccgaagat accgccctgt actattgcgc ccggcacgac 300

tactcatcct actcctactg gggacaggga gtcatggtga ccgtgtcctc cggcggtgga 360

ggctcagggg ggggcggctc gggaggggggt ggaagcggag gaggaggctc ccaagtcgtg 420

ctgacgcaac ccaagtccgt gagcaccagc ctggagagca ccgtgaagct cagctgcaag 480

attaactcgg gcaacattgg gtcctacttc atccattggt accagcagca cgaaggacgg 540

tcccctacca ctatgatcta ccgggacgac aagcggccgc acggagtgcc ggacagattc 600

tcgggttcaa tcgattcctc atctaactcg gcgtttctca ccatcaacaa cgtgcagacc 660

gaggacgaag cgatctactt ctgccactcc tacgactcgg gtattaacat tgtgttcggc 720

ggcgggacta agctgacagt gctg 744

<210> 808
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 808
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaggtgc agctcgtcga atccggtgga ggactggtgc agccaggaag atccctgaag 120

ctgtcctgtc tcgcctcggg cttcactttc tccaaatacg gcatgaattg gattcgccag 180

gcacccggaa aggggctgga atgggtggcc agcatcagct cgactagcat ctacatctac 240

tatgccgata ccgtcaaggg ccgcttcact atctcccgcg agaacgctaa gaacaccctt 300

tacttgcaaa tgacctccct gaggtccgaa gataccgccc tgtactattg cgcccggcac 360

gactactcat cctactccta ctggggacag ggagtcatgg tgaccgtgtc ctccggcggt 420

ggaggctcag gggggggcgg ctcgggaggg ggtggaagcg gaggaggagg ctcccaagtc 480

gtgctgacgc aacccaagtc cgtgagcacc agcctggaga gcaccgtgaa gctcagctgc 540

aagattaact cgggcaacat tgggtcctac ttcatccatt ggtaccagca gcacgaagga 600

cggtccccta ccactatgat ctaccgggac gacaagcggc cgcacggagt gccggacaga 660

ttctcgggtt caatcgattc ctcatctaac tcggcgtttc tcaccatcaa caacgtgcag 720

accgaggacg aagcgatcta cttctgccac tcctacgact cgggtattaa cattgtgttc 780

ggcggcggga ctaagctgac agtgctggga tcgcaccacc atcaccatca tcatcac 837

<210> 809
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 809
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Arg Ser Leu Lys Leu Ser Cys Leu Ala Ser Gly Phe
35 40 45

Thr Phe Ser Lys Tyr Gly Met Asn Trp Ile Arg Gln Ala Pro Gly Lys
50 55 60

```
Gly Leu Glu Trp Val Ala Ser Ile Ser Ser Thr Ser Ile Tyr Ile Tyr
65                  70                  75                  80

Tyr Ala Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala
                85                  90                  95

Lys Asn Thr Leu Tyr Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Leu Tyr Tyr Cys Ala Arg His Asp Tyr Ser Ser Tyr Ser Tyr Trp
        115                 120                 125

Gly Gln Gly Val Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
145                 150                 155                 160

Val Leu Thr Gln Pro Lys Ser Val Ser Thr Ser Leu Glu Ser Thr Val
                165                 170                 175

Lys Leu Ser Cys Lys Ile Asn Ser Gly Asn Ile Gly Ser Tyr Phe Ile
            180                 185                 190

His Trp Tyr Gln Gln His Glu Gly Arg Ser Pro Thr Thr Met Ile Tyr
        195                 200                 205

Arg Asp Asp Lys Arg Pro His Gly Val Pro Asp Arg Phe Ser Gly Ser
    210                 215                 220

Ile Asp Ser Ser Ser Asn Ser Ala Phe Leu Thr Ile Asn Asn Val Gln
225                 230                 235                 240

Thr Glu Asp Glu Ala Ile Tyr Phe Cys His Ser Tyr Asp Ser Gly Ile
                245                 250                 255
```

Asn Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Ser His
260 265 270

His His His His His His His
275

<210> 810
<211> 1476
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 810
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaggtgc agctcgtcga atccggtgga ggactggtgc agccaggaag atccctgaag 120

ctgtcctgtc tcgcctcggg cttcactttc tccaaatacg gcatgaattg gattcgccag 180

gcacccggaa aggggctgga atgggtggcc agcatcagct cgactagcat ctacatctac 240

tatgccgata ccgtcaaggg ccgcttcact atctcccgcg agaacgctaa gaacaccctt 300

tacttgcaaa tgacctccct gaggtccgaa gataccgccc tgtactattg cgcccggcac 360

gactactcat cctactccta ctggggacag ggagtcatgg tgaccgtgtc ctccggcggt 420

ggaggctcag gggggggcgg ctcgggaggg ggtggaagcg gaggaggagg ctcccaagtc 480

gtgctgacgc aacccaagtc cgtgagcacc agcctggaga gcaccgtgaa gctcagctgc 540

aagattaact cgggcaacat tgggtcctac ttcatccatt ggtaccagca gcacgaagga 600

cggtccccta ccactatgat ctaccgggac gacaagcggc cgcacggagt gccggacaga 660

ttctcgggtt caatcgattc ctcatctaac tcggcgtttc tcaccatcaa caacgtgcag 720

accgaggacg aagcgatcta cttctgccac tcctacgact cgggtattaa cattgtgttc 780

ggcggcggga ctaagctgac agtgctgacc actaccccag caccgaggcc acccaccccg 840

gctcctacca tcgcctccca gcctctgtcc ctgcgtccgg aggcatgtag acccgcagct 900

ggtggggccg tgcatacccg gggtcttgac ttcgcctgcg atatctacat ttgggcccct 960

ctggctggta cttgcggggt cctgctgctt tcactcgtga tcactcttta ctgtaagcgc 1020

ggtcggaaga agctgctgta catctttaag caacccttca tgaggcctgt gcagactact 1080

caagaggagg acggctgttc atgccggttc ccagaggagg aggaaggcgg ctgcgaactg 1140

cgcgtgaaat tcagccgcag cgcagatgct ccagcctaca agcaggggca gaaccagctc 1200

tacaacgaac tcaatcttgg tcggagagag gagtacgacg tgctggacaa gcggagagga 1260

cgggacccag aaatgggcgg gaagccgcgc agaaagaatc cccaagaggg cctgtacaac 1320

gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggtatgaa aggggaacgc 1380

agaagaggca aaggccacga cggactgtac cagggactca gcaccgccac caaggacacc 1440

tatgacgctc ttcacatgca ggccctgccg cctcgg 1476

<210> 811
<211> 492
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 811
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Arg Ser Leu Lys Leu Ser Cys Leu Ala Ser Gly Phe
35 40 45

Thr Phe Ser Lys Tyr Gly Met Asn Trp Ile Arg Gln Ala Pro Gly Lys
50 55 60

```
Gly Leu Glu Trp Val Ala Ser Ile Ser Ser Thr Ser Ile Tyr Ile Tyr
65                  70                  75                  80

Tyr Ala Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala
                85                  90                  95

Lys Asn Thr Leu Tyr Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Leu Tyr Tyr Cys Ala Arg His Asp Tyr Ser Ser Tyr Ser Tyr Trp
        115                 120                 125

Gly Gln Gly Val Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
145                 150                 155                 160

Val Leu Thr Gln Pro Lys Ser Val Ser Thr Ser Leu Glu Ser Thr Val
                165                 170                 175

Lys Leu Ser Cys Lys Ile Asn Ser Gly Asn Ile Gly Ser Tyr Phe Ile
            180                 185                 190

His Trp Tyr Gln Gln His Glu Gly Arg Ser Pro Thr Thr Met Ile Tyr
        195                 200                 205

Arg Asp Asp Lys Arg Pro His Gly Val Pro Asp Arg Phe Ser Gly Ser
    210                 215                 220

Ile Asp Ser Ser Ser Asn Ser Ala Phe Leu Thr Ile Asn Asn Val Gln
225                 230                 235                 240

Thr Glu Asp Glu Ala Ile Tyr Phe Cys His Ser Tyr Asp Ser Gly Ile
                245                 250                 255
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Asn Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Thr Thr Thr
            260                 265                 270

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        275                 280                 285

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    290                 295                 300

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
305                 310                 315                 320

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
                325                 330                 335

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
            340                 345                 350

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
        355                 360                 365

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
    370                 375                 380

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
385                 390                 395                 400

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                405                 410                 415

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            420                 425                 430

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        435                 440                 445
```

```
Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    450                 455                 460


Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
465                 470                 475                 480


Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 812
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 812
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Asp Tyr
            20                  25                  30


Tyr Met Ala Trp Val Arg Gln Ala Pro Lys Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys
    50                  55                  60


Gly Arg Phe Thr Ile Ser Arg Asn Asn Ala Lys Ser Thr Leu Tyr Leu
65                  70                  75                  80


Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
                85                  90                  95
```

```
Arg His Asp His Asn Asn Val Asp Trp Phe Ala Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125


Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr
    130                 135                 140


Gln Thr Pro Ser Ser Gln Ala Val Ser Ala Gly Glu Lys Val Thr Met
145                 150                 155                 160


Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn
                165                 170                 175


Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu
            180                 185                 190


Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ile
        195                 200                 205


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln
    210                 215                 220


Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asn Phe Pro
225                 230                 235                 240


Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
                245                 250


<210> 813
<211> 753
<212> DNA
<213> Artificial Sequence

<220>
<221> source
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<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 813
gaagtgcagc ttgtggagtc tggcggcggt ctggtgcagc cgggaagatc cctgaagctg 60

tcatgcgccg cgtccgggtt taccttccgc gattactaca tggcctgggt cagacaggca 120

cctaagaagg ggctggaatg ggtggcatcc atctcatatg aaggaaaccc gtactacgga 180

gactcggtga aaggccgctt cactatctca cggaacaacg ctaagagcac gctgtacttg 240

caaatgaact ccctccggtc ggaggacaca gccacttact actgtgcccg gcacgaccat 300

aacaacgtcg attggttcgc ctactggggt caaggaaccc tcgtgaccgt gtcctccggc 360

ggtggaggct cagggggggg cggctcggga gggggtggaa gcggaggagg aggctccgac 420

atcgtgatga ctcagactcc aagcagccag gccgtgtccg ccggagagaa agtcaccatg 480

tcgtgcaaga gctcccagtc cctgctgtac tccgaaaaca agaagaatta tctcgcctgg 540

taccagcaga agcctggaca gtccccgaag ctcctgatct tttgggcgtc gaccagggaa 600

tccggcgtgc ccgatcgctt cattggctcc ggttccggca ccgacttcac cctgaccatt 660

agcagcgtcc aggcggagga cctggctgtg tactactgcc aacagtacta caacttcccc 720

actttcggat cggggaccaa gctggagatc aag 753

<210> 814
<211> 846
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 814
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agcttgtgga gtctggcggc ggtctggtgc agccgggaag atccctgaag 120

ctgtcatgcg ccgcgtccgg gtttaccttc cgcgattact acatggcctg ggtcagacag 180

gcacctaaga aggggctgga atgggtggca tccatctcat atgaaggaaa cccgtactac 240

ggagactcgg tgaaaggccg cttcactatc tcacggaaca acgctaagag cacgctgtac 300

ttgcaaatga actccctccg gtcggaggac acagccactt actactgtgc ccggcacgac 360

cataacaacg tcgattggtt cgcctactgg ggtcaaggaa ccctcgtgac cgtgtcctcc 420

ggcggtggag gctcaggggg gggcggctcg ggagggggtg gaagcggagg aggaggctcc 480

gacatcgtga tgactcagac tccaagcagc caggccgtgt ccgccggaga gaaagtcacc 540

atgtcgtgca agagctccca gtccctgctg tactccgaaa acaagaagaa ttatctcgcc 600

tggtaccagc agaagcctgg acagtccccg aagctcctga tcttttgggc gtcgaccagg 660

gaatccggcg tgcccgatcg cttcattggc tccggttccg gcaccgactt caccctgacc 720

attagcagcg tccaggcgga ggacctggct gtgtactact gccaacagta ctacaacttc 780

cccactttcg gatcggggac caagctggag atcaagggat cgcaccacca tcaccatcat 840

catcac 846

<210> 815
<211> 282
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 815
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Arg Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

```
Thr Phe Arg Asp Tyr Tyr Met Ala Trp Val Arg Gln Ala Pro Lys Lys
    50                  55                  60

Gly Leu Glu Trp Val Ala Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr
65                  70                  75                  80

Gly Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asn Asn Ala Lys
                85                  90                  95

Ser Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala
            100                 105                 110

Thr Tyr Tyr Cys Ala Arg His Asp His Asn Asn Val Asp Trp Phe Ala
        115                 120                 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145                 150                 155                 160

Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln Ala Val Ser Ala Gly
                165                 170                 175

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            180                 185                 190

Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        195                 200                 205

Ser Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val
    210                 215                 220

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
225                 230                 235                 240
```

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
245 250 255

Tyr Tyr Asn Phe Pro Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
260 265 270

Gly Ser His His His His His His His His
275 280

<210> 816
<211> 1485
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 816
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agcttgtgga gtctggcggc ggtctggtgc agccgggaag atccctgaag 120

ctgtcatgcg ccgcgtccgg gtttaccttc cgcgattact acatggcctg ggtcagacag 180

gcacctaaga aggggctgga atgggtggca tccatctcat atgaaggaaa cccgtactac 240

ggagactcgg tgaaaggccg cttcactatc tcacggaaca acgctaagag cacgctgtac 300

ttgcaaatga actccctccg gtcggaggac acagccactt actactgtgc ccggcacgac 360

cataacaacg tcgattggtt cgcctactgg ggtcaaggaa ccctcgtgac cgtgtcctcc 420

ggcggtggag gctcaggggg gggcggctcg ggaggggggtg gaagcggagg aggaggctcc 480

gacatcgtga tgactcagac tccaagcagc caggccgtgt ccgccggaga gaaagtcacc 540

atgtcgtgca agagctccca gtccctgctg tactccgaaa acaagaagaa ttatctcgcc 600

tggtaccagc agaagcctgg acagtccccg aagctcctga tcttttgggc gtcgaccagg 660

gaatccggcg tgcccgatcg cttcattggc tccggttccg gcaccgactt caccctgacc 720

attagcagcg tccaggcgga ggacctggct gtgtactact gccaacagta ctacaacttc 780

cccactttcg gatcggggac caagctggag atcaagacca ctaccccagc accgaggcca 840

cccaccccgg ctcctaccat cgcctcccag cctctgtccc tgcgtccgga ggcatgtaga 900

cccgcagctg gtggggccgt gcatacccgg ggtcttgact tcgcctgcga tatctacatt 960

tgggcccctc tggctggtac ttgcggggtc ctgctgcttt cactcgtgat cactctttac 1020

tgtaagcgcg gtcggaagaa gctgctgtac atctttaagc aacccttcat gaggcctgtg 1080

cagactactc aagaggagga cggctgttca tgccggttcc cagaggagga ggaaggcggc 1140

tgcgaactgc gcgtgaaatt cagccgcagc gcagatgctc cagcctacaa gcaggggcag 1200

aaccagctct acaacgaact caatcttggt cggagagagg agtacgacgt gctggacaag 1260

cggagaggac gggacccaga aatgggcggg aagccgcgca gaaagaatcc ccaagagggc 1320

ctgtacaacg agctccaaaa ggataagatg gcagaagcct atagcgagat tggtatgaaa 1380

ggggaacgca gaagaggcaa aggccacgac ggactgtacc agggactcag caccgccacc 1440

aaggacacct atgacgctct tcacatgcag gccctgccgc ctcgg 1485

<210> 817
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 817
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Arg Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
35 40 45

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Thr Phe Arg Asp Tyr Tyr Met Ala Trp Val Arg Gln Ala Pro Lys Lys
    50                  55                  60

Gly Leu Glu Trp Val Ala Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr
65                  70                  75                  80

Gly Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asn Asn Ala Lys
                85                  90                  95

Ser Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala
            100                 105                 110

Thr Tyr Tyr Cys Ala Arg His Asp His Asn Asn Val Asp Trp Phe Ala
        115                 120                 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145                 150                 155                 160

Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln Ala Val Ser Ala Gly
                165                 170                 175

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            180                 185                 190

Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        195                 200                 205

Ser Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val
    210                 215                 220

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
225                 230                 235                 240
```

```
Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
                245                 250                 255

Tyr Tyr Asn Phe Pro Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430
```

```
Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445


Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
    450                 455                 460


Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465                 470                 475                 480


Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490                 495


<210> 818
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 818
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Thr Phe Thr Arg Phe Ser Leu Ser Thr Tyr
            20                  25                  30


Gly Met Ser Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
        35                  40                  45


Trp Leu Ala Asp Ile Trp Trp Asp Asp Asp Lys His Tyr Asn Pro Ser
    50                  55                  60


Leu Lys Asn Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Ala
65                  70                  75                  80
```

```
Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Ser Ser Thr Thr Asp Gly Ile Val Thr Tyr Val Met Asp
            100                 105                 110

Val Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

Asp Val Gln Met Thr Gln Ser Pro Ser Leu Leu Ser Ala Ser Val Gly
145                 150                 155                 160

Asp Ala Val Thr Ile Asn Cys Lys Ala Ser Gln Asn Ile Asn Arg Tyr
                165                 170                 175

Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Gly Pro Arg Leu Leu Ile
            180                 185                 190

Tyr Ser Ala Asn Ser Leu Gln Thr Gly Ile Pro Ser Arg Phe Ser Gly
        195                 200                 205

Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile Thr Ser Pro Gln Pro
    210                 215                 220

Glu Asp Val Ala Thr Tyr Phe Cys Leu Gln His Asn Ser Trp Pro Leu
225                 230                 235                 240

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
                245                 250
```

<210> 819
<211> 753
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 819
caagtcacgc tgaaggaatc gggccctgga attctgcagc caagccagac cctctcgctt 60

acttgcacct tcacccgctt ctcactgtcc acttacggaa tgtccgtggg atggattcgg 120

cagcccagcg gaaagggttt ggagtggctg gccgacattt ggtgggatga cgacaagcat 180

tacaacccta gcctgaagaa tcggctcacc atcagcaaag acacctccaa gaaccaggcg 240

ttcctgaaga tcaccaacgt ggataccgcc gacactgcaa catactattg tgcccgctcc 300

tcaaccaccg atgggatcgt gacctacgtg atggacgtct ggggccaggg agcttccgtg 360

accgtgtcct ccggcggtgg aggctcaggg gggggcggct cgggaggggg tggaagcgga 420

ggaggaggct ccgacgtgca gatgactcag tccccgtcgc tcctgtccgc ctccgtcggc 480

gacgccgtga ctattaactg caaggcgtcc cagaacatca atcggtacct gaactggtac 540

cagcaaaaac tgggagaagg gccgagactt ctcatctact ccgccaactc cctgcaaact 600

ggcatcccgt cgaggttcag cggatcaggc tctggtgccg acttcacttt gaccatcacg 660

agccctcagc ccgaagatgt ggccacctac ttctgcctcc aacacaactc ctggcccctg 720

acctttggtt cgggcaccaa gctggagatc aag 753

<210> 820
<211> 846
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 820
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtca cgctgaagga atcgggccct ggaattctgc agccaagcca gaccctctcg 120

cttacttgca ccttcacccg cttctcactg tccacttacg gaatgtccgt gggatggatt 180

cggcagccca gcggaaaggg tttggagtgg ctggccgaca tttggtggga tgacgacaag 240

cattacaacc ctagcctgaa gaatcggctc accatcagca aagacacctc caagaaccag 300

gcgttcctga agatcaccaa cgtggatacc gccgacactg caacatacta ttgtgcccgc 360

tcctcaacca ccgatgggat cgtgacctac gtgatggacg tctggggcca gggagcttcc 420

gtgaccgtgt cctccggcgg tggaggctca ggggggggcg gctcgggagg gggtggaagc 480

ggaggaggag gctccgacgt gcagatgact cagtccccgt cgctcctgtc cgcctccgtc 540

ggcgacgccg tgactattaa ctgcaaggcg tcccagaaca tcaatcggta cctgaactgg 600

taccagcaaa aactgggaga agggccgaga cttctcatct actccgccaa ctccctgcaa 660

actggcatcc cgtcgaggtt cagcggatca ggctctggtg ccgacttcac tttgaccatc 720

acgagccctc agcccgaaga tgtggccacc tacttctgcc tccaacacaa ctcctggccc 780

ctgacctttg gttcgggcac caagctggag atcaagggat cgcaccacca tcaccatcat 840

catcac 846

<210> 821
<211> 282
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 821
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile
20 25 30

Leu Gln Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Phe Thr Arg Phe

35 40 45

Ser Leu Ser Thr Tyr Gly Met Ser Val Gly Trp Ile Arg Gln Pro Ser
50 55 60

Gly Lys Gly Leu Glu Trp Leu Ala Asp Ile Trp Trp Asp Asp Asp Lys
65 70 75 80

His Tyr Asn Pro Ser Leu Lys Asn Arg Leu Thr Ile Ser Lys Asp Thr
85 90 95

Ser Lys Asn Gln Ala Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp
100 105 110

Thr Ala Thr Tyr Tyr Cys Ala Arg Ser Ser Thr Thr Asp Gly Ile Val
115 120 125

Thr Tyr Val Met Asp Val Trp Gly Gln Gly Ala Ser Val Thr Val Ser
130 135 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145 150 155 160

Gly Gly Gly Gly Ser Asp Val Gln Met Thr Gln Ser Pro Ser Leu Leu
165 170 175

Ser Ala Ser Val Gly Asp Ala Val Thr Ile Asn Cys Lys Ala Ser Gln
180 185 190

Asn Ile Asn Arg Tyr Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Gly
195 200 205

Pro Arg Leu Leu Ile Tyr Ser Ala Asn Ser Leu Gln Thr Gly Ile Pro
210 215 220

Ser Arg Phe Ser Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile

225 230 235 240

Thr Ser Pro Gln Pro Glu Asp Val Ala Thr Tyr Phe Cys Leu Gln His
245 250 255

Asn Ser Trp Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
260 265 270

Gly Ser His His His His His His His His
275 280

<210> 822
<211> 1485
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 822
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtca cgctgaagga atcgggccct ggaattctgc agccaagcca gaccctctcg 120

cttacttgca ccttcacccg cttctcactg tccacttacg gaatgtccgt gggatggatt 180

cggcagccca gcggaaaggg tttggagtgg ctggccgaca tttggtggga tgacgacaag 240

cattacaacc ctagcctgaa gaatcggctc accatcagca aagacacctc caagaaccag 300

gcgttcctga agatcaccaa cgtggatacc gccgacactg caacatacta ttgtgcccgc 360

tcctcaacca ccgatgggat cgtgacctac gtgatggacg tctggggcca gggagcttcc 420

gtgaccgtgt cctccggcgg tggaggctca ggggggggcg gctcgggagg gggtggaagc 480

ggaggaggag gctccgacgt gcagatgact cagtccccgt cgctcctgtc cgcctccgtc 540

ggcgacgccg tgactattaa ctgcaaggcg tcccagaaca tcaatcggta cctgaactgg 600

taccagcaaa aactgggaga agggccgaga cttctcatct actccgccaa ctccctgcaa 660

actggcatcc cgtcgaggtt cagcggatca ggctctggtg ccgacttcac tttgaccatc 720

acgagccctc agcccgaaga tgtggccacc tacttctgcc tccaacacaa ctcctggccc 780

ctgacctttg gttcgggcac caagctggag atcaagacca ctaccccagc accgaggcca 840

cccaccccgg ctcctaccat cgcctcccag cctctgtccc tgcgtccgga ggcatgtaga 900

cccgcagctg gtggggccgt gcatacccgg ggtcttgact tcgcctgcga tatctacatt 960

tgggcccctc tggctggtac ttgcggggtc ctgctgcttt cactcgtgat cactctttac 1020

tgtaagcgcg gtcggaagaa gctgctgtac atctttaagc aacccttcat gaggcctgtg 1080

cagactactc aagaggagga cggctgttca tgccggttcc cagaggagga ggaaggcggc 1140

tgcgaactgc gcgtgaaatt cagccgcagc gcagatgctc cagcctacaa gcaggggcag 1200

aaccagctct acaacgaact caatcttggt cggagagagg agtacgacgt gctggacaag 1260

cggagaggac gggacccaga aatgggcggg aagccgcgca gaaagaatcc ccaagagggc 1320

ctgtacaacg agctccaaaa ggataagatg gcagaagcct atagcgagat tggtatgaaa 1380

ggggaacgca gaagaggcaa aggccacgac ggactgtacc agggactcag caccgccacc 1440

aaggacacct atgacgctct tcacatgcag gccctgccgc ctcgg 1485

<210> 823
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 823
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile
20 25 30

```
Leu Gln Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Phe Thr Arg Phe
        35                  40                  45

Ser Leu Ser Thr Tyr Gly Met Ser Val Gly Trp Ile Arg Gln Pro Ser
    50                  55                  60

Gly Lys Gly Leu Glu Trp Leu Ala Asp Ile Trp Trp Asp Asp Asp Lys
65                  70                  75                  80

His Tyr Asn Pro Ser Leu Lys Asn Arg Leu Thr Ile Ser Lys Asp Thr
                85                  90                  95

Ser Lys Asn Gln Ala Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp
            100                 105                 110

Thr Ala Thr Tyr Tyr Cys Ala Arg Ser Ser Thr Thr Asp Gly Ile Val
        115                 120                 125

Thr Tyr Val Met Asp Val Trp Gly Gln Gly Ala Ser Val Thr Val Ser
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
145                 150                 155                 160

Gly Gly Gly Gly Ser Asp Val Gln Met Thr Gln Ser Pro Ser Leu Leu
                165                 170                 175

Ser Ala Ser Val Gly Asp Ala Val Thr Ile Asn Cys Lys Ala Ser Gln
            180                 185                 190

Asn Ile Asn Arg Tyr Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Gly
        195                 200                 205

Pro Arg Leu Leu Ile Tyr Ser Ala Asn Ser Leu Gln Thr Gly Ile Pro
    210                 215                 220
```

```
Ser Arg Phe Ser Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile
225                 230                 235                 240


Thr Ser Pro Gln Pro Glu Asp Val Ala Thr Tyr Phe Cys Leu Gln His
                245                 250                 255


Asn Ser Trp Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
            260                 265                 270


Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285


Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300


Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320


Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335


Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350


Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365


Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380


Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln
385                 390                 395                 400


Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415
```

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
420 425 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
435 440 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
450 455 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465 470 475 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490 495

<210> 824
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 824
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Thr
1 5 10 15

Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Ser
20 25 30

Gly Met Gln Trp Ile Arg Gln Ala Pro Lys Lys Gly Leu Glu Trp Ile
35 40 45

Ser Gly Ile Tyr Tyr Asp Ser Tyr Lys Lys Ser Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Glu Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Ala Lys Ser Ala Tyr Tyr Gly Tyr Lys Asp Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Val Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
130 135 140

Met Thr Gln Ser Pro Pro Ser Leu Ser Ala Ser Leu Gly Asp Lys Val
145 150 155 160

Thr Ile Thr Cys Gln Ala Ser Gln Asn Ile Asn Lys Tyr Ile Ala Trp
165 170 175

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Arg Leu Leu Ile Arg Tyr Thr
180 185 190

Ser Thr Leu Glu Ser Gly Thr Pro Ser Arg Phe Ser Gly Ser Gly Ser
195 200 205

Gly Arg Asp Tyr Ser Phe Ser Ile Ser Asn Val Glu Ser Gly Asp Val
210 215 220

Ala Ser Tyr Tyr Cys Leu Gln Tyr Asp Asp Leu Pro Tyr Thr Phe Gly
225 230 235 240

Pro Gly Thr Lys Leu Glu Leu Lys
245

<210> 825

<211> 744
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 825
gaggtccagc ttgtggaatc aggaggcgga ctcgtccagc cgggtactag cctgaagctc 60

agctgtgtgg ccagcggttt taccttctcg tcctccggga tgcagtggat tcggcaggct 120

cccaagaagg gactggaatg gatctcgggc atctactacg actcgtacaa gaagtcctac 180

gccgattccg tgaaaggtcg cttcaccatc tcccgggaca acagcaagaa cactctgtac 240

ctcgagatga actccttgcg ctccgaggat accgcaacct attactgcgc caagtcggcc 300

tactacggct acaaggacta cttcgactat tggggccagg gagtgatggt gaccgtgtcc 360

tccggcggtg gaggctcagg ggggggcggc tcgggagggg gtggaagcgg aggaggaggc 420

tccgacatcc aaatgacaca gtcaccccct tctctttccg cgagcctggg agataaggtc 480

accattacgt gccaagcgtc ccagaacatc aacaagtaca tcgcctggta ccagcagaaa 540

ccgggaaagg ccccgcggct gctgattaga tacacctcga ctctggaatc cggcactcca 600

tcaagattca gcggctccgg cagcgggagg gactactcgt tctccatctc caatgtggag 660

tccggggacg tggccagcta ctattgcctg caatacgacg atctgcccta caccttcgga 720

cctggaacca agctggaact caag 744

<210> 826
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 826

atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaggtcc agcttgtgga atcaggaggc ggactcgtcc agccgggtac tagcctgaag 120

ctcagctgtg tggccagcgg ttttaccttc tcgtcctccg ggatgcagtg gattcggcag 180

gctcccaaga agggactgga atggatctcg ggcatctact acgactcgta caagaagtcc 240

tacgccgatt ccgtgaaagg tcgcttcacc atctcccggg acaacagcaa gaacactctg 300

tacctcgaga tgaactcctt gcgctccgag gataccgcaa cctattactg cgccaagtcg 360

gcctactacg gctacaagga ctacttcgac tattggggcc agggagtgat ggtgaccgtg 420

tcctccggcg gtggaggctc agggggggggc ggctcgggag ggggtggaag cggaggagga 480

ggctccgaca tccaaatgac acagtcaccc ccttctcttt ccgcgagcct gggagataag 540

gtcaccatta cgtgccaagc gtcccagaac atcaacaagt acatcgcctg gtaccagcag 600

aaaccgggaa aggccccgcg gctgctgatt agatacacct cgactctgga atccggcact 660

ccatcaagat tcagcggctc cggcagcggg agggactact cgttctccat ctccaatgtg 720

gagtccgggg acgtggccag ctactattgc ctgcaatacg acgatctgcc ctacaccttc 780

ggacctggaa ccaagctgga actcaaggga tcgcaccacc atcaccatca tcatcac 837

<210> 827
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 827
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

```
Val Gln Pro Gly Thr Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe
        35                  40                  45

Thr Phe Ser Ser Ser Gly Met Gln Trp Ile Arg Gln Ala Pro Lys Lys
    50                  55                  60

Gly Leu Glu Trp Ile Ser Gly Ile Tyr Tyr Asp Ser Tyr Lys Lys Ser
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
                85                  90                  95

Lys Asn Thr Leu Tyr Leu Glu Met Asn Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Thr Tyr Tyr Cys Ala Lys Ser Ala Tyr Tyr Gly Tyr Lys Asp Tyr
        115                 120                 125

Phe Asp Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
145                 150                 155                 160

Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Pro Ser Leu Ser Ala Ser
                165                 170                 175

Leu Gly Asp Lys Val Thr Ile Thr Cys Gln Ala Ser Gln Asn Ile Asn
            180                 185                 190

Lys Tyr Ile Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Arg Leu
        195                 200                 205

Leu Ile Arg Tyr Thr Ser Thr Leu Glu Ser Gly Thr Pro Ser Arg Phe
    210                 215                 220
```

Ser Gly Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser Asn Val
225 230 235 240

Glu Ser Gly Asp Val Ala Ser Tyr Tyr Cys Leu Gln Tyr Asp Asp Leu
245 250 255

Pro Tyr Thr Phe Gly Pro Gly Thr Lys Leu Glu Leu Lys Gly Ser His
260 265 270

His His His His His His His
275

<210> 828
<211> 1476
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 828
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaggtcc agcttgtgga atcaggaggc ggactcgtcc agccgggtac tagcctgaag 120

ctcagctgtg tggccagcgg ttttaccttc tcgtcctccg ggatgcagtg gattcggcag 180

gctcccaaga agggactgga atggatctcg ggcatctact acgactcgta caagaagtcc 240

tacgccgatt ccgtgaaagg tcgcttcacc atctcccggg acaacagcaa gaacactctg 300

tacctcgaga tgaactcctt gcgctccgag gataccgcaa cctattactg cgccaagtcg 360

gcctactacg gctacaagga ctacttcgac tattggggcc agggagtgat ggtgaccgtg 420

tcctccggcg gtggaggctc agggggggggc ggctcgggag ggggtggaag cggaggagga 480

ggctccgaca tccaaatgac acagtcaccc ccttctcttt ccgcgagcct gggagataag 540

gtcaccatta cgtgccaagc gtcccagaac atcaacaagt acatcgcctg gtaccagcag 600

aaaccgggaa aggccccgcg gctgctgatt agatacacct cgactctgga atccggcact 660

ccatcaagat tcagcggctc cggcagcggg agggactact cgttctccat ctccaatgtg 720

gagtccgggg acgtggccag ctactattgc ctgcaatacg acgatctgcc ctacaccttc 780

ggacctggaa ccaagctgga actcaagacc actaccccag caccgaggcc acccaccccg 840

gctcctacca tcgcctccca gcctctgtcc ctgcgtccgg aggcatgtag acccgcagct 900

ggtggggccg tgcatacccg gggtcttgac ttcgcctgcg atatctacat ttgggcccct 960

ctggctggta cttgcggggt cctgctgctt tcactcgtga tcactcttta ctgtaagcgc 1020

ggtcggaaga agctgctgta catctttaag caacccttca tgaggcctgt gcagactact 1080

caagaggagg acggctgttc atgccggttc ccagaggagg aggaaggcgg ctgcgaactg 1140

cgcgtgaaat tcagccgcag cgcagatgct ccagcctaca agcaggggca gaaccagctc 1200

tacaacgaac tcaatcttgg tcggagagag gagtacgacg tgctggacaa gcggagagga 1260

cgggacccag aaatgggcgg gaagccgcgc agaaagaatc cccaagaggg cctgtacaac 1320

gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggtatgaa aggggaacgc 1380

agaagaggca aaggccacga cggactgtac cagggactca gcaccgccac caaggacacc 1440

tatgacgctc ttcacatgca ggccctgccg cctcgg 1476

<210> 829
<211> 492
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 829
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

```
Val Gln Pro Gly Thr Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe
        35                  40                  45

Thr Phe Ser Ser Ser Gly Met Gln Trp Ile Arg Gln Ala Pro Lys Lys
    50                  55                  60

Gly Leu Glu Trp Ile Ser Gly Ile Tyr Tyr Asp Ser Tyr Lys Lys Ser
65                  70                  75                  80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
                85                  90                  95

Lys Asn Thr Leu Tyr Leu Glu Met Asn Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Thr Tyr Tyr Cys Ala Lys Ser Ala Tyr Tyr Gly Tyr Lys Asp Tyr
        115                 120                 125

Phe Asp Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
145                 150                 155                 160

Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Pro Ser Leu Ser Ala Ser
                165                 170                 175

Leu Gly Asp Lys Val Thr Ile Thr Cys Gln Ala Ser Gln Asn Ile Asn
            180                 185                 190

Lys Tyr Ile Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Arg Leu
        195                 200                 205

Leu Ile Arg Tyr Thr Ser Thr Leu Glu Ser Gly Thr Pro Ser Arg Phe
    210                 215                 220
```

```
Ser Gly Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser Asn Val
225                 230                 235                 240


Glu Ser Gly Asp Val Ala Ser Tyr Tyr Cys Leu Gln Tyr Asp Asp Leu
                245                 250                 255


Pro Tyr Thr Phe Gly Pro Gly Thr Lys Leu Glu Leu Lys Thr Thr Thr
            260                 265                 270


Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        275                 280                 285


Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    290                 295                 300


His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
305                 310                 315                 320


Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
                325                 330                 335


Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
            340                 345                 350


Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
        355                 360                 365


Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
    370                 375                 380


Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
385                 390                 395                 400


Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                405                 410                 415
```

```
Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            420                 425                 430


Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        435                 440                 445


Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    450                 455                 460


Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
465                 470                 475                 480


Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 830
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 830
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Leu Leu Gln Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Thr Phe Ala Gly Phe Ser Leu Asn Thr His
            20                  25                  30


Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
        35                  40                  45


Trp Leu Ala Asn Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser
    50                  55                  60
```

```
Leu Lys Asn Arg Leu Thr Met Ser Lys Asp Thr Ser Asn Asn Gln Ala
65                  70                  75                  80


Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95


Cys Ala Arg Ile Glu Gly Ser Pro Val Val Thr Thr Val Phe Asp Tyr
            100                 105                 110


Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser
        115                 120                 125


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
    130                 135                 140


Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly Asp
145                 150                 155                 160


Arg Val Thr Ile Asn Cys Lys Ala Ser Gln Asn Ile Asn Arg Tyr Leu
                165                 170                 175


Asn Trp Tyr Gln Gln Lys Leu Gly Glu Ala Pro Lys Leu Leu Ile Tyr
            180                 185                 190


Asn Ala Asn Ser Leu Gln Thr Gly Ile Pro Ser Arg Phe Ser Gly Ser
        195                 200                 205


Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Ala
    210                 215                 220


Asp Val Ala Thr Tyr Phe Cys Leu Gln His Asn Ser Arg Pro Leu Thr
225                 230                 235                 240


Phe Gly Ser Gly Thr Ile Leu Glu Ile Lys
                245                 250
```

<210> 831
<211> 750
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 831
caagtcactc ttaaggaatc cgggccagga ctgttgcagc cgagccagac cctgtccctc 60

acttgtacct tcgccggctt ttcactgaac acccacggaa tgggcgtggg atggattagg 120

cagccctcgg gaaagggact ggagtggctg gccaacattt ggtgggacga cgacaagtat 180

tacaacccga gcctcaagaa ccgcctgact atgtccaagg atacctccaa caaccaggcc 240

ttcctgaaaa tcactaacgt ggataccgct gacaccgcaa cgtactactg cgcccggatc 300

gaaggttccc ccgtcgtgac aactgtgttc gactactggg gacagggcgt gatggtgacc 360

gtgtcctccg gcggtggagg ctcaggggg ggcggctcgg gaggggtgg aagcggagga 420

ggaggctccg acatccaaat gacccagtca cctagctttc tgtcggcctc ggtcggcgac 480

agagtgacca ttaactgcaa agcgtcccag aacatcaacc gctacctgaa ttggtaccag 540

cagaagctgg gggaagcccc gaagctgctg atctacaacg cgaacagcct ccagactggt 600

attccttccc ggttctccgg gagcggctcg ggtaccgatt tcaccctcac catctcctcc 660

cttcaacccg ctgacgtggc cacctacttc tgcttgcaac ataattctcg gcctctgacc 720

ttcggaagcg gcactatcct cgagatcaag 750

<210> 832
<211> 843
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 832
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtca ctcttaagga atccgggcca ggactgttgc agccgagcca gaccctgtcc 120

ctcacttgta ccttcgccgg cttttcactg aacacccacg gaatgggcgt gggatggatt 180

aggcagccct cgggaaaggg actggagtgg ctggccaaca tttggtggga cgacgacaag 240

tattacaacc cgagcctcaa gaaccgcctg actatgtcca aggatacctc caacaaccag 300

gccttcctga aaatcactaa cgtggatacc gctgacaccg caacgtacta ctgcgcccgg 360

atcgaaggtt cccccgtcgt gacaactgtg ttcgactact ggggacaggg cgtgatggtg 420

accgtgtcct ccggcggtgg aggctcaggg gggggcggct cgggaggggg tggaagcgga 480

ggaggaggct ccgacatcca aatgacccag tcacctagct ttctgtcggc ctcggtcggc 540

gacagagtga ccattaactg caaagcgtcc cagaacatca accgctacct gaattggtac 600

cagcagaagc tgggggaagc cccgaagctg ctgatctaca acgcgaacag cctccagact 660

ggtattcctt cccggttctc cgggagcggc tcgggtaccg atttcaccct caccatctcc 720

tcccttcaac ccgctgacgt ggccacctac ttctgcttgc aacataattc tcggcctctg 780

accttcggaa gcggcactat cctcgagatc aagggatcgc accaccatca ccatcatcat 840

cac 843

<210> 833
<211> 281
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 833
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Leu

```
            20                  25                  30

Leu Gln Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Phe Ala Gly Phe
        35                  40                  45

Ser Leu Asn Thr His Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser
    50                  55                  60

Gly Lys Gly Leu Glu Trp Leu Ala Asn Ile Trp Trp Asp Asp Asp Lys
65                  70                  75                  80

Tyr Tyr Asn Pro Ser Leu Lys Asn Arg Leu Thr Met Ser Lys Asp Thr
                85                  90                  95

Ser Asn Asn Gln Ala Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp
            100                 105                 110

Thr Ala Thr Tyr Tyr Cys Ala Arg Ile Glu Gly Ser Pro Val Val Thr
        115                 120                 125

Thr Val Phe Asp Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
145                 150                 155                 160

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser
                165                 170                 175

Ala Ser Val Gly Asp Arg Val Thr Ile Asn Cys Lys Ala Ser Gln Asn
            180                 185                 190

Ile Asn Arg Tyr Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Ala Pro
        195                 200                 205

Lys Leu Leu Ile Tyr Asn Ala Asn Ser Leu Gln Thr Gly Ile Pro Ser
```

210 215 220

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
225 230 235 240

Ser Leu Gln Pro Ala Asp Val Ala Thr Tyr Phe Cys Leu Gln His Asn
245 250 255

Ser Arg Pro Leu Thr Phe Gly Ser Gly Thr Ile Leu Glu Ile Lys Gly
260 265 270

Ser His His His His His His His His
275 280

<210> 834
<211> 1482
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 834
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtca ctcttaagga atccgggcca ggactgttgc agccgagcca gaccctgtcc 120

ctcacttgta ccttcgccgg cttttcactg aacacccacg gaatgggcgt gggatggatt 180

aggcagccct cgggaaaggg actggagtgg ctggccaaca tttggtggga cgacgacaag 240

tattacaacc cgagcctcaa gaaccgcctg actatgtcca aggatacctc caacaaccag 300

gccttcctga aaatcactaa cgtggatacc gctgacaccg caacgtacta ctgcgcccgg 360

atcgaaggtt cccccgtcgt gacaactgtg ttcgactact ggggacaggg cgtgatggtg 420

accgtgtcct ccggcggtgg aggctcaggg gggggcggct cgggaggggg tggaagcgga 480

ggaggaggct ccgacatcca aatgacccag tcacctagct ttctgtcggc ctcggtcggc 540

gacagagtga ccattaactg caaagcgtcc cagaacatca accgctacct gaattggtac 600

cagcagaagc tgggggaagc cccgaagctg ctgatctaca acgcgaacag cctccagact 660

ggtattcctt cccggttctc cgggagcggc tcgggtaccg atttcaccct caccatctcc 720

tcccttcaac ccgctgacgt ggccacctac ttctgcttgc aacataattc tcggcctctg 780

accttcggaa gcggcactat cctcgagatc aagaccacta ccccagcacc gaggccaccc 840

accccggctc ctaccatcgc ctcccagcct ctgtccctgc gtccggaggc atgtagaccc 900

gcagctggtg gggccgtgca tacccggggt cttgacttcg cctgcgatat ctacatttgg 960

gcccctctgg ctggtacttg cggggtcctg ctgctttcac tcgtgatcac tctttactgt 1020

aagcgcggtc ggaagaagct gctgtacatc tttaagcaac ccttcatgag gcctgtgcag 1080

actactcaag aggaggacgg ctgttcatgc cggttcccag aggaggagga aggcggctgc 1140

gaactgcgcg tgaaattcag ccgcagcgca gatgctccag cctacaagca ggggcagaac 1200

cagctctaca acgaactcaa tcttggtcgg agagaggagt acgacgtgct ggacaagcgg 1260

agaggacggg acccagaaat gggcgggaag ccgcgcagaa agaatcccca agagggcctg 1320

tacaacgagc tccaaaagga taagatggca gaagcctata gcgagattgg tatgaaaggg 1380

gaacgcagaa gaggcaaagg ccacgacgga ctgtaccagg gactcagcac cgccaccaag 1440

gacacctatg acgctcttca catgcaggcc ctgccgcctc gg 1482

<210> 835
<211> 494
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 835
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Leu
            20                  25                  30

Leu Gln Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Phe Ala Gly Phe
        35                  40                  45

Ser Leu Asn Thr His Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser
    50                  55                  60

Gly Lys Gly Leu Glu Trp Leu Ala Asn Ile Trp Trp Asp Asp Asp Lys
65                  70                  75                  80

Tyr Tyr Asn Pro Ser Leu Lys Asn Arg Leu Thr Met Ser Lys Asp Thr
                85                  90                  95

Ser Asn Asn Gln Ala Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp
            100                 105                 110

Thr Ala Thr Tyr Tyr Cys Ala Arg Ile Glu Gly Ser Pro Val Val Thr
        115                 120                 125

Thr Val Phe Asp Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
145                 150                 155                 160

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser
                165                 170                 175

Ala Ser Val Gly Asp Arg Val Thr Ile Asn Cys Lys Ala Ser Gln Asn
            180                 185                 190

Ile Asn Arg Tyr Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Ala Pro
        195                 200                 205
```

```
Lys Leu Leu Ile Tyr Asn Ala Asn Ser Leu Gln Thr Gly Ile Pro Ser
    210                 215                 220

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
225                 230                 235                 240

Ser Leu Gln Pro Ala Asp Val Ala Thr Tyr Phe Cys Leu Gln His Asn
                245                 250                 255

Ser Arg Pro Leu Thr Phe Gly Ser Gly Thr Ile Leu Glu Ile Lys Thr
            260                 265                 270

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
        275                 280                 285

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
    290                 295                 300

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
305                 310                 315                 320

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
                325                 330                 335

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
            340                 345                 350

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
        355                 360                 365

Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
    370                 375                 380

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn
385                 390                 395                 400
```

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
405 410 415

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
420 425 430

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
435 440 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
450 455 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465 470 475 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 836
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 836
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Met Leu Gln Pro Ser Lys
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

Gly Met Val Val Ser Trp Ile Arg Gln Pro Ser Gly Lys Ser Leu Glu
35 40 45

Trp Leu Ala Ala Ile Ala Trp Asp Gly Asp Lys Tyr Tyr Asn Pro Ser

```
    50                  55                  60

Leu Lys Ser Arg Val Thr Val Ser Lys Asp Thr Ser Asn Thr Gln Val
65                  70                  75                  80

Phe Leu Arg Ile Thr Ser Val Asp Ile Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Thr Arg Arg Asp Tyr Asp Val Gly Tyr Tyr Tyr Phe Asp Phe Trp
            100                 105                 110

Gly Gln Gly Val Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Lys Ile
    130                 135                 140

Val Leu Thr Gln Ser Pro Thr Ile Thr Ala Ala Ser Pro Gly Glu Lys
145                 150                 155                 160

Val Thr Ile Thr Cys Leu Ala Ser Ser Arg Val Ser Asn Ile Tyr Trp
                165                 170                 175

Tyr Gln Gln Lys Ser Gly Ala Ser Pro Lys Leu Leu Ile Tyr Ser Thr
            180                 185                 190

Ser Ser Leu Ala Ser Gly Val Pro Tyr Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

Gly Thr Ser Tyr Ser Leu Thr Ile Asn Thr Met Glu Ala Glu Asp Ala
    210                 215                 220

Ala Thr Tyr Tyr Cys His Gln Trp Ser Ser Asn Pro Trp Thr Phe Gly
225                 230                 235                 240

Gly Gly Thr Lys Leu Glu Leu Lys
```

<210> 837
<211> 744
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 837
caagtcaccc tgaaagaatc gggtcccgga atgctgcagc catccaagac gctgtccctt 60

acatgctcct tctccgggtt cagcctctca acttccggga tggtggtgtc atggatcaga 120

cagccgagcg gaaagtccct ggagtggctg gcggccatcg catgggatgg cgataagtac 180

tacaacccga gcctgaagtc aagggtcact gtgtccaagg acacctccaa cacccaagtg 240

ttccttcgga tcacctccgt ggacattgct gacaccgcca cctattactg cactcgccgg 300

gactacgacg tgggctacta ctacttcgat ttctggggac agggtgtcat ggtgaccgtg 360

tcctccggcg gtggaggctc agggggggggc ggctcgggag ggggtggaag cggaggagga 420

ggctccaaga ttgtgctgac ccagagcccc actattaccg ccgcctcccc gggggaaaag 480

gtcaccatca cttgtctggc gtcctcacgc gtgtcgaata tctactggta tcagcagaag 540

tccggcgcca gccccaagct gctgatctac tcgacctcct ccctcgcgtc gggagtgcct 600

taccggtttt ctggctcggg aagcggaacc agctactcct tgaccatcaa caccatggaa 660

gccgaggacg ctgccactta ctactgccac cagtggtcga gcaacccttg gactttcggt 720

ggaggcacca aactcgagct caag 744

<210> 838
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 838
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtca ccctgaaaga atcgggtccc ggaatgctgc agccatccaa gacgctgtcc 120

cttacatgct ccttctccgg gttcagcctc tcaacttccg ggatggtggt gtcatggatc 180

agacagccga gcggaaagtc cctggagtgg ctggcggcca tcgcatggga tggcgataag 240

tactacaacc cgagcctgaa gtcaagggtc actgtgtcca aggacacctc caacacccaa 300

gtgttccttc ggatcacctc cgtggacatt gctgacaccg ccacctatta ctgcactcgc 360

cgggactacg acgtgggcta ctactacttc gatttctggg gacagggtgt catggtgacc 420

gtgtcctccg gcggtggagg ctcaggggggg ggcggctcgg gaggggggtgg aagcggagga 480

ggaggctcca agattgtgct gacccagagc cccactatta ccgccgcctc cccgggggaa 540

aaggtcacca tcacttgtct ggcgtcctca cgcgtgtcga atatctactg gtatcagcag 600

aagtccggcg ccagccccaa gctgctgatc tactcgacct cctccctcgc gtcgggagtg 660

ccttaccggt tttctggctc gggaagcgga accagctact ccttgaccat caacaccatg 720

gaagccgagg acgctgccac ttactactgc caccagtggt cgagcaaccc ttggactttc 780

ggtggaggca ccaaactcga gctcaaggga tcgcaccacc atcaccatca tcatcac 837

<210> 839
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 839
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Met
            20                  25                  30

Leu Gln Pro Ser Lys Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe
        35                  40                  45

Ser Leu Ser Thr Ser Gly Met Val Val Ser Trp Ile Arg Gln Pro Ser
    50                  55                  60

Gly Lys Ser Leu Glu Trp Leu Ala Ala Ile Ala Trp Asp Gly Asp Lys
65                  70                  75                  80

Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Val Ser Lys Asp Thr
                85                  90                  95

Ser Asn Thr Gln Val Phe Leu Arg Ile Thr Ser Val Asp Ile Ala Asp
            100                 105                 110

Thr Ala Thr Tyr Tyr Cys Thr Arg Arg Asp Tyr Asp Val Gly Tyr Tyr
        115                 120                 125

Tyr Phe Asp Phe Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Lys Ile Val Leu Thr Gln Ser Pro Thr Ile Thr Ala Ala
                165                 170                 175

Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Leu Ala Ser Ser Arg Val
            180                 185                 190

Ser Asn Ile Tyr Trp Tyr Gln Gln Lys Ser Gly Ala Ser Pro Lys Leu
        195                 200                 205
```

Leu Ile Tyr Ser Thr Ser Ser Leu Ala Ser Gly Val Pro Tyr Arg Phe
210 215 220

Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Asn Thr Met
225 230 235 240

Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Trp Ser Ser Asn
245 250 255

Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Gly Ser His
260 265 270

His His His His His His His
275

<210> 840
<211> 1476
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 840
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtca ccctgaaaga atcgggtccc ggaatgctgc agccatccaa gacgctgtcc 120

cttacatgct ccttctccgg gttcagcctc tcaacttccg ggatggtggt gtcatggatc 180

agacagccga gcggaaagtc cctggagtgg ctggcggcca tcgcatggga tggcgataag 240

tactacaacc cgagcctgaa gtcaagggtc actgtgtcca aggacacctc caacacccaa 300

gtgttccttc ggatcacctc cgtggacatt gctgacaccg ccacctatta ctgcactcgc 360

cgggactacg acgtgggcta ctactacttc gatttctggg gacagggtgt catggtgacc 420

gtgtcctccg gcggtggagg ctcaggggggg ggcggctcgg gaggggggtgg aagcggagga 480

ggaggctcca agattgtgct gacccagagc cccactatta ccgccgcctc cccgggggaa 540

aaggtcacca tcacttgtct ggcgtcctca cgcgtgtcga atatctactg gtatcagcag 600

aagtccggcg ccagccccaa gctgctgatc tactcgacct cctccctcgc gtcgggagtg 660

ccttaccggt tttctggctc gggaagcgga accagctact ccttgaccat caacaccatg 720

gaagccgagg acgctgccac ttactactgc caccagtggt cgagcaaccc ttggactttc 780

ggtggaggca ccaaactcga gctcaagacc actaccccag caccgaggcc acccaccccg 840

gctcctacca tcgcctccca gcctctgtcc ctgcgtccgg aggcatgtag acccgcagct 900

ggtggggccg tgcatacccg gggtcttgac ttcgcctgcg atatctacat ttgggcccct 960

ctggctggta cttgcggggt cctgctgctt tcactcgtga tcactcttta ctgtaagcgc 1020

ggtcggaaga agctgctgta catctttaag caacccttca tgaggcctgt gcagactact 1080

caagaggagg acggctgttc atgccggttc ccagaggagg aggaaggcgg ctgcgaactg 1140

cgcgtgaaat tcagccgcag cgcagatgct ccagcctaca agcaggggca gaaccagctc 1200

tacaacgaac tcaatcttgg tcggagagag gagtacgacg tgctggacaa gcggagagga 1260

cgggacccag aaatgggcgg gaagccgcgc agaaagaatc cccaagaggg cctgtacaac 1320

gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggtatgaa aggggaacgc 1380

agaagaggca aaggccacga cggactgtac cagggactca gcaccgccac caaggacacc 1440

tatgacgctc ttcacatgca ggccctgccg cctcgg 1476

<210> 841
<211> 492
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 841
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Met
            20                  25                  30

Leu Gln Pro Ser Lys Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe
        35                  40                  45

Ser Leu Ser Thr Ser Gly Met Val Val Ser Trp Ile Arg Gln Pro Ser
    50                  55                  60

Gly Lys Ser Leu Glu Trp Leu Ala Ala Ile Ala Trp Asp Gly Asp Lys
65                  70                  75                  80

Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Val Ser Lys Asp Thr
                85                  90                  95

Ser Asn Thr Gln Val Phe Leu Arg Ile Thr Ser Val Asp Ile Ala Asp
            100                 105                 110

Thr Ala Thr Tyr Tyr Cys Thr Arg Arg Asp Tyr Asp Val Gly Tyr Tyr
        115                 120                 125

Tyr Phe Asp Phe Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Lys Ile Val Leu Thr Gln Ser Pro Thr Ile Thr Ala Ala
                165                 170                 175

Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Leu Ala Ser Ser Arg Val
            180                 185                 190

Ser Asn Ile Tyr Trp Tyr Gln Gln Lys Ser Gly Ala Ser Pro Lys Leu
        195                 200                 205
```

```
Leu Ile Tyr Ser Thr Ser Ser Leu Ala Ser Gly Val Pro Tyr Arg Phe
    210                 215                 220

Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Asn Thr Met
225                 230                 235                 240

Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Trp Ser Ser Asn
                245                 250                 255

Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Thr Thr Thr
            260                 265                 270

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        275                 280                 285

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    290                 295                 300

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
305                 310                 315                 320

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
                325                 330                 335

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
            340                 345                 350

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
        355                 360                 365

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
    370                 375                 380

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
385                 390                 395                 400
```

```
Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                405                 410                 415


Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            420                 425                 430


Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        435                 440                 445


Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    450                 455                 460


Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
465                 470                 475                 480


Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 842
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 842
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1               5                   10                  15


Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Asn Thr Val Thr Gly Tyr
            20                  25                  30


Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
        35                  40                  45
```

```
Gly Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe
    50                  55                  60

Lys Gly Arg Cys Val Phe Ser Leu Glu Ala Ser Ala Ser Thr Ala His
65                  70                  75                  80

Leu Gln Ile Ser Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
                85                  90                  95

Ala Arg Ser Thr Tyr Tyr Gly Tyr Lys Asp Trp Phe Ala Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn Ile Gln
    130                 135                 140

Leu Thr Gln Ser Pro Ser Arg Leu Ser Ala Ser Val Gly Asp Arg Val
145                 150                 155                 160

Thr Leu Ser Cys Lys Gly Ser Gln Asn Ile Asn Asn Tyr Leu Ala Trp
                165                 170                 175

Tyr Gln Gln Lys Leu Gly Glu Ala Pro Lys Leu Leu Ile Tyr Asn Thr
            180                 185                 190

Asn Asn Leu Gln Thr Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

Gly Thr Asp Tyr Thr Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Val
    210                 215                 220

Ala Thr Tyr Phe Cys Cys Gln Tyr Asn Asn Gly Asn Thr Phe Gly Ala
225                 230                 235                 240
```

Gly Thr Lys Leu Glu Leu Lys
245

<210> 843
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 843
caaattcagt tggtgcagtc cggcccggag ctgaagaagc ctggagaatc cgtgaagatc 60

tcgtgcaaag cttccgggaa caccgtgacc ggatacgcaa tgcactgggt ccgccaggca 120

ccgggaaagg gactgaagtg gatggggtgg atcaacacct acagcggaaa gccgacttac 180

gccgatgact ttaagggacg ctgtgtgttc tccctggaag cgtccgcctc gactgcccat 240

cttcaaatct ccaacctgaa gaatgaggac accgccactt acttctgcgc ccggagcacc 300

tattacggct acaaggactg gttcgcgtat tggggccagg gcactctcgt gaccgtgtcc 360

tccggcggtg gaggctcagg ggggggcggc tcgggagggg gtggaagcgg aggaggaggc 420

tccaacatcc aactgactca gagccccagc cggctgtccg cctccgtggg ggacagggtc 480

acactgagct gcaagggttc tcagaacatc aacaactacc tcgcgtggta ccagcagaag 540

ctgggagagg cccccaagct gctcatctac aacaccaaca atctgcaaac tggcattcca 600

tcgagattct caggatcagg gtccggtacc gactacacct tcacgatttc gggacttcag 660

cctgaggatg tggccaccta cttctgctgt cagtacaaca acggcaacac cttcggtgct 720

ggcaccaagc tggaactcaa a 741

<210> 844
<211> 834
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 844
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaaattc agttggtgca gtccggcccg gagctgaaga agcctggaga atccgtgaag 120

atctcgtgca aagcttccgg gaacaccgtg accggatacg caatgcactg ggtccgccag 180

gcaccgggaa agggactgaa gtggatgggg tggatcaaca cctacagcgg aaagccgact 240

tacgccgatg actttaaggg acgctgtgtg ttctccctgg aagcgtccgc ctcgactgcc 300

catcttcaaa tctccaacct gaagaatgag gacaccgcca cttacttctg cgcccggagc 360

acctattacg gctacaagga ctggttcgcg tattggggcc agggcactct cgtgaccgtg 420

tcctccggcg gtggaggctc agggggggggc ggctcgggag ggggtggaag cggaggagga 480

ggctccaaca tccaactgac tcagagcccc agccggctgt ccgcctccgt gggggacagg 540

gtcacactga gctgcaaggg ttctcagaac atcaacaact acctcgcgtg gtaccagcag 600

aagctgggag aggcccccaa gctgctcatc tacaacacca acaatctgca aactggcatt 660

ccatcgagat tctcaggatc agggtccggt accgactaca ccttcacgat ttcgggactt 720

cagcctgagg atgtggccac ctacttctgc tgtcagtaca acaacggcaa caccttcggt 780

gctggcacca agctggaact caaaggatcg caccaccatc accatcatca tcac 834

<210> 845
<211> 278
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 845
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu
            20                  25                  30

Lys Lys Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Asn
        35                  40                  45

Thr Val Thr Gly Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr
65                  70                  75                  80

Tyr Ala Asp Asp Phe Lys Gly Arg Cys Val Phe Ser Leu Glu Ala Ser
                85                  90                  95

Ala Ser Thr Ala His Leu Gln Ile Ser Asn Leu Lys Asn Glu Asp Thr
            100                 105                 110

Ala Thr Tyr Phe Cys Ala Arg Ser Thr Tyr Tyr Gly Tyr Lys Asp Trp
        115                 120                 125

Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
145                 150                 155                 160

Gly Ser Asn Ile Gln Leu Thr Gln Ser Pro Ser Arg Leu Ser Ala Ser
                165                 170                 175

Val Gly Asp Arg Val Thr Leu Ser Cys Lys Gly Ser Gln Asn Ile Asn
            180                 185                 190

Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Leu Gly Glu Ala Pro Lys Leu
        195                 200                 205
```

```
Leu Ile Tyr Asn Thr Asn Asn Leu Gln Thr Gly Ile Pro Ser Arg Phe
    210                 215                 220


Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Gly Leu
225                 230                 235                 240


Gln Pro Glu Asp Val Ala Thr Tyr Phe Cys Cys Gln Tyr Asn Asn Gly
                245                 250                 255


Asn Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Gly Ser His His
            260                 265                 270


His His His His His His
        275
```

<210> 846
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 846

```
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg       60

ccccaaattc agttggtgca gtccggcccg gagctgaaga agcctggaga atccgtgaag      120

atctcgtgca aagcttccgg gaacaccgtg accggatacg caatgcactg ggtccgccag      180

gcaccgggaa agggactgaa gtggatgggg tggatcaaca cctacagcgg aaagccgact      240

tacgccgatg actttaaggg acgctgtgtg ttctccctgg aagcgtccgc ctcgactgcc      300

catcttcaaa tctccaacct gaagaatgag gacaccgcca cttacttctg cgcccggagc      360

acctattacg gctacaagga ctggttcgcg tattggggcc agggcactct cgtgaccgtg      420

tcctccggcg gtggaggctc agggggggggc ggctcgggag ggggtggaag cggaggagga      480
```

ggctccaaca tccaactgac tcagagcccc agccggctgt ccgcctccgt gggggacagg 540

gtcacactga gctgcaaggg ttctcagaac atcaacaact acctcgcgtg gtaccagcag 600

aagctgggag aggcccccaa gctgctcatc tacaacacca acaatctgca aactggcatt 660

ccatcgagat tctcaggatc agggtccggt accgactaca ccttcacgat ttcgggactt 720

cagcctgagg atgtggccac ctacttctgc tgtcagtaca acaacggcaa caccttcggt 780

gctggcacca agctggaact caaaaccact accccagcac cgaggccacc caccccggct 840

cctaccatcg cctcccagcc tctgtccctg cgtccggagg catgtagacc cgcagctggt 900

ggggccgtgc atacccgggg tcttgacttc gcctgcgata tctacatttg ggcccctctg 960

gctggtactt gcggggtcct gctgctttca ctcgtgatca ctctttactg taagcgcggt 1020

cggaagaagc tgctgtacat ctttaagcaa cccttcatga ggcctgtgca gactactcaa 1080

gaggaggacg gctgttcatg ccggttccca gaggaggagg aaggcggctg cgaactgcgc 1140

gtgaaattca gccgcagcgc agatgctcca gcctacaagc aggggcagaa ccagctctac 1200

aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

gacccagaaa tgggcgggaa gccgcgcaga aagaatcccc aagagggcct gtacaacgag 1320

ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 847
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 847
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu
            20                  25                  30

Lys Lys Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Asn
        35                  40                  45

Thr Val Thr Gly Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr
65                  70                  75                  80

Tyr Ala Asp Asp Phe Lys Gly Arg Cys Val Phe Ser Leu Glu Ala Ser
                85                  90                  95

Ala Ser Thr Ala His Leu Gln Ile Ser Asn Leu Lys Asn Glu Asp Thr
            100                 105                 110

Ala Thr Tyr Phe Cys Ala Arg Ser Thr Tyr Tyr Gly Tyr Lys Asp Trp
        115                 120                 125

Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
145                 150                 155                 160

Gly Ser Asn Ile Gln Leu Thr Gln Ser Pro Ser Arg Leu Ser Ala Ser
                165                 170                 175

Val Gly Asp Arg Val Thr Leu Ser Cys Lys Gly Ser Gln Asn Ile Asn
            180                 185                 190

Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Leu Gly Glu Ala Pro Lys Leu
        195                 200                 205
```

```
Leu Ile Tyr Asn Thr Asn Asn Leu Gln Thr Gly Ile Pro Ser Arg Phe
    210                 215                 220

Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Gly Leu
225                 230                 235                 240

Gln Pro Glu Asp Val Ala Thr Tyr Phe Cys Cys Gln Tyr Asn Asn Gly
                245                 250                 255

Asn Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320

Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400
```

```
Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415


Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430


Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445


Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460


His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480


Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 848
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 848
Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln Ala Val Ser Ala Gly
1               5                   10                  15


Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20                  25                  30


Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45
```

```
Ser Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
                85                  90                  95

Tyr Tyr Asn Phe Pro Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
    130                 135                 140

Gln Pro Gly Arg Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr
145                 150                 155                 160

Phe Arg Asp Tyr Tyr Met Ala Trp Val Arg Gln Ala Pro Lys Lys Gly
                165                 170                 175

Leu Glu Trp Val Ala Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly
            180                 185                 190

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asn Asn Ala Lys Ser
        195                 200                 205

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr
    210                 215                 220

Tyr Tyr Cys Ala Arg His Asp His Asn Asn Val Asp Trp Phe Ala Tyr
225                 230                 235                 240
```

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
245 250

<210> 849
<211> 753
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 849
gacatcgtga tgactcagac tccaagcagc caggccgtgt ccgccggaga gaaagtcacc 60

atgtcgtgca agagctccca gtccctgctg tactccgaaa acaagaagaa ttatctcgcc 120

tggtaccagc agaagcctgg acagtccccg aagctcctga tcttttgggc gtcgaccagg 180

gaatccggcg tgcccgatcg cttcattggc tccggttccg gcaccgactt caccctgacc 240

attagcagcg tccaggcgga ggacctggct gtgtactact gccaacagta ctacaacttc 300

cccactttcg gatcggggac caagctggag atcaagggcg gtggaggctc agggggggggc 360

ggctcgggag ggggtggaag cggaggagga ggctccgaag tgcagcttgt ggagtctggc 420

ggcggtctgg tgcagccggg aagatccctg aagctgtcat gcgccgcgtc cgggtttacc 480

ttccgcgatt actacatggc ctgggtcaga caggcaccta agaaggggct ggaatgggtg 540

gcatccatct catatgaagg aaacccgtac tacggagact cggtgaaagg ccgcttcact 600

atctcacgga acaacgctaa gagcacgctg tacttgcaaa tgaactccct ccggtcggag 660

gacacagcca cttactactg tgcccggcac gaccataaca acgtcgattg gttcgcctac 720

tggggtcaag gaaccctcgt gaccgtgtcc tcc 753

<210> 850
<211> 846
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 850
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacatcg tgatgactca gactccaagc agccaggccg tgtccgccgg agagaaagtc 120

accatgtcgt gcaagagctc ccagtccctg ctgtactccg aaaacaagaa gaattatctc 180

gcctggtacc agcagaagcc tggacagtcc ccgaagctcc tgatcttttg ggcgtcgacc 240

agggaatccg gcgtgcccga tcgcttcatt ggctccggtt ccggcaccga cttcaccctg 300

accattagca gcgtccaggc ggaggacctg gctgtgtact actgccaaca gtactacaac 360

ttccccactt tcggatcggg gaccaagctg gagatcaagg gcggtggagg ctcagggggg 420

ggcggctcgg gaggggggtgg aagcggagga ggaggctccg aagtgcagct tgtggagtct 480

ggcggcggtc tggtgcagcc gggaagatcc ctgaagctgt catgcgccgc gtccgggttt 540

accttccgcg attactacat ggcctgggtc agacaggcac ctaagaaggg gctggaatgg 600

gtggcatcca tctcatatga aggaaacccg tactacggag actcggtgaa aggccgcttc 660

actatctcac ggaacaacgc taagagcacg ctgtacttgc aaatgaactc cctccggtcg 720

gaggacacag ccacttacta ctgtgcccgg cacgaccata acaacgtcga ttggttcgcc 780

tactggggtc aaggaaccct cgtgaccgtg tcctccggat cgcaccacca tcaccatcat 840

catcac 846

<210> 851
<211> 282
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 851

N2067-7072WO_SL (1)

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15

His Ala Ala Arg Pro Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln
            20                  25                  30

Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln
        35                  40                  45

Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln
    50                  55                  60

Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr
65                  70                  75                  80

Arg Glu Ser Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr
                85                  90                  95

Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val
            100                 105                 110

Tyr Tyr Cys Gln Gln Tyr Tyr Asn Phe Pro Thr Phe Gly Ser Gly Thr
        115                 120                 125

Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser
145                 150                 155                 160

Gly Gly Gly Leu Val Gln Pro Gly Arg Ser Leu Lys Leu Ser Cys Ala
                165                 170                 175

Ala Ser Gly Phe Thr Phe Arg Asp Tyr Tyr Met Ala Trp Val Arg Gln
            180                 185                 190
```

Ala Pro Lys Lys Gly Leu Glu Trp Val Ala Ser Ile Ser Tyr Glu Gly
195 200 205

Asn Pro Tyr Tyr Gly Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
210 215 220

Asn Asn Ala Lys Ser Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ser
225 230 235 240

Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg His Asp His Asn Asn Val
245 250 255

Asp Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
260 265 270

Gly Ser His His His His His His His His
275 280

<210> 852
<211> 1485
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 852
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacatcg tgatgactca gactccaagc agccaggccg tgtccgccgg agagaaagtc 120

accatgtcgt gcaagagctc ccagtccctg ctgtactccg aaaacaagaa gaattatctc 180

gcctggtacc agcagaagcc tggacagtcc ccgaagctcc tgatcttttg ggcgtcgacc 240

agggaatccg gcgtgcccga tcgcttcatt ggctccggtt ccggcaccga cttcaccctg 300

accattagca gcgtccaggc ggaggacctg gctgtgtact actgccaaca gtactacaac 360

ttccccactt tcggatcggg gaccaagctg gagatcaagg gcggtggagg ctcagggggg 420

ggcggctcgg gagggggtgg aagcggagga ggaggctccg aagtgcagct tgtggagtct 480

ggcggcggtc tggtgcagcc gggaagatcc ctgaagctgt catgcgccgc gtccgggttt 540

accttccgcg attactacat ggcctgggtc agacaggcac ctaagaaggg gctggaatgg 600

gtggcatcca tctcatatga aggaaacccg tactacggag actcggtgaa aggccgcttc 660

actatctcac ggaacaacgc taagagcacg ctgtacttgc aaatgaactc cctccggtcg 720

gaggacacag ccacttacta ctgtgcccgg cacgaccata acaacgtcga ttggttcgcc 780

tactggggtc aaggaaccct cgtgaccgtg tcctccacca ctaccccagc accgaggcca 840

cccaccccgg ctcctaccat cgcctcccag cctctgtccc tgcgtccgga ggcatgtaga 900

cccgcagctg gtggggccgt gcatacccgg ggtcttgact tcgcctgcga tatctacatt 960

tgggcccctc tggctggtac ttgcggggtc ctgctgcttt cactcgtgat cactctttac 1020

tgtaagcgcg gtcggaagaa gctgctgtac atctttaagc aacccttcat gaggcctgtg 1080

cagactactc aagaggagga cggctgttca tgccggttcc cagaggagga ggaaggcggc 1140

tgcgaactgc gcgtgaaatt cagccgcagc gcagatgctc cagcctacaa gcaggggcag 1200

aaccagctct acaacgaact caatcttggt cggagagagg agtacgacgt gctggacaag 1260

cggagaggac gggacccaga aatgggcggg aagccgcgca gaaagaatcc ccaagagggc 1320

ctgtacaacg agctccaaaa ggataagatg gcagaagcct atagcgagat tggtatgaaa 1380

ggggaacgca gaagaggcaa aggccacgac ggactgtacc agggactcag caccgccacc 1440

aaggacacct atgacgctct tcacatgcag gccctgccgc ctcgg 1485

<210> 853
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 853

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln
            20                  25                  30

Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln
        35                  40                  45

Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln
    50                  55                  60

Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr
65                  70                  75                  80

Arg Glu Ser Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr
                85                  90                  95

Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val
            100                 105                 110

Tyr Tyr Cys Gln Gln Tyr Tyr Asn Phe Pro Thr Phe Gly Ser Gly Thr
        115                 120                 125

Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser
145                 150                 155                 160

Gly Gly Gly Leu Val Gln Pro Gly Arg Ser Leu Lys Leu Ser Cys Ala
                165                 170                 175

Ala Ser Gly Phe Thr Phe Arg Asp Tyr Tyr Met Ala Trp Val Arg Gln
            180                 185                 190
```

```
Ala Pro Lys Lys Gly Leu Glu Trp Val Ala Ser Ile Ser Tyr Glu Gly
        195                 200                 205

Asn Pro Tyr Tyr Gly Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
    210                 215                 220

Asn Asn Ala Lys Ser Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ser
225                 230                 235                 240

Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg His Asp His Asn Asn Val
                245                 250                 255

Asp Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            260                 265                 270

Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285

Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300

Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320

Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335

Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380
```

```
Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln
385                 390                 395                 400


Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415


Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430


Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445


Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
    450                 455                 460


Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465                 470                 475                 480


Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490                 495


<210> 854
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 854
Asp Ile Gln Met Thr Gln Ser Pro Pro Ser Leu Ser Ala Ser Leu Gly
1               5                   10                  15


Asp Lys Val Thr Ile Thr Cys Gln Ala Ser Gln Asn Ile Asn Lys Tyr
            20                  25                  30
```

```
Ile Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Arg Leu Leu Ile
        35                  40                  45

Arg Tyr Thr Ser Thr Leu Glu Ser Gly Thr Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser Asn Val Glu Ser
65                  70                  75                  80

Gly Asp Val Ala Ser Tyr Tyr Cys Leu Gln Tyr Asp Asp Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Leu Glu Leu Lys Gly Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
        115                 120                 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Thr Ser
    130                 135                 140

Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Ser Gly
145                 150                 155                 160

Met Gln Trp Ile Arg Gln Ala Pro Lys Lys Gly Leu Glu Trp Ile Ser
                165                 170                 175

Gly Ile Tyr Tyr Asp Ser Tyr Lys Lys Ser Tyr Ala Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
        195                 200                 205

Glu Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
    210                 215                 220
```

Lys Ser Ala Tyr Tyr Gly Tyr Lys Asp Tyr Phe Asp Tyr Trp Gly Gln
225 230 235 240

Gly Val Met Val Thr Val Ser Ser
245

<210> 855
<211> 744
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 855
gacatccaaa tgacacagtc acccccttct ctttccgcga gcctgggaga taaggtcacc 60

attacgtgcc aagcgtccca gaacatcaac aagtacatcg cctggtacca gcagaaaccg 120

ggaaaggccc cgcggctgct gattagatac acctcgactc tggaatccgg cactccatca 180

agattcagcg gctccggcag cgggagggac tactcgttct ccatctccaa tgtggagtcc 240

ggggacgtgg ccagctacta ttgcctgcaa tacgacgatc tgccctacac cttcggacct 300

ggaaccaagc tggaactcaa gggcggtgga ggctcagggg ggggcggctc gggaggggt 360

ggaagcggag gaggaggctc cgaggtccag cttgtggaat caggaggcgg actcgtccag 420

ccgggtacta gcctgaagct cagctgtgtg gccagcggtt ttaccttctc gtcctccggg 480

atgcagtgga ttcggcaggc tcccaagaag ggactggaat ggatctcggg catctactac 540

gactcgtaca agaagtccta cgccgattcc gtgaaaggtc gcttcaccat ctcccgggac 600

aacagcaaga acactctgta cctcgagatg aactccttgc gctccgagga taccgcaacc 660

tattactgcg ccaagtcggc ctactacggc tacaaggact acttcgacta ttggggccag 720

ggagtgatgg tgaccgtgtc ctcc 744

<210> 856
<211> 837

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 856
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacatcc aaatgacaca gtcaccccct tctctttccg cgagcctggg agataaggtc 120

accattacgt gccaagcgtc ccagaacatc aacaagtaca tcgcctggta ccagcagaaa 180

ccgggaaagg ccccgcggct gctgattaga tacacctcga ctctggaatc cggcactcca 240

tcaagattca gcggctccgg cagcgggagg gactactcgt tctccatctc caatgtggag 300

tccggggacg tggccagcta ctattgcctg caatacgacg atctgcccta caccttcgga 360

cctggaacca agctggaact caagggcggt ggaggctcag gggggggcgg ctcgggaggg 420

ggtggaagcg gaggaggagg ctccgaggtc agcttgtgg aatcaggagg cggactcgtc 480

cagccgggta ctagcctgaa gctcagctgt gtggccagcg gttttacctt ctcgtcctcc 540

gggatgcagt ggattcggca ggctcccaag aagggactgg aatggatctc gggcatctac 600

tacgactcgt acaagaagtc ctacgccgat tccgtgaaag gtcgcttcac catctcccgg 660

gacaacagca agaacactct gtacctcgag atgaactcct tgcgctccga ggataccgca 720

acctattact gcgccaagtc ggcctactac ggctacaagg actacttcga ctattggggc 780

cagggagtga tggtgaccgt gtcctccgga tcgcaccacc atcaccatca tcatcac 837

<210> 857
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 857

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Ser Pro Pro Ser Leu
            20                  25                  30

Ser Ala Ser Leu Gly Asp Lys Val Thr Ile Thr Cys Gln Ala Ser Gln
        35                  40                  45

Asn Ile Asn Lys Tyr Ile Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala
    50                  55                  60

Pro Arg Leu Leu Ile Arg Tyr Thr Ser Thr Leu Glu Ser Gly Thr Pro
65                  70                  75                  80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile
                85                  90                  95

Ser Asn Val Glu Ser Gly Asp Val Ala Ser Tyr Tyr Cys Leu Gln Tyr
            100                 105                 110

Asp Asp Leu Pro Tyr Thr Phe Gly Pro Gly Thr Lys Leu Glu Leu Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
145                 150                 155                 160

Gln Pro Gly Thr Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Thr
                165                 170                 175

Phe Ser Ser Ser Gly Met Gln Trp Ile Arg Gln Ala Pro Lys Lys Gly
            180                 185                 190
```

```
Leu Glu Trp Ile Ser Gly Ile Tyr Tyr Asp Ser Tyr Lys Lys Ser Tyr
        195                 200                 205


Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys
    210                 215                 220


Asn Thr Leu Tyr Leu Glu Met Asn Ser Leu Arg Ser Glu Asp Thr Ala
225                 230                 235                 240


Thr Tyr Tyr Cys Ala Lys Ser Ala Tyr Tyr Gly Tyr Lys Asp Tyr Phe
                245                 250                 255


Asp Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Gly Ser His
            260                 265                 270


His His His His His His His
        275
```

<210> 858
<211> 1476
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 858

```
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg       60

cccgacatcc aaatgacaca gtcacccccc tctctttccg cgagcctggg agataaggtc      120

accattacgt gccaagcgtc ccagaacatc aacaagtaca tcgcctggta ccagcagaaa      180

ccgggaaagg ccccgcggct gctgattaga tacacctcga ctctggaatc cggcactcca      240

tcaagattca gcggctccgg cagcgggagg gactactcgt tctccatctc caatgtggag      300

tccggggacg tggccagcta ctattgcctg caatacgacg atctgcccta caccttcgga      360
```

cctggaacca agctggaact caagggcggt ggaggctcag ggggggggcgg ctcgggaggg 420

ggtggaagcg gaggaggagg ctccgaggtc cagcttgtgg aatcaggagg cggactcgtc 480

cagccgggta ctagcctgaa gctcagctgt gtggccagcg gttttacctt ctcgtcctcc 540

gggatgcagt ggattcggca ggctcccaag aagggactgg aatggatctc gggcatctac 600

tacgactcgt acaagaagtc ctacgccgat tccgtgaaag gtcgcttcac catctcccgg 660

gacaacagca agaacactct gtacctcgag atgaactcct tgcgctccga ggataccgca 720

acctattact gcgccaagtc ggcctactac ggctacaagg actacttcga ctattggggc 780

cagggagtga tggtgaccgt gtcctccacc actaccccag caccgaggcc acccaccccg 840

gctcctacca tcgcctccca gcctctgtcc ctgcgtccgg aggcatgtag acccgcagct 900

ggtggggccg tgcatacccg gggtcttgac ttcgcctgcg atatctacat ttgggcccct 960

ctggctggta cttgcggggt cctgctgctt tcactcgtga tcactcttta ctgtaagcgc 1020

ggtcggaaga agctgctgta catctttaag caacccttca tgaggcctgt gcagactact 1080

caagaggagg acggctgttc atgccggttc ccagaggagg aggaaggcgg ctgcgaactg 1140

cgcgtgaaat tcagccgcag cgcagatgct ccagcctaca agcaggggca gaaccagctc 1200

tacaacgaac tcaatcttgg tcggagagag gagtacgacg tgctggacaa gcggagagga 1260

cgggacccag aaatgggcgg gaagccgcgc agaaagaatc cccaagaggg cctgtacaac 1320

gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggtatgaa aggggaacgc 1380

agaagaggca aaggccacga cggactgtac cagggactca gcaccgccac caaggacacc 1440

tatgacgctc ttcacatgca ggccctgccg cctcgg 1476

<210> 859
<211> 492
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 859

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Ser Pro Pro Ser Leu
            20                  25                  30

Ser Ala Ser Leu Gly Asp Lys Val Thr Ile Thr Cys Gln Ala Ser Gln
        35                  40                  45

Asn Ile Asn Lys Tyr Ile Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala
    50                  55                  60

Pro Arg Leu Leu Ile Arg Tyr Thr Ser Thr Leu Glu Ser Gly Thr Pro
65                  70                  75                  80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile
                85                  90                  95

Ser Asn Val Glu Ser Gly Asp Val Ala Ser Tyr Tyr Cys Leu Gln Tyr
            100                 105                 110

Asp Asp Leu Pro Tyr Thr Phe Gly Pro Gly Thr Lys Leu Glu Leu Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
145                 150                 155                 160

Gln Pro Gly Thr Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Thr
                165                 170                 175

Phe Ser Ser Ser Gly Met Gln Trp Ile Arg Gln Ala Pro Lys Lys Gly
            180                 185                 190
```

```
Leu Glu Trp Ile Ser Gly Ile Tyr Tyr Asp Ser Tyr Lys Lys Ser Tyr
        195                 200                 205

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys
    210                 215                 220

Asn Thr Leu Tyr Leu Glu Met Asn Ser Leu Arg Ser Glu Asp Thr Ala
225                 230                 235                 240

Thr Tyr Tyr Cys Ala Lys Ser Ala Tyr Tyr Gly Tyr Lys Asp Tyr Phe
                245                 250                 255

Asp Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Thr Thr Thr
            260                 265                 270

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        275                 280                 285

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    290                 295                 300

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
305                 310                 315                 320

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
                325                 330                 335

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
            340                 345                 350

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
        355                 360                 365

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
    370                 375                 380
```

```
Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
385                 390                 395                 400


Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                405                 410                 415


Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            420                 425                 430


Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        435                 440                 445


Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    450                 455                 460


Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
465                 470                 475                 480


Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490


<210> 860
<211> 255
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 860
Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln Ala Val Ser Ala Gly
1               5                   10                  15


Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20                  25                  30
```

```
Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
                85                  90                  95

Tyr Tyr Asn Phe Pro Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu
            100                 105                 110

Leu Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gln Ile Gln Leu Val Gln Ser Gly Pro Glu
    130                 135                 140

Leu Lys Lys Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Thr Ser Glu
145                 150                 155                 160

Tyr Thr Phe Thr Asp Tyr Ala Phe His Trp Val Lys Gln Ala Pro Gly
                165                 170                 175

Lys Gly Leu Lys Trp Met Gly Trp Ile Asn Thr Tyr Ser Gly Lys Pro
            180                 185                 190

Thr Tyr Ala Asp Asp Phe Lys Gly Arg Phe Val Phe Ser Leu Glu Asp
        195                 200                 205

Ser Ala Arg Thr Ala Asn Leu Gln Ile Ser Asn Leu Lys Asn Glu Asp
    210                 215                 220
```

Thr Ala Thr Tyr Phe Cys Ala Arg Gly Ala Tyr Tyr Gly Tyr Arg Asp
225 230 235 240

Trp Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
245 250 255

<210> 861
<211> 765
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 861
gatattgtga tgacccagac cccgtcgagc caggcagtgt ccgctggaga aaaggtcacc 60

atgtcctgca agagctcaca gtccctgttg tactccgaaa acaagaagaa ttacctggcc 120

tggtaccagc agaagcccgg acagtcccct aaactgctga tctactgggc ctcgactagg 180

gaatctggcg tgcccgaccg ctttatcgga agcggttcag ggactgactt caccctgacc 240

attagcagcg tgcaggccga ggacctggcg gtgtactact gtcaacagta ctacaacttc 300

ccgccctgga ctttcggcgg tggaacgaag ctcgaactca agggcggtgg aggctcaggg 360

gggggcggct cgggaggggg tggaagcgga ggaggaggct cccaaattca actggtccag 420

tccggccctg agctgaagaa gccgggagaa tccgtgaaga tctcctgcaa gacctcggag 480

tacaccttca ctgactacgc cttccactgg gtcaagcagg cacctgggaa aggcctgaag 540

tggatgggct ggatcaacac ttactcgggg aagccaacct acgccgatga tttcaaggga 600

agattcgtgt ttagcctgga ggactccgcc cggacagcta acctccaaat ctccaacctt 660

aagaacgagg acactgcgac ctacttctgc gcgcggggag cctattacgg ttatcgcgac 720

tggttcacct actggggaca gggcaccctc gtgaccgtgt cctcc 765

<210> 862

<211> 858
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 862
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgatattg tgatgaccca gaccccgtcg agccaggcag tgtccgctgg agaaaaggtc 120

accatgtcct gcaagagctc acagtccctg ttgtactccg aaaacaagaa gaattacctg 180

gcctggtacc agcagaagcc cggacagtcc cctaaactgc tgatctactg ggcctcgact 240

agggaatctg gcgtgcccga ccgctttatc ggaagcggtt cagggactga cttcaccctg 300

accattagca gcgtgcaggc cgaggacctg gcggtgtact actgtcaaca gtactacaac 360

ttcccgccct ggactttcgg cggtggaacg aagctcgaac tcaagggcgg tggaggctca 420

gggggggggcg gctcgggagg gggtggaagc ggaggaggag gctcccaaat tcaactggtc 480

cagtccggcc ctgagctgaa gaagccggga gaatccgtga agatctcctg caagacctcg 540

gagtacacct tcactgacta cgccttccac tgggtcaagc aggcacctgg gaaaggcctg 600

aagtggatgg gctggatcaa cacttactcg gggaagccaa cctacgccga tgatttcaag 660

ggaagattcg tgtttagcct ggaggactcc gcccggacag ctaacctcca aatctccaac 720

cttaagaacg aggacactgc gacctacttc tgcgcgcggg gagcctatta cggttatcgc 780

gactggttca cctactgggg acagggcacc ctcgtgaccg tgtcctccgg atcgcaccac 840

catcaccatc atcatcac 858

<210> 863
<211> 286
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 863
```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15


His Ala Ala Arg Pro Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln
            20                  25                  30


Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln
        35                  40                  45


Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln
    50                  55                  60


Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
65                  70                  75                  80


Arg Glu Ser Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr
                85                  90                  95


Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val
            100                 105                 110


Tyr Tyr Cys Gln Gln Tyr Tyr Asn Phe Pro Pro Trp Thr Phe Gly Gly
        115                 120                 125


Gly Thr Lys Leu Glu Leu Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130                 135                 140


Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Gln Leu Val
145                 150                 155                 160


Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Ser Val Lys Ile Ser
                165                 170                 175
```

```
Cys Lys Thr Ser Glu Tyr Thr Phe Thr Asp Tyr Ala Phe His Trp Val
            180                 185                 190


Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met Gly Trp Ile Asn Thr
        195                 200                 205


Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe Lys Gly Arg Phe Val
    210                 215                 220


Phe Ser Leu Glu Asp Ser Ala Arg Thr Ala Asn Leu Gln Ile Ser Asn
225                 230                 235                 240


Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Gly Ala Tyr
                245                 250                 255


Tyr Gly Tyr Arg Asp Trp Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val
            260                 265                 270


Thr Val Ser Ser Gly Ser His His His His His His His His
        275                 280                 285
```

<210> 864
<211> 1497
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 864

```
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg       60

cccgatattg tgatgaccca gaccccgtcg agccaggcag tgtccgctgg agaaaaggtc      120

accatgtcct gcaagagctc acagtccctg ttgtactccg aaaacaagaa gaattacctg      180

gcctggtacc agcagaagcc cggacagtcc cctaaactgc tgatctactg ggcctcgact      240

agggaatctg gcgtgcccga ccgctttatc ggaagcggtt cagggactga cttcaccctg      300
```

accattagca gcgtgcaggc cgaggacctg gcggtgtact actgtcaaca gtactacaac 360

ttcccgccct ggactttcgg cggtggaacg aagctcgaac tcaagggcgg tggaggctca 420

gggggggcg gctcgggagg gggtggaagc ggaggaggag gctcccaaat tcaactggtc 480

cagtccggcc ctgagctgaa gaagccggga gaatccgtga agatctcctg caagacctcg 540

gagtacacct tcactgacta cgccttccac tgggtcaagc aggcacctgg gaaaggcctg 600

aagtggatgg gctggatcaa cacttactcg gggaagccaa cctacgccga tgatttcaag 660

ggaagattcg tgtttagcct ggaggactcc gcccggacag ctaacctcca aatctccaac 720

cttaagaacg aggacactgc gacctacttc tgcgcgcggg gagcctatta cggttatcgc 780

gactggttca cctactgggg acagggcacc ctcgtgaccg tgtcctccac cactacccca 840

gcaccgaggc cacccacccc ggctcctacc atcgcctccc agcctctgtc cctgcgtccg 900

gaggcatgta gacccgcagc tggtggggcc gtgcataccc ggggtcttga cttcgcctgc 960

gatatctaca tttgggcccc tctggctggt acttgcgggg tcctgctgct ttcactcgtg 1020

atcactcttt actgtaagcg cggtcggaag aagctgctgt acatctttaa gcaacccttc 1080

atgaggcctg tgcagactac tcaagaggag gacggctgtt catgccggtt cccagaggag 1140

gaggaaggcg gctgcgaact gcgcgtgaaa ttcagccgca gcgcagatgc tccagcctac 1200

aagcaggggc agaaccagct ctacaacgaa ctcaatcttg gtcggagaga ggagtacgac 1260

gtgctggaca agcggagagg acgggaccca gaaatgggcg ggaagccgcg cagaaagaat 1320

ccccaagagg gcctgtacaa cgagctccaa aaggataaga tggcagaagc ctatagcgag 1380

attggtatga aaggggaacg cagaagaggc aaaggccacg acggactgta ccagggactc 1440

agcaccgcca ccaaggacac ctatgacgct cttcacatgc aggccctgcc gcctcgg 1497

<210> 865
<211> 499
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 865

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln
            20                  25                  30

Ala Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln
        35                  40                  45

Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln
    50                  55                  60

Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
65                  70                  75                  80

Arg Glu Ser Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr
                85                  90                  95

Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val
            100                 105                 110

Tyr Tyr Cys Gln Gln Tyr Tyr Asn Phe Pro Pro Trp Thr Phe Gly Gly
        115                 120                 125

Gly Thr Lys Leu Glu Leu Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile Gln Leu Val
145                 150                 155                 160

Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Ser Val Lys Ile Ser
                165                 170                 175
```

```
Cys Lys Thr Ser Glu Tyr Thr Phe Thr Asp Tyr Ala Phe His Trp Val
            180                 185                 190

Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met Gly Trp Ile Asn Thr
        195                 200                 205

Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe Lys Gly Arg Phe Val
    210                 215                 220

Phe Ser Leu Glu Asp Ser Ala Arg Thr Ala Asn Leu Gln Ile Ser Asn
225                 230                 235                 240

Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Gly Ala Tyr
                245                 250                 255

Tyr Gly Tyr Arg Asp Trp Phe Thr Tyr Trp Gly Gln Gly Thr Leu Val
            260                 265                 270

Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala
        275                 280                 285

Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg
    290                 295                 300

Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys
305                 310                 315                 320

Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu
                325                 330                 335

Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu
            340                 345                 350

Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
        355                 360                 365
```

```
Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly
    370                 375                 380


Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
385                 390                 395                 400


Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
                405                 410                 415


Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
            420                 425                 430


Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
        435                 440                 445


Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
    450                 455                 460


Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
465                 470                 475                 480


Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu
                485                 490                 495


Pro Pro Arg
```

<210> 866
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 866

```
Gln Val Val Leu Thr Gln Pro Lys Ser Val Ser Thr Ser Leu Glu Ser
1               5                  10                  15

Thr Val Lys Leu Ser Cys Lys Ile Asn Ser Gly Asn Ile Gly Ser Tyr
            20                  25                  30

Phe Ile His Trp Tyr Gln Gln His Glu Gly Arg Ser Pro Thr Thr Met
        35                  40                  45

Ile Tyr Arg Asp Asp Lys Arg Pro His Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Phe Leu Thr Ile Asn Asn
65                  70                  75                  80

Val Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys His Ser Tyr Asp Ser
                85                  90                  95

Gly Ile Asn Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
    130                 135                 140

Pro Gly Arg Ser Leu Lys Leu Ser Cys Leu Ala Ser Gly Phe Thr Phe
145                 150                 155                 160

Ser Lys Tyr Gly Met Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
                165                 170                 175

Glu Trp Val Ala Ser Ile Ser Ser Thr Ser Ile Tyr Ile Tyr Tyr Ala
            180                 185                 190
```

Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn
195 200 205

Thr Leu Tyr Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Leu
210 215 220

Tyr Tyr Cys Ala Arg His Asp Tyr Ser Ser Tyr Ser Tyr Trp Gly Gln
225 230 235 240

Gly Val Met Val Thr Val Ser Ser
245

<210> 867
<211> 744
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 867
caagtcgtgc tgacgcaacc caagtccgtg agcaccagcc tggagagcac cgtgaagctc 60

agctgcaaga ttaactcggg caacattggg tcctacttca tccattggta ccagcagcac 120

gaaggacggt cccctaccac tatgatctac cgggacgaca agcggccgca cggagtgccg 180

gacagattct cgggttcaat cgattcctca tctaactcgg cgtttctcac catcaacaac 240

gtgcagaccg aggacgaagc gatctacttc tgccactcct acgactcggg tattaacatt 300

gtgttcggcg gcgggactaa gctgacagtg ctgggcggtg gaggctcagg ggggggcggc 360

tcgggagggg gtggaagcgg aggaggaggc tccgaggtgc agctcgtcga atccggtgga 420

ggactggtgc agccaggaag atccctgaag ctgtcctgtc tcgcctcggg cttcactttc 480

tccaaatacg gcatgaattg gattcgccag gcacccggaa aggggctgga atgggtggcc 540

agcatcagct cgactagcat ctacatctac tatgccgata ccgtcaaggg ccgcttcact 600

atctcccgcg agaacgctaa gaacaccctt tacttgcaaa tgacctccct gaggtccgaa 660

gataccgccc tgtactattg cgcccggcac gactactcat cctactccta ctggggacag 720

ggagtcatgg tgaccgtgtc ctcc 744

<210> 868
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 868
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcg tgctgacgca acccaagtcc gtgagcacca gcctggagag caccgtgaag 120

ctcagctgca agattaactc gggcaacatt gggtcctact tcatccattg gtaccagcag 180

cacgaaggac ggtcccctac cactatgatc taccgggacg acaagcggcc gcacggagtg 240

ccggacagat tctcgggttc aatcgattcc tcatctaact cggcgtttct caccatcaac 300

aacgtgcaga ccgaggacga agcgatctac ttctgccact cctacgactc gggtattaac 360

attgtgttcg gcggcgggac taagctgaca gtgctgggcg gtggaggctc agggggggggc 420

ggctcgggag ggggtggaag cggaggagga ggctccgagg tgcagctcgt cgaatccggt 480

ggaggactgg tgcagccagg aagatccctg aagctgtcct gtctcgcctc gggcttcact 540

ttctccaaat acggcatgaa ttggattcgc caggcacccg gaaaggggct ggaatgggtg 600

gccagcatca gctcgactag catctacatc tactatgccg ataccgtcaa gggccgcttc 660

actatctccc gcgagaacgc taagaacacc ctttacttgc aaatgacctc cctgaggtcc 720

gaagataccg ccctgtacta ttgcgcccgg cacgactact catcctactc ctactgggga 780

cagggagtca tggtgaccgt gtcctccgga tcgcaccacc atcaccatca tcatcac 837

<210> 869
<211> 279

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 869

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Val Leu Thr Gln Pro Lys Ser Val Ser
            20                  25                  30

Thr Ser Leu Glu Ser Thr Val Lys Leu Ser Cys Lys Ile Asn Ser Gly
        35                  40                  45

Asn Ile Gly Ser Tyr Phe Ile His Trp Tyr Gln Gln His Glu Gly Arg
    50                  55                  60

Ser Pro Thr Thr Met Ile Tyr Arg Asp Asp Lys Arg Pro His Gly Val
65                  70                  75                  80

Pro Asp Arg Phe Ser Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Phe
                85                  90                  95

Leu Thr Ile Asn Asn Val Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys
            100                 105                 110

His Ser Tyr Asp Ser Gly Ile Asn Ile Val Phe Gly Gly Gly Thr Lys
        115                 120                 125

Leu Thr Val Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
145                 150                 155                 160
```

```
Gly Gly Leu Val Gln Pro Gly Arg Ser Leu Lys Leu Ser Cys Leu Ala
                165                 170                 175


Ser Gly Phe Thr Phe Ser Lys Tyr Gly Met Asn Trp Ile Arg Gln Ala
            180                 185                 190


Pro Gly Lys Gly Leu Glu Trp Val Ala Ser Ile Ser Ser Thr Ser Ile
        195                 200                 205


Tyr Ile Tyr Tyr Ala Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg
    210                 215                 220


Glu Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Thr Ser Leu Arg Ser
225                 230                 235                 240


Glu Asp Thr Ala Leu Tyr Tyr Cys Ala Arg His Asp Tyr Ser Ser Tyr
                245                 250                 255


Ser Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Gly Ser His
            260                 265                 270


His His His His His His His
        275
```

<210> 870
<211> 1476
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 870
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcg tgctgacgca acccaagtcc gtgagcacca gcctggagag caccgtgaag 120

ctcagctgca agattaactc gggcaacatt gggtcctact tcatccattg gtaccagcag 180

cacgaaggac ggtcccctac cactatgatc taccgggacg acaagcggcc gcacggagtg 240

ccggacagat tctcgggttc aatcgattcc tcatctaact cggcgtttct caccatcaac 300

aacgtgcaga ccgaggacga agcgatctac ttctgccact cctacgactc gggtattaac 360

attgtgttcg gcggcgggac taagctgaca gtgctgggcg gtggaggctc agggggggggc 420

ggctcgggag ggggtggaag cggaggagga ggctccgagg tgcagctcgt cgaatccggt 480

ggaggactgg tgcagccagg aagatccctg aagctgtcct gtctcgcctc gggcttcact 540

ttctccaaat acggcatgaa ttggattcgc caggcacccg gaaaggggct ggaatgggtg 600

gccagcatca gctcgactag catctacatc tactatgccg ataccgtcaa gggccgcttc 660

actatctccc gcgagaacgc taagaacacc ctttacttgc aaatgacctc cctgaggtcc 720

gaagataccg ccctgtacta ttgcgcccgg cacgactact catcctactc ctactgggga 780

cagggagtca tggtgaccgt gtcctccacc actaccccag caccgaggcc acccaccccg 840

gctcctacca tcgcctccca gcctctgtcc ctgcgtccgg aggcatgtag acccgcagct 900

ggtggggccg tgcatacccg gggtcttgac ttcgcctgcg atatctacat ttgggccct 960

ctggctggta cttgcggggt cctgctgctt tcactcgtga tcactcttta ctgtaagcgc 1020

ggtcggaaga agctgctgta catctttaag caacccttca tgaggcctgt gcagactact 1080

caagaggagg acggctgttc atgccggttc ccagaggagg aggaaggcgg ctgcgaactg 1140

cgcgtgaaat tcagccgcag cgcagatgct ccagcctaca agcaggggca gaaccagctc 1200

tacaacgaac tcaatcttgg tcggagagag gagtacgacg tgctggacaa gcggagagga 1260

cgggacccag aaatgggcgg gaagccgcgc agaaagaatc cccaagaggg cctgtacaac 1320

gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggtatgaa aggggaacgc 1380

agaagaggca aaggccacga cggactgtac cagggactca gcaccgccac caaggacacc 1440

tatgacgctc ttcacatgca ggccctgccg cctcgg 1476

<210> 871

<211> 492
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 871

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Val Leu Thr Gln Pro Lys Ser Val Ser
            20                  25                  30

Thr Ser Leu Glu Ser Thr Val Lys Leu Ser Cys Lys Ile Asn Ser Gly
        35                  40                  45

Asn Ile Gly Ser Tyr Phe Ile His Trp Tyr Gln Gln His Glu Gly Arg
    50                  55                  60

Ser Pro Thr Thr Met Ile Tyr Arg Asp Asp Lys Arg Pro His Gly Val
65                  70                  75                  80

Pro Asp Arg Phe Ser Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Phe
                85                  90                  95

Leu Thr Ile Asn Asn Val Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys
            100                 105                 110

His Ser Tyr Asp Ser Gly Ile Asn Ile Val Phe Gly Gly Gly Thr Lys
        115                 120                 125

Leu Thr Val Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
145                 150                 155                 160
```

```
Gly Gly Leu Val Gln Pro Gly Arg Ser Leu Lys Leu Ser Cys Leu Ala
                165                 170                 175

Ser Gly Phe Thr Phe Ser Lys Tyr Gly Met Asn Trp Ile Arg Gln Ala
            180                 185                 190

Pro Gly Lys Gly Leu Glu Trp Val Ala Ser Ile Ser Ser Thr Ser Ile
        195                 200                 205

Tyr Ile Tyr Tyr Ala Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg
    210                 215                 220

Glu Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Thr Ser Leu Arg Ser
225                 230                 235                 240

Glu Asp Thr Ala Leu Tyr Tyr Cys Ala Arg His Asp Tyr Ser Ser Tyr
                245                 250                 255

Ser Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Thr Thr Thr
            260                 265                 270

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        275                 280                 285

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    290                 295                 300

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
305                 310                 315                 320

Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
                325                 330                 335

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
            340                 345                 350
```

```
Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
        355                 360                 365

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
    370                 375                 380

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
385                 390                 395                 400

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                405                 410                 415

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            420                 425                 430

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        435                 440                 445

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    450                 455                 460

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
465                 470                 475                 480

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 872
<211> 251
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 872

```
Asp Val Gln Met Thr Gln Ser Pro Ser Leu Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Ala Val Thr Ile Asn Cys Lys Ala Ser Gln Asn Ile Asn Arg Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Gly Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Ser Ala Asn Ser Leu Gln Thr Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile Thr Ser Pro Gln Pro
65                  70                  75                  80

Glu Asp Val Ala Thr Tyr Phe Cys Leu Gln His Asn Ser Trp Pro Leu
                85                  90                  95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
        115                 120                 125

Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln Thr
    130                 135                 140

Leu Ser Leu Thr Cys Thr Phe Thr Arg Phe Ser Leu Ser Thr Tyr Gly
145                 150                 155                 160

Met Ser Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu Trp
                165                 170                 175

Leu Ala Asp Ile Trp Trp Asp Asp Asp Lys His Tyr Asn Pro Ser Leu
            180                 185                 190
```

```
Lys Asn Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Ala Phe
        195                 200                 205


Leu Lys Ile Thr Asn Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr Cys
    210                 215                 220


Ala Arg Ser Ser Thr Thr Asp Gly Ile Val Thr Tyr Val Met Asp Val
225                 230                 235                 240


Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser
                245                 250


<210> 873
<211> 753
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"

<400> 873
gacgtgcaga tgactcagtc cccgtcgctc ctgtccgcct ccgtcggcga cgccgtgact       60

attaactgca aggcgtccca gaacatcaat cggtacctga actggtacca gcaaaaactg      120

ggagaagggc cgagacttct catctactcc gccaactccc tgcaaactgg catcccgtcg      180

aggttcagcg gatcaggctc tggtgccgac ttcactttga ccatcacgag ccctcagccc      240

gaagatgtgg ccacctactt ctgcctccaa cacaactcct ggcccctgac ctttggttcg      300

ggcaccaagc tggagatcaa gggcggtgga ggctcagggg ggggcggctc gggaggggggt      360

ggaagcggag gaggaggctc ccaagtcacg ctgaaggaat cgggccctgg aattctgcag      420

ccaagccaga ccctctcgct tacttgcacc ttcacccgct tctcactgtc cacttacgga      480

atgtccgtgg gatggattcg gcagcccagc ggaaagggtt tggagtggct ggccgacatt      540

tggtgggatg acgacaagca ttacaaccct agcctgaaga atcggctcac catcagcaaa      600
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gacacctcca agaaccaggc gttcctgaag atcaccaacg tggataccgc cgacactgca 660

acatactatt gtgcccgctc ctcaaccacc gatgggatcg tgacctacgt gatggacgtc 720

tggggccagg gagcttccgt gaccgtgtcc tcc 753

<210> 874
<211> 846
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 874
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacgtgc agatgactca gtccccgtcg ctcctgtccg cctccgtcgg cgacgccgtg 120

actattaact gcaaggcgtc ccagaacatc aatcggtacc tgaactggta ccagcaaaaa 180

ctgggagaag ggccgagact tctcatctac tccgccaact ccctgcaaac tggcatcccg 240

tcgaggttca gcggatcagg ctctggtgcc gacttcactt tgaccatcac gagccctcag 300

cccgaagatg tggccaccta cttctgcctc caacacaact cctggcccct gacctttggt 360

tcgggcacca agctggagat caagggcggt ggaggctcag gggggggcgg ctcgggaggg 420

ggtggaagcg gaggaggagg ctcccaagtc acgctgaagg aatcgggccc tggaattctg 480

cagccaagcc agaccctctc gcttacttgc accttcaccc gcttctcact gtccacttac 540

ggaatgtccg tgggatggat tcggcagccc agcggaaagg gtttggagtg gctggccgac 600

atttggtggg atgacgacaa gcattacaac cctagcctga agaatcggct caccatcagc 660

aaagacacct ccaagaacca ggcgttcctg aagatcacca acgtggatac cgccgacact 720

gcaacatact attgtgcccg ctcctcaacc accgatggga tcgtgaccta cgtgatggac 780

gtctggggcc agggagcttc cgtgaccgtg tcctccggat cgcaccacca tcaccatcat 840

catcac 846

<210> 875
<211> 282
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 875
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Gln Met Thr Gln Ser Pro Ser Leu Leu
20 25 30

Ser Ala Ser Val Gly Asp Ala Val Thr Ile Asn Cys Lys Ala Ser Gln
35 40 45

Asn Ile Asn Arg Tyr Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Gly
50 55 60

Pro Arg Leu Leu Ile Tyr Ser Ala Asn Ser Leu Gln Thr Gly Ile Pro
65 70 75 80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile
85 90 95

Thr Ser Pro Gln Pro Glu Asp Val Ala Thr Tyr Phe Cys Leu Gln His
100 105 110

Asn Ser Trp Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu
145 150 155 160

Gln Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Phe Thr Arg Phe Ser
165 170 175

Leu Ser Thr Tyr Gly Met Ser Val Gly Trp Ile Arg Gln Pro Ser Gly
180 185 190

Lys Gly Leu Glu Trp Leu Ala Asp Ile Trp Trp Asp Asp Asp Lys His
195 200 205

Tyr Asn Pro Ser Leu Lys Asn Arg Leu Thr Ile Ser Lys Asp Thr Ser
210 215 220

Lys Asn Gln Ala Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp Thr
225 230 235 240

Ala Thr Tyr Tyr Cys Ala Arg Ser Ser Thr Thr Asp Gly Ile Val Thr
245 250 255

Tyr Val Met Asp Val Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser
260 265 270

Gly Ser His His His His His His His His
275 280

<210> 876
<211> 1485
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 876
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacgtgc agatgactca gtccccgtcg ctcctgtccg cctccgtcgg cgacgccgtg 120

actattaact gcaaggcgtc ccagaacatc aatcggtacc tgaactggta ccagcaaaaa 180

ctgggagaag ggccgagact tctcatctac tccgccaact ccctgcaaac tggcatcccg 240

tcgaggttca gcggatcagg ctctggtgcc gacttcactt tgaccatcac gagccctcag 300

cccgaagatg tggccaccta cttctgcctc caacacaact cctggcccct gacctttggt 360

tcgggcacca agctggagat caagggcggt ggaggctcag gggggggcgg ctcgggaggg 420

ggtggaagcg gaggaggagg ctcccaagtc acgctgaagg aatcgggccc tggaattctg 480

cagccaagcc agaccctctc gcttacttgc accttcaccc gcttctcact gtccacttac 540

ggaatgtccg tgggatggat tcggcagccc agcggaaagg gtttggagtg gctggccgac 600

atttggtggg atgacgacaa gcattacaac cctagcctga agaatcggct caccatcagc 660

aaagacacct ccaagaacca ggcgttcctg aagatcacca acgtggatac cgccgacact 720

gcaacatact attgtgcccg ctcctcaacc accgatggga tcgtgaccta cgtgatggac 780

gtctggggcc agggagcttc cgtgaccgtg tcctccacca ctaccccagc accgaggcca 840

cccaccccgg ctcctaccat cgcctcccag cctctgtccc tgcgtccgga ggcatgtaga 900

cccgcagctg gtggggccgt gcatacccgg ggtcttgact tcgcctgcga tatctacatt 960

tgggcccctc tggctggtac ttgcggggtc ctgctgcttt cactcgtgat cactctttac 1020

tgtaagcgcg gtcggaagaa gctgctgtac atctttaagc aacccttcat gaggcctgtg 1080

cagactactc aagaggagga cggctgttca tgccggttcc cagaggagga ggaaggcggc 1140

tgcgaactgc gcgtgaaatt cagccgcagc gcagatgctc cagcctacaa gcaggggcag 1200

aaccagctct acaacgaact caatcttggt cggagagagg agtacgacgt gctggacaag 1260

cggagaggac gggacccaga aatgggcggg aagccgcgca gaaagaatcc ccaagagggc 1320

ctgtacaacg agctccaaaa ggataagatg gcagaagcct atagcgagat tggtatgaaa 1380

ggggaacgca gaagaggcaa aggccacgac ggactgtacc agggactcag caccgccacc 1440

aaggacacct atgacgctct tcacatgcag gccctgccgc ctcgg 1485

<210> 877
<211> 495
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 877
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Gln Met Thr Gln Ser Pro Ser Leu Leu
20 25 30

Ser Ala Ser Val Gly Asp Ala Val Thr Ile Asn Cys Lys Ala Ser Gln
35 40 45

Asn Ile Asn Arg Tyr Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Gly
50 55 60

Pro Arg Leu Leu Ile Tyr Ser Ala Asn Ser Leu Gln Thr Gly Ile Pro
65 70 75 80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile
85 90 95

Thr Ser Pro Gln Pro Glu Asp Val Ala Thr Tyr Phe Cys Leu Gln His
100 105 110

Asn Ser Trp Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

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Gly Gly Gly Ser Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu
145                 150                 155                 160


Gln Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Phe Thr Arg Phe Ser
                165                 170                 175


Leu Ser Thr Tyr Gly Met Ser Val Gly Trp Ile Arg Gln Pro Ser Gly
            180                 185                 190


Lys Gly Leu Glu Trp Leu Ala Asp Ile Trp Trp Asp Asp Asp Lys His
        195                 200                 205


Tyr Asn Pro Ser Leu Lys Asn Arg Leu Thr Ile Ser Lys Asp Thr Ser
    210                 215                 220


Lys Asn Gln Ala Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp Thr
225                 230                 235                 240


Ala Thr Tyr Tyr Cys Ala Arg Ser Ser Thr Thr Asp Gly Ile Val Thr
                245                 250                 255


Tyr Val Met Asp Val Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser
            260                 265                 270


Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala
        275                 280                 285


Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly
    290                 295                 300


Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile
305                 310                 315                 320


Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val
                325                 330                 335
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Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
            340                 345                 350

Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
        355                 360                 365

Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg
    370                 375                 380

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln
385                 390                 395                 400

Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
                405                 410                 415

Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
            420                 425                 430

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
        435                 440                 445

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
    450                 455                 460

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
465                 470                 475                 480

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490                 495
```

<210> 878
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 878

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Asn Cys Lys Ala Ser Gln Asn Ile Asn Arg Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Asn Ala Asn Ser Leu Gln Thr Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Ala Asp Val Ala Thr Tyr Phe Cys Leu Gln His Asn Ser Arg Pro Leu
                85                  90                  95

Thr Phe Gly Ser Gly Thr Ile Leu Glu Ile Lys Gly Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln
        115                 120                 125

Val Thr Leu Lys Glu Ser Gly Pro Gly Leu Leu Gln Pro Ser Gln Thr
    130                 135                 140

Leu Ser Leu Thr Cys Thr Phe Ala Gly Phe Ser Leu Asn Thr His Gly
145                 150                 155                 160

Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu Trp
                165                 170                 175
```

Leu Ala Asn Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu
180 185 190

Lys Asn Arg Leu Thr Met Ser Lys Asp Thr Ser Asn Asn Gln Ala Phe
195 200 205

Leu Lys Ile Thr Asn Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr Cys
210 215 220

Ala Arg Ile Glu Gly Ser Pro Val Val Thr Thr Val Phe Asp Tyr Trp
225 230 235 240

Gly Gln Gly Val Met Val Thr Val Ser Ser
245 250

<210> 879
<211> 750
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 879
gacatccaaa tgacccagtc acctagcttt ctgtcggcct cggtcggcga cagagtgacc 60

attaactgca aagcgtccca gaacatcaac cgctacctga attggtacca gcagaagctg 120

ggggaagccc cgaagctgct gatctacaac gcgaacagcc tccagactgg tattccttcc 180

cggttctccg ggagcggctc gggtaccgat ttcaccctca ccatctcctc ccttcaaccc 240

gctgacgtgg ccacctactt ctgcttgcaa cataattctc ggcctctgac cttcggaagc 300

ggcactatcc tcgagatcaa gggcggtgga ggctcagggg ggggcggctc gggagggggt 360

ggaagcggag gaggaggctc ccaagtcact cttaaggaat ccgggccagg actgttgcag 420

ccgagccaga ccctgtccct cacttgtacc ttcgccggct tttcactgaa cacccacgga 480

atgggcgtgg gatggattag gcagccctcg ggaaagggac tggagtggct ggccaacatt 540

tggtgggacg acgacaagta ttacaacccg agcctcaaga accgcctgac tatgtccaag 600

gatacctcca acaaccaggc cttcctgaaa atcactaacg tggataccgc tgacaccgca 660

acgtactact gcgcccggat cgaaggttcc cccgtcgtga caactgtgtt cgactactgg 720

ggacagggcg tgatggtgac cgtgtcctcc 750

<210> 880
<211> 843
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 880
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacatcc aaatgaccca gtcacctagc tttctgtcgg cctcggtcgg cgacagagtg 120

accattaact gcaaagcgtc ccagaacatc aaccgctacc tgaattggta ccagcagaag 180

ctgggggaag ccccgaagct gctgatctac aacgcgaaca gcctccagac tggtattcct 240

tcccggttct ccgggagcgg ctcgggtacc gatttcaccc tcaccatctc ctcccttcaa 300

cccgctgacg tggccaccta cttctgcttg caacataatt ctcggcctct gaccttcgga 360

agcggcacta tcctcgagat caagggcggt ggaggctcag gggggggcgg ctcgggaggg 420

ggtggaagcg gaggaggagg ctcccaagtc actcttaagg aatccgggcc aggactgttg 480

cagccgagcc agaccctgtc cctcacttgt accttcgccg gcttttcact gaacacccac 540

ggaatgggcg tgggatggat taggcagccc tcgggaaagg gactggagtg gctggccaac 600

atttggtggg acgacgacaa gtattacaac ccgagcctca agaaccgcct gactatgtcc 660

aaggatacct ccaacaacca ggccttcctg aaaatcacta acgtggatac cgctgacacc 720

gcaacgtact actgcgcccg gatcgaaggt tcccccgtcg tgacaactgt gttcgactac 780

tggggacagg gcgtgatggt gaccgtgtcc tccggatcgc accaccatca ccatcatcat 840

cac 843

<210> 881
<211> 281
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 881
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu
20 25 30

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Asn Cys Lys Ala Ser Gln
35 40 45

Asn Ile Asn Arg Tyr Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Ala
50 55 60

Pro Lys Leu Leu Ile Tyr Asn Ala Asn Ser Leu Gln Thr Gly Ile Pro
65 70 75 80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Ala Asp Val Ala Thr Tyr Phe Cys Leu Gln His
100 105 110

Asn Ser Arg Pro Leu Thr Phe Gly Ser Gly Thr Ile Leu Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly

```
    130                 135                 140

Gly Gly Gly Ser Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Leu Leu
145                 150                 155                 160

Gln Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Phe Ala Gly Phe Ser
                165                 170                 175

Leu Asn Thr His Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly
            180                 185                 190

Lys Gly Leu Glu Trp Leu Ala Asn Ile Trp Trp Asp Asp Asp Lys Tyr
        195                 200                 205

Tyr Asn Pro Ser Leu Lys Asn Arg Leu Thr Met Ser Lys Asp Thr Ser
    210                 215                 220

Asn Asn Gln Ala Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp Thr
225                 230                 235                 240

Ala Thr Tyr Tyr Cys Ala Arg Ile Glu Gly Ser Pro Val Val Thr Thr
                245                 250                 255

Val Phe Asp Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Gly
            260                 265                 270

Ser His His His His His His His His
        275                 280
```

<210> 882
<211> 1482
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 882
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacatcc aaatgaccca gtcacctagc tttctgtcgg cctcggtcgg cgacagagtg 120

accattaact gcaaagcgtc ccagaacatc aaccgctacc tgaattggta ccagcagaag 180

ctgggggaag ccccgaagct gctgatctac aacgcgaaca gcctccagac tggtattcct 240

tcccggttct ccgggagcgg ctcgggtacc gatttcaccc tcaccatctc ctcccttcaa 300

cccgctgacg tggccaccta cttctgcttg caacataatt ctcggcctct gaccttcgga 360

agcggcacta tcctcgagat caagggcggt ggaggctcag gggggggcgg ctcgggaggg 420

ggtggaagcg gaggaggagg ctcccaagtc actcttaagg aatccgggcc aggactgttg 480

cagccgagcc agaccctgtc cctcacttgt accttcgccg gcttttcact gaacacccac 540

ggaatgggcg tgggatggat taggcagccc tcgggaaagg gactggagtg gctggccaac 600

atttggtggg acgacgacaa gtattacaac ccgagcctca agaaccgcct gactatgtcc 660

aaggatacct ccaacaacca ggccttcctg aaaatcacta acgtggatac cgctgacacc 720

gcaacgtact actgcgcccg gatcgaaggt tcccccgtcg tgacaactgt gttcgactac 780

tggggacagg gcgtgatggt gaccgtgtcc tccaccacta ccccagcacc gaggccaccc 840

accccggctc ctaccatcgc ctcccagcct ctgtccctgc gtccggaggc atgtagaccc 900

gcagctggtg gggccgtgca tacccggggt cttgacttcg cctgcgatat ctacatttgg 960

gcccctctgg ctggtacttg cggggtcctg ctgctttcac tcgtgatcac tctttactgt 1020

aagcgcggtc ggaagaagct gctgtacatc tttaagcaac ccttcatgag gcctgtgcag 1080

actactcaag aggaggacgg ctgttcatgc cggttcccag aggaggagga aggcggctgc 1140

gaactgcgcg tgaaattcag ccgcagcgca gatgctccag cctacaagca ggggcagaac 1200

cagctctaca acgaactcaa tcttggtcgg agagaggagt acgacgtgct ggacaagcgg 1260

agaggacggg acccagaaat gggcgggaag ccgcgcagaa agaatcccca agagggcctg 1320

tacaacgagc tccaaaagga taagatggca gaagcctata gcgagattgg tatgaaaggg 1380

gaacgcagaa gaggcaaagg ccacgacgga ctgtaccagg gactcagcac cgccaccaag 1440

gacacctatg acgctcttca catgcaggcc ctgccgcctc gg 1482

<210> 883
<211> 494
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 883
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu
20 25 30

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Asn Cys Lys Ala Ser Gln
35 40 45

Asn Ile Asn Arg Tyr Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Ala
50 55 60

Pro Lys Leu Leu Ile Tyr Asn Ala Asn Ser Leu Gln Thr Gly Ile Pro
65 70 75 80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Ala Asp Val Ala Thr Tyr Phe Cys Leu Gln His
100 105 110

Asn Ser Arg Pro Leu Thr Phe Gly Ser Gly Thr Ile Leu Glu Ile Lys
115 120 125

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Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Leu Leu
145                 150                 155                 160

Gln Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Phe Ala Gly Phe Ser
                165                 170                 175

Leu Asn Thr His Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly
            180                 185                 190

Lys Gly Leu Glu Trp Leu Ala Asn Ile Trp Trp Asp Asp Asp Lys Tyr
        195                 200                 205

Tyr Asn Pro Ser Leu Lys Asn Arg Leu Thr Met Ser Lys Asp Thr Ser
    210                 215                 220

Asn Asn Gln Ala Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp Thr
225                 230                 235                 240

Ala Thr Tyr Tyr Cys Ala Arg Ile Glu Gly Ser Pro Val Val Thr Thr
                245                 250                 255

Val Phe Asp Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Thr
            260                 265                 270

Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser
        275                 280                 285

Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly
    290                 295                 300

Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp
305                 310                 315                 320
```

Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile
325 330 335

Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
340 345 350

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
355 360 365

Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
370 375 380

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn
385 390 395 400

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
405 410 415

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg
420 425 430

Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys
435 440 445

Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg
450 455 460

Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys
465 470 475 480

Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
485 490

<210> 884
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 884
Lys Ile Val Leu Thr Gln Ser Pro Thr Ile Thr Ala Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Leu Ala Ser Ser Arg Val Ser Asn Ile
20 25 30

Tyr Trp Tyr Gln Gln Lys Ser Gly Ala Ser Pro Lys Leu Leu Ile Tyr
35 40 45

Ser Thr Ser Ser Leu Ala Ser Gly Val Pro Tyr Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Asn Thr Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys His Gln Trp Ser Ser Asn Pro Trp Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Gly Gly Gly Gly Ser Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
115 120 125

Thr Leu Lys Glu Ser Gly Pro Gly Met Leu Gln Pro Ser Lys Thr Leu
130 135 140

Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser Gly Met
145 150 155 160

Val Val Ser Trp Ile Arg Gln Pro Ser Gly Lys Ser Leu Glu Trp Leu

165 170 175

Ala Ala Ile Ala Trp Asp Gly Asp Lys Tyr Tyr Asn Pro Ser Leu Lys
180 185 190

Ser Arg Val Thr Val Ser Lys Asp Thr Ser Asn Thr Gln Val Phe Leu
195 200 205

Arg Ile Thr Ser Val Asp Ile Ala Asp Thr Ala Thr Tyr Tyr Cys Thr
210 215 220

Arg Arg Asp Tyr Asp Val Gly Tyr Tyr Tyr Phe Asp Phe Trp Gly Gln
225 230 235 240

Gly Val Met Val Thr Val Ser Ser
245

<210> 885
<211> 744
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 885
aagattgtgc tgacccagag ccccactatt accgccgcct ccccgggggga aaaggtcacc 60

atcacttgtc tggcgtcctc acgcgtgtcg aatatctact ggtatcagca gaagtccggc 120

gccagcccca agctgctgat ctactcgacc tcctccctcg cgtcgggagt gccttaccgg 180

ttttctggct cgggaagcgg aaccagctac tccttgacca tcaacaccat ggaagccgag 240

gacgctgcca cttactactg ccaccagtgg tcgagcaacc cttggacttt cggtggaggc 300

accaaactcg agctcaaggg cggtggaggc tcagggggggg gcggctcggg agggggtgga 360

agcggaggag gaggctccca agtcaccctg aaagaatcgg gtcccggaat gctgcagcca 420

tccaagacgc tgtcccttac atgctccttc tccgggttca gcctctcaac ttccgggatg 480

gtggtgtcat ggatcagaca gccgagcgga aagtccctgg agtggctggc ggccatcgca 540

tgggatggcg ataagtacta caacccgagc ctgaagtcaa gggtcactgt gtccaaggac 600

acctccaaca cccaagtgtt ccttcggatc acctccgtgg acattgctga caccgccacc 660

tattactgca ctcgccggga ctacgacgtg ggctactact acttcgattt ctggggacag 720

ggtgtcatgg tgaccgtgtc ctcc 744

<210> 886
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 886
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccaagattg tgctgaccca gagccccact attaccgccg cctccccggg ggaaaaggtc 120

accatcactt gtctggcgtc ctcacgcgtg tcgaatatct actggtatca gcagaagtcc 180

ggcgccagcc ccaagctgct gatctactcg acctcctccc tcgcgtcggg agtgccttac 240

cggttttctg gctcgggaag cggaaccagc tactccttga ccatcaacac catggaagcc 300

gaggacgctg ccacttacta ctgccaccag tggtcgagca acccttggac tttcggtgga 360

ggcaccaaac tcgagctcaa gggcggtgga ggctcagggg ggggcggctc gggaggggt 420

ggaagcggag gaggaggctc ccaagtcacc ctgaaagaat cgggtcccgg aatgctgcag 480

ccatccaaga cgctgtccct tacatgctcc ttctccgggt tcagcctctc aacttccggg 540

atggtggtgt catggatcag acagccgagc ggaaagtccc tggagtggct ggcggccatc 600

gcatgggatg gcgataagta ctacaacccg agcctgaagt caagggtcac tgtgtccaag 660

gacacctcca acacccaagt gttccttcgg atcacctccg tggacattgc tgacaccgcc 720

acctattact gcactcgccg ggactacgac gtgggctact actacttcga tttctgggga 780

cagggtgtca tggtgaccgt gtcctccgga tcgcaccacc atcaccatca tcatcac 837

<210> 887
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 887
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Lys Ile Val Leu Thr Gln Ser Pro Thr Ile Thr
20 25 30

Ala Ala Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Leu Ala Ser Ser
35 40 45

Arg Val Ser Asn Ile Tyr Trp Tyr Gln Gln Lys Ser Gly Ala Ser Pro
50 55 60

Lys Leu Leu Ile Tyr Ser Thr Ser Ser Leu Ala Ser Gly Val Pro Tyr
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Asn
85 90 95

Thr Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Trp Ser
100 105 110

Ser Asn Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Gly
115 120 125

```
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Met Leu Gln
145                 150                 155                 160

Pro Ser Lys Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu
                165                 170                 175

Ser Thr Ser Gly Met Val Val Ser Trp Ile Arg Gln Pro Ser Gly Lys
            180                 185                 190

Ser Leu Glu Trp Leu Ala Ala Ile Ala Trp Asp Gly Asp Lys Tyr Tyr
        195                 200                 205

Asn Pro Ser Leu Lys Ser Arg Val Thr Val Ser Lys Asp Thr Ser Asn
    210                 215                 220

Thr Gln Val Phe Leu Arg Ile Thr Ser Val Asp Ile Ala Asp Thr Ala
225                 230                 235                 240

Thr Tyr Tyr Cys Thr Arg Arg Asp Tyr Asp Val Gly Tyr Tyr Tyr Phe
                245                 250                 255

Asp Phe Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Gly Ser His
            260                 265                 270

His His His His His His His
        275
```

<210> 888
<211> 1476
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<400> 888

atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccaagattg tgctgaccca gagccccact attaccgccg cctccccggg ggaaaaggtc 120

accatcactt gtctggcgtc ctcacgcgtg tcgaatatct actggtatca gcagaagtcc 180

ggcgccagcc ccaagctgct gatctactcg acctcctccc tcgcgtcggg agtgccttac 240

cggttttctg gctcgggaag cggaaccagc tactccttga ccatcaacac catggaagcc 300

gaggacgctg ccacttacta ctgccaccag tggtcgagca acccttggac tttcggtgga 360

ggcaccaaac tcgagctcaa gggcggtgga ggctcagggg ggggcggctc gggagggggt 420

ggaagcggag gaggaggctc ccaagtcacc ctgaaagaat cgggtcccgg aatgctgcag 480

ccatccaaga cgctgtccct tacatgctcc ttctccgggt tcagcctctc aacttccggg 540

atggtggtgt catggatcag acagccgagc ggaaagtccc tggagtggct ggcggccatc 600

gcatgggatg gcgataagta ctacaacccg agcctgaagt caagggtcac tgtgtccaag 660

gacacctcca acacccaagt gttccttcgg atcacctccg tggacattgc tgacaccgcc 720

acctattact gcactcgccg ggactacgac gtgggctact actacttcga tttctgggga 780

cagggtgtca tggtgaccgt gtcctccacc actaccccag caccgaggcc acccaccccg 840

gctcctacca tcgcctccca gcctctgtcc ctgcgtccgg aggcatgtag acccgcagct 900

ggtggggccg tgcatacccg gggtcttgac ttcgcctgcg atatctacat ttgggccct 960

ctggctggta cttgcggggt cctgctgctt tcactcgtga tcactcttta ctgtaagcgc 1020

ggtcggaaga agctgctgta catctttaag caacccttca tgaggcctgt gcagactact 1080

caagaggagg acggctgttc atgccggttc ccagaggagg aggaaggcgg ctgcgaactg 1140

cgcgtgaaat tcagccgcag cgcagatgct ccagcctaca agcaggggca gaaccagctc 1200

tacaacgaac tcaatcttgg tcggagagag gagtacgacg tgctggacaa gcggagagga 1260

cgggacccag aaatgggcgg gaagccgcgc agaaagaatc cccaagaggg cctgtacaac 1320

gagctccaaa aggataagat ggcagaagcc tatagcgaga ttggtatgaa aggggaacgc 1380

agaagaggca aaggccacga cggactgtac cagggactca gcaccgccac caaggacacc 1440

tatgacgctc ttcacatgca ggccctgccg cctcgg 1476

<210> 889
<211> 492
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 889
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Lys Ile Val Leu Thr Gln Ser Pro Thr Ile Thr
20 25 30

Ala Ala Ser Pro Gly Glu Lys Val Thr Ile Thr Cys Leu Ala Ser Ser
35 40 45

Arg Val Ser Asn Ile Tyr Trp Tyr Gln Gln Lys Ser Gly Ala Ser Pro
50 55 60

Lys Leu Leu Ile Tyr Ser Thr Ser Ser Leu Ala Ser Gly Val Pro Tyr
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Asn
85 90 95

Thr Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Trp Ser
100 105 110

Ser Asn Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Gly
115 120 125

```
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Met Leu Gln
145                 150                 155                 160

Pro Ser Lys Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu
                165                 170                 175

Ser Thr Ser Gly Met Val Val Ser Trp Ile Arg Gln Pro Ser Gly Lys
            180                 185                 190

Ser Leu Glu Trp Leu Ala Ala Ile Ala Trp Asp Gly Asp Lys Tyr Tyr
        195                 200                 205

Asn Pro Ser Leu Lys Ser Arg Val Thr Val Ser Lys Asp Thr Ser Asn
    210                 215                 220

Thr Gln Val Phe Leu Arg Ile Thr Ser Val Asp Ile Ala Asp Thr Ala
225                 230                 235                 240

Thr Tyr Tyr Cys Thr Arg Arg Asp Tyr Asp Val Gly Tyr Tyr Tyr Phe
                245                 250                 255

Asp Phe Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Thr Thr Thr
            260                 265                 270

Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro
        275                 280                 285

Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val
    290                 295                 300

His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro
305                 310                 315                 320
```

```
Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu
                325                 330                 335

Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
            340                 345                 350

Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
        355                 360                 365

Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
    370                 375                 380

Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu
385                 390                 395                 400

Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
                405                 410                 415

Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys
            420                 425                 430

Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
        435                 440                 445

Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
    450                 455                 460

Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
465                 470                 475                 480

Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 890
<211> 247
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 890

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Asn Ile Gln Leu Thr Gln Ser Pro Ser Arg Leu Ser Ala Ser Val Gly
1               5                  10                  15


Asp Arg Val Thr Leu Ser Cys Lys Gly Ser Gln Asn Ile Asn Asn Tyr
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Leu Gly Glu Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Asn Thr Asn Asn Leu Gln Thr Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Gly Leu Gln Pro
65                  70                  75                  80


Glu Asp Val Ala Thr Tyr Phe Cys Cys Gln Tyr Asn Asn Gly Asn Thr
                85                  90                  95


Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Gly Gly Gly Gly Ser Gly
            100                 105                 110


Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ile
        115                 120                 125


Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Ser Val
    130                 135                 140


Lys Ile Ser Cys Lys Ala Ser Gly Asn Thr Val Thr Gly Tyr Ala Met
145                 150                 155                 160
```

His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Lys Trp Met Gly Trp
165 170 175

Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe Lys Gly
180 185 190

Arg Cys Val Phe Ser Leu Glu Ala Ser Ala Ser Thr Ala His Leu Gln
195 200 205

Ile Ser Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg
210 215 220

Ser Thr Tyr Tyr Gly Tyr Lys Asp Trp Phe Ala Tyr Trp Gly Gln Gly
225 230 235 240

Thr Leu Val Thr Val Ser Ser
245

<210> 891
<211> 741
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 891
aacatccaac tgactcagag ccccagccgg ctgtccgcct ccgtgggggga cagggtcaca 60

ctgagctgca agggttctca gaacatcaac aactacctcg cgtggtacca gcagaagctg 120

ggagaggccc ccaagctgct catctacaac accaacaatc tgcaaactgg cattccatcg 180

agattctcag gatcagggtc cggtaccgac tacaccttca cgatttcggg acttcagcct 240

gaggatgtgg ccacctactt ctgctgtcag tacaacaacg gcaacacctt cggtgctggc 300

accaagctgg aactcaaagg cggtggaggc tcagggggggg gcggctcggg agggggtgga 360

agcggaggag gaggctccca aattcagttg gtgcagtccg gcccggagct gaagaagcct 420

ggagaatccg tgaagatctc gtgcaaagct tccgggaaca ccgtgaccgg atacgcaatg 480

cactgggtcc gccaggcacc gggaaaggga ctgaagtgga tggggtggat caacacctac 540

agcggaaagc cgacttacgc cgatgacttt aagggacgct gtgtgttctc cctggaagcg 600

tccgcctcga ctgcccatct tcaaatctcc aacctgaaga atgaggacac cgccacttac 660

ttctgcgccc ggagcaccta ttacggctac aaggactggt tcgcgtattg gggccagggc 720

actctcgtga ccgtgtcctc c 741

<210> 892
<211> 834
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 892
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccaacatcc aactgactca gagccccagc cggctgtccg cctccgtggg ggacagggtc 120

acactgagct gcaagggttc tcagaacatc aacaactacc tcgcgtggta ccagcagaag 180

ctgggagagg cccccaagct gctcatctac aacaccaaca atctgcaaac tggcattcca 240

tcgagattct caggatcagg gtccggtacc gactacacct tcacgatttc gggacttcag 300

cctgaggatg tggccaccta cttctgctgt cagtacaaca acggcaacac cttcggtgct 360

ggcaccaagc tggaactcaa aggcggtgga ggctcagggg ggggcggctc gggaggggt 420

ggaagcggag gaggaggctc ccaaattcag ttggtgcagt ccggcccgga gctgaagaag 480

cctggagaat ccgtgaagat ctcgtgcaaa gcttccggga acaccgtgac cggatacgca 540

atgcactggg tccgccaggc accgggaaag ggactgaagt ggatggggtg gatcaacacc 600

tacagcggaa agccgactta cgccgatgac tttaagggac gctgtgtgtt ctccctggaa 660

gcgtccgcct cgactgccca tcttcaaatc tccaacctga agaatgagga caccgccact 720

tacttctgcg cccggagcac ctattacggc tacaaggact ggttcgcgta ttggggccag 780

ggcactctcg tgaccgtgtc ctccggatcg caccaccatc accatcatca tcac 834

<210> 893
<211> 278
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 893
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asn Ile Gln Leu Thr Gln Ser Pro Ser Arg Leu
20 25 30

Ser Ala Ser Val Gly Asp Arg Val Thr Leu Ser Cys Lys Gly Ser Gln
35 40 45

Asn Ile Asn Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Leu Gly Glu Ala
50 55 60

Pro Lys Leu Leu Ile Tyr Asn Thr Asn Asn Leu Gln Thr Gly Ile Pro
65 70 75 80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile
85 90 95

Ser Gly Leu Gln Pro Glu Asp Val Ala Thr Tyr Phe Cys Cys Gln Tyr
100 105 110

Asn Asn Gly Asn Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Gly
115 120 125

```
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys
145                 150                 155                 160

Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Asn Thr Val
                165                 170                 175

Thr Gly Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
            180                 185                 190

Lys Trp Met Gly Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala
        195                 200                 205

Asp Asp Phe Lys Gly Arg Cys Val Phe Ser Leu Glu Ala Ser Ala Ser
    210                 215                 220

Thr Ala His Leu Gln Ile Ser Asn Leu Lys Asn Glu Asp Thr Ala Thr
225                 230                 235                 240

Tyr Phe Cys Ala Arg Ser Thr Tyr Tyr Gly Tyr Lys Asp Trp Phe Ala
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Ser His His
            260                 265                 270

His His His His His His
        275
```

<210> 894
<211> 1473
<212> DNA
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 894
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccaacatcc aactgactca gagccccagc cggctgtccg cctccgtggg ggacagggtc 120

acactgagct gcaagggttc tcagaacatc aacaactacc tcgcgtggta ccagcagaag 180

ctgggagagg cccccaagct gctcatctac aacaccaaca atctgcaaac tggcattcca 240

tcgagattct caggatcagg gtccggtacc gactacacct tcacgatttc gggacttcag 300

cctgaggatg tggccaccta cttctgctgt cagtacaaca acggcaacac cttcggtgct 360

ggcaccaagc tggaactcaa aggcggtgga ggctcagggg ggggcggctc gggaggggggt 420

ggaagcggag gaggaggctc ccaaattcag ttggtgcagt ccggcccgga gctgaagaag 480

cctggagaat ccgtgaagat ctcgtgcaaa gcttccggga acaccgtgac cggatacgca 540

atgcactggg tccgccaggc accgggaaag ggactgaagt ggatggggtg gatcaacacc 600

tacagcggaa agccgactta cgccgatgac tttaagggac gctgtgtgtt ctccctggaa 660

gcgtccgcct cgactgccca tcttcaaatc tccaacctga agaatgagga caccgccact 720

tacttctgcg cccggagcac ctattacggc tacaaggact ggttcgcgta ttggggccag 780

ggcactctcg tgaccgtgtc ctccaccact accccagcac cgaggccacc caccccggct 840

cctaccatcg cctcccagcc tctgtccctg cgtccggagg catgtagacc cgcagctggt 900

ggggccgtgc atacccgggg tcttgacttc gcctgcgata tctacatttg ggcccctctg 960

gctggtactt gcggggtcct gctgctttca ctcgtgatca ctctttactg taagcgcggt 1020

cggaagaagc tgctgtacat ctttaagcaa cccttcatga ggcctgtgca gactactcaa 1080

gaggaggacg gctgttcatg ccggttccca gaggaggagg aaggcggctg cgaactgcgc 1140

gtgaaattca gccgcagcgc agatgctcca gcctacaagc aggggcagaa ccagctctac 1200

aacgaactca atcttggtcg gagagaggag tacgacgtgc tggacaagcg gagaggacgg 1260

gacccagaaa tgggcgggaa gccgcgcaga aagaatcccc aagagggcct gtacaacgag 1320

ctccaaaagg ataagatggc agaagcctat agcgagattg gtatgaaagg ggaacgcaga 1380

agaggcaaag gccacgacgg actgtaccag ggactcagca ccgccaccaa ggacacctat 1440

gacgctcttc acatgcaggc cctgccgcct cgg 1473

<210> 895
<211> 491
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 895
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asn Ile Gln Leu Thr Gln Ser Pro Ser Arg Leu
20 25 30

Ser Ala Ser Val Gly Asp Arg Val Thr Leu Ser Cys Lys Gly Ser Gln
35 40 45

Asn Ile Asn Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Leu Gly Glu Ala
50 55 60

Pro Lys Leu Leu Ile Tyr Asn Thr Asn Asn Leu Gln Thr Gly Ile Pro
65 70 75 80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile
85 90 95

Ser Gly Leu Gln Pro Glu Asp Val Ala Thr Tyr Phe Cys Cys Gln Tyr
100 105 110

Asn Asn Gly Asn Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Gly
115 120 125

```
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys
145                 150                 155                 160

Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Asn Thr Val
                165                 170                 175

Thr Gly Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
            180                 185                 190

Lys Trp Met Gly Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala
        195                 200                 205

Asp Asp Phe Lys Gly Arg Cys Val Phe Ser Leu Glu Ala Ser Ala Ser
    210                 215                 220

Thr Ala His Leu Gln Ile Ser Asn Leu Lys Asn Glu Asp Thr Ala Thr
225                 230                 235                 240

Tyr Phe Cys Ala Arg Ser Thr Tyr Tyr Gly Tyr Lys Asp Trp Phe Ala
                245                 250                 255

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Thr Thr Thr Pro
            260                 265                 270

Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu
        275                 280                 285

Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His
    290                 295                 300

Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu
305                 310                 315                 320
```

```
Ala Gly Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr
                325                 330                 335

Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
            340                 345                 350

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
        355                 360                 365

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
    370                 375                 380

Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr
385                 390                 395                 400

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
                405                 410                 415

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
            420                 425                 430

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
        435                 440                 445

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
    450                 455                 460

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
465                 470                 475                 480

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
                485                 490
```

<210> 896
<211> 17

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 896
Gly Ile Tyr Tyr Asp Ser Tyr Lys Lys Ser Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 897
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 897
Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gly

<210> 898
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 898
Ser Ile Ser Ser Thr Ser Ile Tyr Ile Tyr Tyr Ala Asp Thr Val Lys

1 5 10 15

Gly

<210> 899
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 899
Asp Ile Trp Trp Asp Asp Asp Lys His Tyr Asn Pro Ser Leu Lys Asn
1 5 10 15

<210> 900
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 900
Asn Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Asn
1 5 10 15

<210> 901
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 901

Ala Ile Ala Trp Asp Gly Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 902
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 902
Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gly

<210> 903
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 903
Asp Trp Phe Thr Tyr
1 5

<210> 904
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 904
His Asp Tyr Ser Ser Tyr Ser Tyr
1 5

<210> 905
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 905
His Asp His Asn Asn Val Asp Trp Phe Ala Tyr
1 5 10

<210> 906
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 906
Ser Ser Thr Thr Asp Gly Ile Val Thr Tyr Val Met Asp Val
1 5 10

<210> 907
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 907
Ser Ala Tyr Tyr Gly Tyr Lys Asp Tyr Phe Asp Tyr
1 5 10

<210> 908
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 908
Ile Glu Gly Ser Pro Val Val Thr Thr Val Phe Asp Tyr
1 5 10

<210> 909
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 909
Arg Asp Tyr Asp Val Gly Tyr Tyr Tyr Phe Asp Phe
1 5 10

<210> 910
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 910
Asp Trp Phe Ala Tyr
1 5

<210> 911

<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 911
His Asp His Asn Asn Val Asp Trp Phe Ala Tyr
1 5 10

<210> 912
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 912
Ser Ala Tyr Tyr Gly Tyr Lys Asp Tyr Phe Asp Tyr
1 5 10

<210> 913
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 913
Gly Ala Tyr Tyr Gly Tyr Arg Asp Trp Phe Thr Tyr
1 5 10

<210> 914
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 914
His Asp Tyr Ser Ser Tyr Ser Tyr
1 5

<210> 915
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 915
Ser Ser Thr Thr Asp Gly Ile Val Thr Tyr Val Met Asp Val
1 5 10

<210> 916
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 916
Ile Glu Gly Ser Pro Val Val Thr Thr Val Phe Asp Tyr
1 5 10

<210> 917
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 917
Arg Asp Tyr Asp Val Gly Tyr Tyr Tyr Phe Asp Phe
1 5 10

<210> 918
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 918
Ser Thr Tyr Tyr Gly Tyr Lys Asp Trp Phe Ala Tyr
1 5 10

<210> 919
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 919
Lys Ser Ser Gln Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 920
<211> 13
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 920
Lys Ile Asn Ser Gly Asn Ile Gly Ser Tyr Phe Ile His
1 5 10

<210> 921
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 921
Lys Ser Ser Gln Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 922
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 922
Lys Ala Ser Gln Asn Ile Asn Arg Tyr Leu Asn
1 5 10

<210> 923
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 923
Gln Ala Ser Gln Asn Ile Asn Lys Tyr Ile Ala
1 5 10

<210> 924
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 924
Lys Ala Ser Gln Asn Ile Asn Arg Tyr Leu Asn
1 5 10

<210> 925
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 925
Leu Ala Ser Ser Arg Val Ser Asn Ile Tyr
1 5 10

<210> 926
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 926
Lys Gly Ser Gln Asn Ile Asn Asn Tyr Leu Ala
1 5 10

<210> 927
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 927
Lys Ser Ser Gln Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 928
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 928
Gln Ala Ser Gln Asn Ile Asn Lys Tyr Ile Ala
1 5 10

<210> 929
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 929
Lys Ser Ser Gln Ser Leu Leu Tyr Ser Glu Asn Lys Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 930
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 930
Lys Ile Asn Ser Gly Asn Ile Gly Ser Tyr Phe Ile His
1 5 10

<210> 931
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 931
Lys Ala Ser Gln Asn Ile Asn Arg Tyr Leu Asn
1 5 10

<210> 932
<211> 11
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 932
Lys Ala Ser Gln Asn Ile Asn Arg Tyr Leu Asn
1 5 10

<210> 933
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 933
Leu Ala Ser Ser Arg Val Ser Asn Ile Tyr
1 5 10

<210> 934
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 934
Lys Gly Ser Gln Asn Ile Asn Asn Tyr Leu Ala
1 5 10

<210> 935
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 935
Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 936
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 936
Arg Asp Asp Lys Arg Pro His
1 5

<210> 937
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 937
Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 938
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 938
Ser Ala Asn Ser Leu Gln Thr

1 5

<210> 939
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 939
Tyr Thr Ser Thr Leu Glu Ser
1 5

<210> 940
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 940
Asn Ala Asn Ser Leu Gln Thr
1 5

<210> 941
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 941
Ser Thr Ser Ser Leu Ala Ser
1 5

<210> 942
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 942
Asn Thr Asn Asn Leu Gln Thr
1 5

<210> 943
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 943
Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 944
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 944
Tyr Thr Ser Thr Leu Glu Ser
1 5

<210> 945
<211> 7
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 945
Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 946
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 946
Arg Asp Asp Lys Arg Pro His
1 5

<210> 947
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 947
Ser Ala Asn Ser Leu Gln Thr
1 5

<210> 948
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 948
Asn Ala Asn Ser Leu Gln Thr
1 5

<210> 949
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 949
Ser Thr Ser Ser Leu Ala Ser
1 5

<210> 950
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 950
Asn Thr Asn Asn Leu Gln Thr
1 5

<210> 951
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 951
Gln Gln Tyr Tyr Asn Phe Pro Pro Trp Thr
1 5 10

<210> 952
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 952
His Ser Tyr Asp Ser Gly Ile Asn Ile Val
1 5 10

<210> 953
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 953
Gln Gln Tyr Tyr Asn Phe Pro Thr
1 5

<210> 954
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 954
Leu Gln His Asn Ser Trp Pro Leu Thr

1 5

<210> 955
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 955
Leu Gln Tyr Asp Asp Leu Pro Tyr Thr
1 5

<210> 956
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 956
Leu Gln His Asn Ser Arg Pro Leu Thr
1 5

<210> 957
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 957
His Gln Trp Ser Ser Asn Pro Trp Thr
1 5

<210> 958
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 958
Cys Gln Tyr Asn Asn Gly Asn Thr
1 5

<210> 959
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 959
Gln Gln Tyr Tyr Asn Phe Pro Thr
1 5

<210> 960
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 960
Leu Gln Tyr Asp Asp Leu Pro Tyr Thr
1 5

<210> 961
<211> 10
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 961
Gln Gln Tyr Tyr Asn Phe Pro Pro Trp Thr
1 5 10

<210> 962
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 962
His Ser Tyr Asp Ser Gly Ile Asn Ile Val
1 5 10

<210> 963
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 963
Leu Gln His Asn Ser Trp Pro Leu Thr
1 5

<210> 964
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 964
Leu Gln His Asn Ser Arg Pro Leu Thr
1 5

<210> 965
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 965
His Gln Trp Ser Ser Asn Pro Trp Thr
1 5

<210> 966
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 966
Cys Gln Tyr Asn Asn Gly Asn Thr
1 5

<210> 967
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 967
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1   5   10   15

Ser Val Lys Ile Ser Cys Lys Thr Ser Glu Tyr Thr Phe Thr Asp Tyr
            20   25   30

Ala Phe His Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
        35   40   45

Gly Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe
    50   55   60

Lys Gly Arg Phe Val Phe Ser Leu Glu Asp Ser Ala Arg Thr Ala Asn
65   70   75   80

Leu Gln Ile Ser Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
                85   90   95

Ala Arg Gly Ala Tyr Tyr Gly Tyr Arg Asp Trp Phe Thr Tyr Trp Gly
            100   105   110

Gln Gly Thr Leu Val Thr Val
        115

<210> 968
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 968
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1   5   10   15

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Ser Leu Lys Leu Ser Cys Leu Ala Ser Gly Phe Thr Phe Ser Lys Tyr
            20                  25                  30


Gly Met Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Ser Ile Ser Ser Thr Ser Ile Tyr Ile Tyr Tyr Ala Asp Thr Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95


Ala Arg His Asp Tyr Ser Ser Tyr Ser Tyr Trp Gly Gln Gly Val Met
            100                 105                 110


Val Thr Val
        115


<210> 969
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 969
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Asp Tyr
            20                  25                  30
```

Tyr Met Ala Trp Val Arg Gln Ala Pro Lys Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asn Asn Ala Lys Ser Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Arg His Asp His Asn Asn Val Asp Trp Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val
115

<210> 970
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 970
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Phe Thr Arg Phe Ser Leu Ser Thr Tyr
20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Asp Lys His Tyr Asn Pro Ser

50 55 60

Leu Lys Asn Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Ala
65 70 75 80

Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Ser Ser Thr Thr Asp Gly Ile Val Thr Tyr Val Met Asp
100 105 110

Val Trp Gly Gln Gly Ala Ser Val Thr Val
115 120

<210> 971
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 971
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Thr
1 5 10 15

Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Ser
20 25 30

Gly Met Gln Trp Ile Arg Gln Ala Pro Lys Lys Gly Leu Glu Trp Ile
35 40 45

Ser Gly Ile Tyr Tyr Asp Ser Tyr Lys Lys Ser Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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Leu Glu Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95


Ala Lys Ser Ala Tyr Tyr Gly Tyr Lys Asp Tyr Phe Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Val Met Val Thr Val
        115


<210> 972
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 972
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Leu Leu Gln Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Thr Phe Ala Gly Phe Ser Leu Asn Thr His
            20                  25                  30


Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
        35                  40                  45


Trp Leu Ala Asn Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser
    50                  55                  60


Leu Lys Asn Arg Leu Thr Met Ser Lys Asp Thr Ser Asn Asn Gln Ala
65                  70                  75                  80


Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95
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```
Cys Ala Arg Ile Glu Gly Ser Pro Val Val Thr Thr Val Phe Asp Tyr
            100                 105                 110


Trp Gly Gln Gly Val Met Val Thr Val
        115                 120


<210> 973
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 973
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Met Leu Gln Pro Ser Lys
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30


Gly Met Val Val Ser Trp Ile Arg Gln Pro Ser Gly Lys Ser Leu Glu
        35                  40                  45


Trp Leu Ala Ala Ile Ala Trp Asp Gly Asp Lys Tyr Tyr Asn Pro Ser
    50                  55                  60


Leu Lys Ser Arg Val Thr Val Ser Lys Asp Thr Ser Asn Thr Gln Val
65                  70                  75                  80


Phe Leu Arg Ile Thr Ser Val Asp Ile Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95


Cys Thr Arg Arg Asp Tyr Asp Val Gly Tyr Tyr Tyr Phe Asp Phe Trp
            100                 105                 110
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Gly Gln Gly Val Met Val Thr Val
        115   120

<210> 974
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 974
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1   5   10   15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Asn Thr Val Thr Gly Tyr
            20   25   30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
        35   40   45

Gly Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe
    50   55   60

Lys Gly Arg Cys Val Phe Ser Leu Glu Ala Ser Ala Ser Thr Ala His
65   70   75   80

Leu Gln Ile Ser Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
                85   90   95

Ala Arg Ser Thr Tyr Tyr Gly Tyr Lys Asp Trp Phe Ala Tyr Trp Gly
            100   105   110

Gln Gly Thr Leu Val Thr Val
        115

<210> 975

<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 975
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Asp Tyr
20 25 30

Tyr Met Ala Trp Val Arg Gln Ala Pro Lys Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asn Asn Ala Lys Ser Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Arg His Asp His Asn Asn Val Asp Trp Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val
115

<210> 976
<211> 119
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 976

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Thr
1               5                  10                  15

Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Ser
            20                  25                  30

Gly Met Gln Trp Ile Arg Gln Ala Pro Lys Lys Gly Leu Glu Trp Ile
        35                  40                  45

Ser Gly Ile Tyr Tyr Asp Ser Tyr Lys Lys Ser Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Glu Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95

Ala Lys Ser Ala Tyr Tyr Gly Tyr Lys Asp Tyr Phe Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Val Met Val Thr Val
        115
```

<210> 977
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 977

Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Thr Ser Glu Tyr Thr Phe Thr Asp Tyr
20 25 30

Ala Phe His Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Glu Asp Ser Ala Arg Thr Ala Asn
65 70 75 80

Leu Gln Ile Ser Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Gly Ala Tyr Tyr Gly Tyr Arg Asp Trp Phe Thr Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val
115

<210> 978
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 978
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Lys Leu Ser Cys Leu Ala Ser Gly Phe Thr Phe Ser Lys Tyr

20 25 30

Gly Met Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ser Ile Ser Ser Thr Ser Ile Tyr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg His Asp Tyr Ser Ser Tyr Ser Tyr Trp Gly Gln Gly Val Met
100 105 110

Val Thr Val
115

<210> 979
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 979
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Phe Thr Arg Phe Ser Leu Ser Thr Tyr
20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45

```
Trp Leu Ala Asp Ile Trp Trp Asp Asp Asp Lys His Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Asn Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Ala
65                  70                  75                  80

Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Ser Ser Thr Thr Asp Gly Ile Val Thr Tyr Val Met Asp
            100                 105                 110

Val Trp Gly Gln Gly Ala Ser Val Thr Val
        115                 120
```

<210> 980
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 980

```
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Leu Leu Gln Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Phe Ala Gly Phe Ser Leu Asn Thr His
            20                  25                  30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
        35                  40                  45

Trp Leu Ala Asn Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser
    50                  55                  60
```

```
Leu Lys Asn Arg Leu Thr Met Ser Lys Asp Thr Ser Asn Asn Gln Ala
65                  70                  75                  80


Phe Leu Lys Ile Thr Asn Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95


Cys Ala Arg Ile Glu Gly Ser Pro Val Val Thr Thr Val Phe Asp Tyr
            100                 105                 110


Trp Gly Gln Gly Val Met Val Thr Val
        115                 120


<210> 981
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 981
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Met Leu Gln Pro Ser Lys
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30


Gly Met Val Val Ser Trp Ile Arg Gln Pro Ser Gly Lys Ser Leu Glu
        35                  40                  45


Trp Leu Ala Ala Ile Ala Trp Asp Gly Asp Lys Tyr Tyr Asn Pro Ser
    50                  55                  60


Leu Lys Ser Arg Val Thr Val Ser Lys Asp Thr Ser Asn Thr Gln Val
65                  70                  75                  80
```

Phe Leu Arg Ile Thr Ser Val Asp Ile Ala Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Thr Arg Arg Asp Tyr Asp Val Gly Tyr Tyr Tyr Phe Asp Phe Trp
100 105 110

Gly Gln Gly Val Met Val Thr Val
115 120

<210> 982
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 982
Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Asn Thr Val Thr Gly Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Cys Val Phe Ser Leu Glu Ala Ser Ala Ser Thr Ala His
65 70 75 80

Leu Gln Ile Ser Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Arg Ser Thr Tyr Tyr Gly Tyr Lys Asp Trp Phe Ala Tyr Trp Gly

100 105 110

Gln Gly Thr Leu Val Thr Val
115

<210> 983
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 983
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Arg Asp Tyr
20 25 30

Tyr Met Ala Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys
50 55 60

Gly Arg Val Thr Met Thr Arg Asp Asn Ser Thr Ser Thr Leu Tyr Met
65 70 75 80

Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg His Asp His Asn Asn Val Asp Trp Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 984
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 984
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Phe Thr Phe Arg Asp Tyr
20 25 30

Tyr Met Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys
50 55 60

Gly Gln Val Thr Ile Ser Arg Asp Asn Ser Ile Ser Thr Leu Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg His Asp His Asn Asn Val Asp Trp Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 985
<211> 119
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 985

Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg
1				5				10					15		

Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Arg	Asp	Tyr
			20					25					30		

Tyr	Met	Ala	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			

Ala	Ser	Ile	Ser	Tyr	Glu	Gly	Asn	Pro	Tyr	Tyr	Gly	Asp	Ser	Val	Lys
	50					55					60				

Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Ser	Thr	Leu	Tyr	Leu
65				70					75					80	

Gln	Met	Ser	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala
				85					90					95	

Arg	His	Asp	His	Asn	Asn	Val	Asp	Trp	Phe	Ala	Tyr	Trp	Gly	Gln	Gly
			100					105					110		

Thr	Leu	Val	Thr	Val	Ser	Ser									
			115												

<210> 986
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polypeptide"

<400> 986
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Arg Asp Tyr
20 25 30

Tyr Met Ala Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Met
35 40 45

Gly Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys
50 55 60

Gly Arg Val Thr Ile Thr Arg Asp Asn Ser Ala Ser Thr Leu Tyr Met
65 70 75 80

Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg His Asp His Asn Asn Val Asp Trp Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 987
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 987
Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln Ala Val Ser Ala Gly
1 5 10 15

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20   25   30

Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35   40   45

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50   55   60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65   70   75   80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
                85   90   95

Tyr Tyr Asn Phe Pro Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu
            100   105   110

Leu Lys

<210> 988
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 988
Gln Val Val Leu Thr Gln Pro Lys Ser Val Ser Thr Ser Leu Glu Ser
1   5   10   15

Thr Val Lys Leu Ser Cys Lys Ile Asn Ser Gly Asn Ile Gly Ser Tyr
            20   25   30

```
Phe Ile His Trp Tyr Gln Gln His Glu Gly Arg Ser Pro Thr Thr Met
        35                  40                  45


Ile Tyr Arg Asp Asp Lys Arg Pro His Gly Val Pro Asp Arg Phe Ser
    50                  55                  60


Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Phe Leu Thr Ile Asn Asn
65                  70                  75                  80


Val Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys His Ser Tyr Asp Ser
                85                  90                  95


Gly Ile Asn Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210> 989
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 989
Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln Ala Val Ser Ala Gly
1               5                   10                  15


Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20                  25                  30


Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45


Ser Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60
```

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Asn Phe Pro Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 990
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 990
Asp Val Gln Met Thr Gln Ser Pro Ser Leu Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Ala Val Thr Ile Asn Cys Lys Ala Ser Gln Asn Ile Asn Arg Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Gly Pro Arg Leu Leu Ile
35 40 45

Tyr Ser Ala Asn Ser Leu Gln Thr Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile Thr Ser Pro Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Phe Cys Leu Gln His Asn Ser Trp Pro Leu
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys

100 105

<210> 991
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 991
Asp Ile Gln Met Thr Gln Ser Pro Pro Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Lys Val Thr Ile Thr Cys Gln Ala Ser Gln Asn Ile Asn Lys Tyr
20 25 30

Ile Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Arg Leu Leu Ile
35 40 45

Arg Tyr Thr Ser Thr Leu Glu Ser Gly Thr Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser Asn Val Glu Ser
65 70 75 80

Gly Asp Val Ala Ser Tyr Tyr Cys Leu Gln Tyr Asp Asp Leu Pro Tyr
85 90 95

Thr Phe Gly Pro Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 992
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 992

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Asn Cys Lys Ala Ser Gln Asn Ile Asn Arg Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Asn Ala Asn Ser Leu Gln Thr Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Ala Asp Val Ala Thr Tyr Phe Cys Leu Gln His Asn Ser Arg Pro Leu
                85                  90                  95

Thr Phe Gly Ser Gly Thr Ile Leu Glu Ile Lys
            100                 105
```

<210> 993
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 993

```
Lys Ile Val Leu Thr Gln Ser Pro Thr Ile Thr Ala Ala Ser Pro Gly
1               5                  10                  15
```

Glu Lys Val Thr Ile Thr Cys Leu Ala Ser Ser Arg Val Ser Asn Ile
20 25 30

Tyr Trp Tyr Gln Gln Lys Ser Gly Ala Ser Pro Lys Leu Leu Ile Tyr
35 40 45

Ser Thr Ser Ser Leu Ala Ser Gly Val Pro Tyr Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Asn Thr Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys His Gln Trp Ser Ser Asn Pro Trp Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 994
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 994
Asn Ile Gln Leu Thr Gln Ser Pro Ser Arg Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Leu Ser Cys Lys Gly Ser Gln Asn Ile Asn Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Leu Gly Glu Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asn Thr Asn Asn Leu Gln Thr Gly Ile Pro Ser Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Gly Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Phe Cys Cys Gln Tyr Asn Asn Gly Asn Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 995
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 995
Asp Ile Val Met Thr Gln Thr Pro Ser Ser Gln Ala Val Ser Ala Gly
1 5 10 15

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Asn Phe Pro Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 996
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 996
Asp Ile Gln Met Thr Gln Ser Pro Pro Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Asp Lys Val Thr Ile Thr Cys Gln Ala Ser Gln Asn Ile Asn Lys Tyr
20 25 30

Ile Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Arg Leu Leu Ile
35 40 45

Arg Tyr Thr Ser Thr Leu Glu Ser Gly Thr Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser Asn Val Glu Ser
65 70 75 80

Gly Asp Val Ala Ser Tyr Tyr Cys Leu Gln Tyr Asp Asp Leu Pro Tyr
85 90 95

Thr Phe Gly Pro Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 997
<211> 114
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 997

Asp	Ile	Val	Met	Thr	Gln	Thr	Pro	Ser	Ser	Gln	Ala	Val	Ser	Ala	Gly
1				5				10						15	

Glu	Lys	Val	Thr	Met	Ser	Cys	Lys	Ser	Ser	Gln	Ser	Leu	Leu	Tyr	Ser
			20					25					30		

Glu	Asn	Lys	Lys	Asn	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln
		35					40					45			

Ser	Pro	Lys	Leu	Leu	Ile	Tyr	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Val
	50					55					60				

Pro	Asp	Arg	Phe	Ile	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr
65				70					75						80

Ile	Ser	Ser	Val	Gln	Ala	Glu	Asp	Leu	Ala	Val	Tyr	Tyr	Cys	Gln	Gln
				85					90					95	

Tyr	Tyr	Asn	Phe	Pro	Pro	Trp	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Glu
			100					105					110		

Leu	Lys

<210> 998
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polypeptide"

<400> 998
Gln Val Val Leu Thr Gln Pro Lys Ser Val Ser Thr Ser Leu Glu Ser
1 5 10 15

Thr Val Lys Leu Ser Cys Lys Ile Asn Ser Gly Asn Ile Gly Ser Tyr
20 25 30

Phe Ile His Trp Tyr Gln Gln His Glu Gly Arg Ser Pro Thr Thr Met
35 40 45

Ile Tyr Arg Asp Asp Lys Arg Pro His Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Phe Leu Thr Ile Asn Asn
65 70 75 80

Val Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys His Ser Tyr Asp Ser
85 90 95

Gly Ile Asn Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 999
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 999
Asp Val Gln Met Thr Gln Ser Pro Ser Leu Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Ala Val Thr Ile Asn Cys Lys Ala Ser Gln Asn Ile Asn Arg Tyr
20 25 30

```
Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Gly Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Ser Ala Asn Ser Leu Gln Thr Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Ala Asp Phe Thr Leu Thr Ile Thr Ser Pro Gln Pro
65                  70                  75                  80


Glu Asp Val Ala Thr Tyr Phe Cys Leu Gln His Asn Ser Trp Pro Leu
                85                  90                  95


Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> 1000
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1000
Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Asn Cys Lys Ala Ser Gln Asn Ile Asn Arg Tyr
            20                  25                  30


Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Asn Ala Asn Ser Leu Gln Thr Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Ala Asp Val Ala Thr Tyr Phe Cys Leu Gln His Asn Ser Arg Pro Leu
85 90 95

Thr Phe Gly Ser Gly Thr Ile Leu Glu Ile Lys
100 105

<210> 1001
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1001
Lys Ile Val Leu Thr Gln Ser Pro Thr Ile Thr Ala Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Leu Ala Ser Ser Arg Val Ser Asn Ile
20 25 30

Tyr Trp Tyr Gln Gln Lys Ser Gly Ala Ser Pro Lys Leu Leu Ile Tyr
35 40 45

Ser Thr Ser Ser Leu Ala Ser Gly Val Pro Tyr Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Asn Thr Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys His Gln Trp Ser Ser Asn Pro Trp Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 1002
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1002
Asn Ile Gln Leu Thr Gln Ser Pro Ser Arg Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Leu Ser Cys Lys Gly Ser Gln Asn Ile Asn Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Leu Gly Glu Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asn Thr Asn Asn Leu Gln Thr Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Gly Leu Gln Pro
65 70 75 80

Glu Asp Val Ala Thr Tyr Phe Cys Cys Gln Tyr Asn Asn Gly Asn Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 1003
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1003
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20 25 30

Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
        35 40 45

Val Pro Lys Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val
    50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln
                85 90 95

Tyr Tyr Asn Phe Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100 105 110

<210> 1004
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1004
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

```
Glu Arg Ala Thr Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20                  25                  30


Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45


Ala Pro Arg Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Ile
    50                  55                  60


Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80


Ile Ser Ser Leu Gln Pro Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
                85                  90                  95


Tyr Tyr Asn Phe Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210> 1005
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1005
Asp Ile Val Met Thr Gln Thr Pro Leu Ser Leu Ser Val Thr Pro Gly
1               5                   10                  15


Gln Pro Val Ser Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20                  25                  30


Glu Asn Lys Lys Asn Tyr Leu Ala Trp Tyr Leu Gln Lys Pro Gly Gln
        35                  40                  45
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Ser Pro Gln Leu Leu Ile Phe Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
65 70 75 80

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Asn Phe Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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1 5 10

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1 5 10

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<212> PRT
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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<211> 17
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Gly

<210> 1011

<211> 17
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic
peptide"

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1 5 10 15

Gly

<210> 1012
<211> 17
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 1012
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1 5 10 15

Gly

<210> 1013
<211> 17
<212> PRT
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<220>
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peptide"

<400> 1013

Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe Gln
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Gly

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<211> 12
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<220>
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Asp Met Asn Ile Leu Ala Thr Val Pro Phe Asp Ile
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<210> 1015
<211> 12
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<211> 12
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<220>
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<400> 1017
Asp Met Asn Ile Leu Ala Thr Val Pro Phe Asp Ile
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<210> 1019
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<400> 1021
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<211> 7
<212> PRT
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<400> 1023
Ala Ala Phe Ser Leu Gln Ser
1 5

<210> 1024
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<400> 1026
Gln Gln Gly Asp Ser Val Pro Leu Thr
1 5

<210> 1027
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peptide"

<400> 1027
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peptide"

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1 5

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Gln Gln Gly Asp Ser Val Pro Leu Thr
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<220>
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1 5 10

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<220>
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1 5 10

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<400> 1032
Gly Tyr Ile Phe Thr Gly Tyr Tyr Ile His
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<400> 1035
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1 5 10 15

Gly

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<400> 1036
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1 5 10 15

Gly

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<211> 17
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<220>
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1 5 10 15

Gly

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<211> 12
<212> PRT
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<220>
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<210> 1039
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<400> 1043
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1 5 10

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1 5

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<220>
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1 5

<210> 1048
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<210> 1049
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Ala Ala Ser Ser Leu Gln Ser
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<212> PRT
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1 5

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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1051
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1 5

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1 5

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<212> PRT
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<220>
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1 5

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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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Gly Tyr Tyr Met His
1 5

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<220>
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<220>
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1 5

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Asp Tyr Tyr Met His
1 5

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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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1 5 10 15

Gly

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Gly

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Gly

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peptide"

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1 5 10 15

Gly

<210> 1062
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peptide"

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<220>
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Asp Met Asn Ile Leu Ala Thr Val Pro Phe Asp Ile
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1 5 10

<210> 1066
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Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5 10

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<210> 1070
<211> 7
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<400> 1071
Ala Ala Ser Ser Leu Gln Ser
1 5

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<212> PRT
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<400> 1073
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1 5

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<400> 1074
Gln Gln Gly Asp Ser Val Pro Leu Thr
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<400> 1075
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<210> 1076
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<400> 1076
Gln Gln Gly Asp Ser Val Pro Leu Thr
1 5

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<400> 1077
Gln Gln Gly Asp Ser Val Pro Leu Thr
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<210> 1078
<211> 7
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<400> 1078
Gly Tyr Thr Phe Thr Gly Tyr
1 5

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<211> 7
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1079
Gly Tyr Thr Phe Thr Gly Tyr
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<210> 1080
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<212> PRT
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<400> 1080
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<220>
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1 5

<210> 1082
<211> 6
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<400> 1082
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1 5

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1 5

<210> 1085
<211> 6
<212> PRT
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Asn Pro Asn Ser Gly Asp
1 5

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1 5 10

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<400> 1090
Ser Gln Ser Ile Ser Thr Tyr
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1   5

<210> 1092
<211> 7
<212> PRT
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Ser Gln Ser Ile Ser Ser Tyr
1   5

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<400> 1093
Ser Gln Ser Ile Ser Ser Tyr
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peptide"

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<210> 1095
<211> 3
<212> PRT
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<400> 1095
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<211> 3
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<400> 1096
Ala Ala Ser
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<210> 1097
<211> 3
<212> PRT
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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Ala Ala Ser
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<211> 6
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<220>
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<400> 1098
Gly Asp Ser Val Pro Leu
1 5

<210> 1099
<211> 6
<212> PRT
<213> Artificial Sequence

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<400> 1099
Gly Asp Ser Val Pro Leu
1 5

<210> 1100
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1100
Gly Asp Ser Val Pro Leu
1 5

<210> 1101
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1101
Gly Asp Ser Val Pro Leu
1 5

<210> 1102
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1102
Gly Tyr Thr Phe Thr Ser Tyr Trp Met Asn
1 5 10

<210> 1103
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1103
Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe Lys
1 5 10 15

Asp

<210> 1104
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1104
Gly Asn Trp Asp Asp Tyr
1 5

<210> 1105
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1105
Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala
1 5 10

<210> 1106
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1106
Ser Gly Ser Thr Leu Gln Ser
1 5

<210> 1107

<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 1107
Gln Gln His Asn Lys Tyr Pro Tyr Thr
1 5

<210> 1108
<211> 762
<212> DNA
<213> Homo sapiens

<400> 1108
gaggtacagc tgcagcagtc aggtccagga ctggtgaagc cctcgcagac cctctcactc 60

acctgtgcca tctccgggga cagtgtctct agcaacagtg ctgcttggaa ctggatcagg 120

cagtccccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggtat 180

agtgattatg cagtatctgt gaaaagtcga ataaccatca acccagacac atccaagaac 240

cagttctccc tgcagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca 300

agagatcctt acgatttttg gagtggttat cctgatgctt ttgatatctg gggccaaggg 360

acaatggtca ccgtctcttc aggtggtggt ggcagcggcg gcggcggctc tggtggtggt 420

ggatcccagt ctgccctgac tcagcctgcc tccgtgtctg ggtctcctgg acagtcgatc 480

accatctcct gcactggaac cagcagtgac gttggtggtt acaactatgt ctcctggtac 540

caacagcacc caggcaaagc ccccaaggtc ataatttctg aggtcaataa tcggccctca 600

ggggtttctc atcgcttctc tgggtccaag tctggcaaca cggcctccct gaccatctct 660

gggctccagg ctgaggacga ggctgattat ttctgcagct catatacaag tggcaggact 720

ctttatgtct tcggaactgg gagcaaggtc accgtcctag gt 762

<210> 1109

<211> 498
<212> PRT
<213> Homo sapiens

<400> 1109

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Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu
            20                  25                  30

Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp
        35                  40                  45

Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro
    50                  55                  60

Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp
65                  70                  75                  80

Tyr Ser Asp Tyr Ala Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro
                85                  90                  95

Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro
            100                 105                 110

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Pro Tyr Asp Phe Trp
        115                 120                 125

Ser Gly Tyr Pro Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val
    130                 135                 140

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
145                 150                 155                 160

Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser
                165                 170                 175
```

```
Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val
            180                 185                 190

Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala
        195                 200                 205

Pro Lys Val Ile Ile Ser Glu Val Asn Asn Arg Pro Ser Gly Val Ser
    210                 215                 220

His Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile
225                 230                 235                 240

Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Phe Cys Ser Ser Tyr
                245                 250                 255

Thr Ser Gly Arg Thr Leu Tyr Val Phe Gly Thr Gly Ser Lys Val Thr
            260                 265                 270

Val Leu Gly Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro
        275                 280                 285

Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro
    290                 295                 300

Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp
305                 310                 315                 320

Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu
                325                 330                 335

Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu
            340                 345                 350

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
        355                 360                 365
```

```
Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
    370                 375                 380


Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys
385                 390                 395                 400


Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
                405                 410                 415


Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
            420                 425                 430


Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu
        435                 440                 445


Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly
    450                 455                 460


Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser
465                 470                 475                 480


Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro
                485                 490                 495


Pro Arg
```

<210> 1110
<211> 1494
<212> DNA
<213> Homo sapiens

<400> 1110
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaggtac agctgcagca gtcaggtcca ggactggtga agccctcgca gaccctctca 120

ctcacctgtg ccatctccgg ggacagtgtc tctagcaaca gtgctgcttg gaactggatc 180

aggcagtccc catcgagagg ccttgagtgg ctgggaagga catactacag gtccaagtgg 240

tatagtgatt atgcagtatc tgtgaaaagt cgaataacca tcaacccaga cacatccaag 300

aaccagttct ccctgcagct gaactctgtg actcccgagg acacggctgt gtattactgt 360

gcaagagatc cttacgattt ttggagtggt tatcctgatg cttttgatat ctggggccaa 420

gggacaatgg tcaccgtctc ttcaggtggt ggtggcagcg gcggcggcgg ctctggtggt 480

ggtggatccc agtctgccct gactcagcct gcctccgtgt ctgggtctcc tggacagtcg 540

atcaccatct cctgcactgg aaccagcagt gacgttggtg gttacaacta tgtctcctgg 600

taccaacagc acccaggcaa agcccccaag gtcataattt ctgaggtcaa taatcggccc 660

tcaggggttt ctcatcgctt ctctgggtcc aagtctggca acacggcctc cctgaccatc 720

tctgggctcc aggctgagga cgaggctgat tatttctgca gctcatatac aagtggcagg 780

actctttatg tcttcggaac tgggagcaag gtcaccgtcc taggtaccac taccccagca 840

ccgaggccac ccaccccggc tcctaccatc gcctcccagc ctctgtccct gcgtccggag 900

gcatgtagac ccgcagctgg tggggccgtg catacccggg gtcttgactt cgcctgcgat 960

atctacattt gggcccctct ggctggtact tgcggggtcc tgctgctttc actcgtgatc 1020

actctttact gtaagcgcgg tcggaagaag ctgctgtaca tctttaagca acccttcatg 1080

aggcctgtgc agactactca agaggaggac ggctgttcat gccggttccc agaggaggag 1140

gaaggcggct gcgaactgcg cgtgaaattc agccgcagcg cagatgctcc agcctacaag 1200

caggggcaga accagctcta caacgaactc aatcttggtc ggagagagga gtacgacgtg 1260

ctggacaagc ggagaggacg ggacccagaa atgggcggga agccgcgcag aaagaatccc 1320

caagagggcc tgtacaacga gctccaaaag gataagatgg cagaagccta tagcgagatt 1380

ggtatgaaag gggaacgcag aagaggcaaa ggccacgacg gactgtacca gggactcagc 1440

accgccacca aggacaccta tgacgctctt cacatgcagg ccctgccgcc tcgg 1494

<210> 1111
<211> 12

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1111
Gly Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn
1 5 10

<210> 1112
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1112
Gly Asp Ser Val Ser Ser Asn Ser Ala Ala
1 5 10

<210> 1113
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1113
Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Ser Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 1114

<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1114
Thr Tyr Tyr Arg Ser Lys Trp Tyr Ser
1 5

<210> 1115
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1115
Asp Pro Tyr Asp Phe Trp Ser Gly Tyr Pro Asp Ala Phe Asp Ile
1 5 10 15

<210> 1116
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1116
Ala Arg Asp Pro Tyr Asp Phe Trp Ser Gly Tyr Pro Asp Ala Phe Asp
1 5 10 15

Ile

<210> 1117
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1117
Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 1118
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1118
Ser Ser Asp Val Gly Gly Tyr Asn Tyr
1 5

<210> 1119
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1119
Glu Val Asn Asn Arg Pro Ser
1 5

<210> 1120
<211> 3
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1120
Glu Val Asn
1

<210> 1121
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1121
Ser Ser Tyr Thr Ser Gly Arg Thr Leu Tyr Val
1 5 10

<210> 1122
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1122
Ser Ser Tyr Thr Ser Gly Arg Thr Leu Tyr Val
1 5 10

<210> 1123
<211> 1461
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1123
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgtcca gtcaggagcg gaagtcaaga agcccggagc gtcagtcaaa 120

gtgtcatgca aagcctcggg ctacactttc actgggtact acatgcactg ggtgcgccag 180

gctccaggac agggactgga atggatggga tggatcaacc cgaactccgg tggcaccaat 240

tacgcccaga agttccaggg gagggtgacc atgactcgcg acacgtcgat cagcaccgca 300

tacatggagc tgtcaagact ccggtccgac gatactgccg tgtactactg cgcacgggac 360

atgaacattc tggccaccgt gccttttgac atctggggtc agggaactat ggttaccgtg 420

tcctctggtg gaggcggctc cggcgggggg ggaagcggag gcggtggaag cgacattcag 480

atgacccagt cgccttcatc cctttcggcg agcgtgggag atcgcgtcac tatcacttgt 540

cgggcctcgc agtccatctc cacctacctc aattggtacc agcagaagcc aggaaaagca 600

ccgaatctgc tgatctacgc cgcgttttcc ttgcaatcgg gagtgccaag cagattcagc 660

ggatcgggat caggcactga tttcaccctc accatcaact cgctgcaacc ggaggatttc 720

gctacgtact attgccaaca aggagacagc gtgccgctca ccttcggcgg agggactaag 780

ctggaaatca agaccactac cccagcaccg aggccaccca ccccggctcc taccatcgcc 840

tcccagcctc tgtccctgcg tccggaggca tgtagacccg cagctggtgg ggccgtgcat 900

acccggggtc ttgacttcgc ctgcgatatc tacatttggg cccctctggc tggtacttgc 960

ggggtcctgc tgctttcact cgtgatcact ctttactgta agcgcggtcg gaagaagctg 1020

ctgtacatct ttaagcaacc cttcatgagg cctgtgcaga ctactcaaga ggaggacggc 1080

tgttcatgcc ggttcccaga ggaggaggaa ggcggctgcg aactgcgcgt gaaattcagc 1140

cgcagcgcag atgctccagc ctacaagcag gggcagaacc agctctacaa cgaactcaat 1200

cttggtcgga gagaggagta cgacgtgctg gacaagcgga gaggacggga cccagaaatg 1260

ggcgggaagc cgcgcagaaa gaatccccaa gagggcctgt acaacgagct ccaaaaggat 1320

aagatggcag aagcctatag cgagattggt atgaaagggg aacgcagaag aggcaaaggc 1380

cacgacggac tgtaccaggg actcagcacc gccaccaagg acacctatga cgctcttcac 1440

atgcaggccc tgccgcctcg g 1461

<210> 1124
<211> 487
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1124
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Met Asn Ile Leu Ala Thr Val Pro

```
        115                 120                 125

Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
145                 150                 155                 160

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
                165                 170                 175

Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Thr Tyr Leu Asn Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile Tyr Ala Ala
        195                 200                 205

Phe Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    210                 215                 220

Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro Glu Asp Phe
225                 230                 235                 240

Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Ser Val Pro Leu Thr Phe Gly
                245                 250                 255

Gly Gly Thr Lys Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro
            260                 265                 270

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
        275                 280                 285

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
    290                 295                 300

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
```

305 310 315 320

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
325 330 335

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
340 345 350

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
355 360 365

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
370 375 380

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
385 390 395 400

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
405 410 415

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
420 425 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
435 440 445

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
450 455 460

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465 470 475 480

Met Gln Ala Leu Pro Pro Arg
485

<210> 1125

<211> 264
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1125

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Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15


His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30


Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45


Thr Phe Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60


Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
65                  70                  75                  80


Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95


Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr
            100                 105                 110


Ala Val Tyr Tyr Cys Ala Arg Asp Met Asn Ile Leu Ala Thr Val Pro
        115                 120                 125


Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
    130                 135                 140


Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
145                 150                 155                 160
```

```
Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
                165                 170                 175


Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Thr Tyr Leu Asn Trp
            180                 185                 190


Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile Tyr Ala Ala
        195                 200                 205


Phe Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    210                 215                 220


Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro Glu Asp Phe
225                 230                 235                 240


Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Ser Val Pro Leu Thr Phe Gly
                245                 250                 255


Gly Gly Thr Lys Leu Glu Ile Lys
            260
```

<210> 1126
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1126

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20                  25                  30
```

```
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Met Asn Ile Leu Ala Thr Val Pro Phe Asp Ile Trp Gly
            100                 105                 110


Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120


<210> 1127
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1127
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Thr Tyr
            20                  25                  30


Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
        35                  40                  45
```

Tyr Ala Ala Phe Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Ser Val Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 1128
<211> 1461
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1128
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc aactcgtcca aagcggagcg gaagtcaaga aacccggagc gagcgtgaaa 120

gtgtcctgca aagcctccgg ctacaccttt acgggctact acatgcactg ggtgcgccag 180

gcaccaggac agggtcttga atggatggga tggatcaacc ctaattcggg cggaactaac 240

tacgcacaga agttccaggg gagagtgact ctgactcggg atacctccat ctcaactgtc 300

tacatggaac tctcccgctt gcggtcagat gatacggcag tgtactactg cgcccgcgac 360

atgaatatcc tggctaccgt gccgttcgac atctggggac aggggactat ggttactgtc 420

tcatcgggcg gtggaggttc aggaggaggc ggctcgggag gcggaggttc ggacattcag 480

atgacccagt ccccatcctc tctgtcggcc agcgtcggag atagggtgac cattacctgt 540

cgggcctcgc aaagcatctc ctcgtacctc aactggtatc agcaaaagcc gggaaaggcg 600

cctaagctgc tgatctacgc cgcttcgagc ttgcaaagcg gggtgccatc cagattctcg 660

ggatcaggct caggaaccga cttcaccctg accgtgaaca gcctccagcc ggaggacttt 720

gccacttact actgccagca gggagactcc gtgccgctta ctttcggggg gggtacccgc 780

ctggagatca agaccactac cccagcaccg aggccaccca ccccggctcc taccatcgcc 840

tcccagcctc tgtccctgcg tccggaggca tgtagacccg cagctggtgg ggccgtgcat 900

acccggggtc ttgacttcgc ctgcgatatc tacatttggg cccctctggc tggtacttgc 960

ggggtcctgc tgctttcact cgtgatcact ctttactgta agcgcggtcg gaagaagctg 1020

ctgtacatct ttaagcaacc cttcatgagg cctgtgcaga ctactcaaga ggaggacggc 1080

tgttcatgcc ggttcccaga ggaggaggaa ggcggctgcg aactgcgcgt gaaattcagc 1140

cgcagcgcag atgctccagc ctacaagcag gggcagaacc agctctacaa cgaactcaat 1200

cttggtcgga gagaggagta cgacgtgctg gacaagcgga gaggacggga cccagaaatg 1260

ggcgggaagc cgcgcagaaa gaatccccaa gagggcctgt acaacgagct ccaaaaggat 1320

aagatggcag aagcctatag cgagattggt atgaaagggg aacgcagaag aggcaaaggc 1380

cacgacggac tgtaccaggg actcagcacc gccaccaagg acacctatga cgctcttcac 1440

atgcaggccc tgccgcctcg g 1461

<210> 1129
<211> 487
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1129
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

```
Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Leu Thr Arg Asp Thr Ser
                85                  90                  95

Ile Ser Thr Val Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Asp Met Asn Ile Leu Ala Thr Val Pro
        115                 120                 125

Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
145                 150                 155                 160

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
                165                 170                 175

Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala
        195                 200                 205

Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    210                 215                 220
```

```
Gly Thr Asp Phe Thr Leu Thr Val Asn Ser Leu Gln Pro Glu Asp Phe
225                 230                 235                 240


Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Ser Val Pro Leu Thr Phe Gly
                245                 250                 255


Gly Gly Thr Arg Leu Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro
            260                 265                 270


Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
        275                 280                 285


Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
    290                 295                 300


Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
305                 310                 315                 320


Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
                325                 330                 335


Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
            340                 345                 350


Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
        355                 360                 365


Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
    370                 375                 380


Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
385                 390                 395                 400


Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
                405                 410                 415
```

```
Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
            420                 425                 430


Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
        435                 440                 445


Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
    450                 455                 460


Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465                 470                 475                 480


Met Gln Ala Leu Pro Pro Arg
                485


<210> 1130
<211> 264
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1130
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30


Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45


Thr Phe Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60
```

```
Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
65                  70                  75                  80


Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Leu Thr Arg Asp Thr Ser
                85                  90                  95


Ile Ser Thr Val Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr
            100                 105                 110


Ala Val Tyr Tyr Cys Ala Arg Asp Met Asn Ile Leu Ala Thr Val Pro
        115                 120                 125


Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly
    130                 135                 140


Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
145                 150                 155                 160


Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
                165                 170                 175


Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp
            180                 185                 190


Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala
        195                 200                 205


Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    210                 215                 220


Gly Thr Asp Phe Thr Leu Thr Val Asn Ser Leu Gln Pro Glu Asp Phe
225                 230                 235                 240


Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Ser Val Pro Leu Thr Phe Gly
                245                 250                 255
```

Gly Gly Thr Arg Leu Glu Ile Lys
            260

<210> 1131
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1131
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20   25   30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35   40   45

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Leu Thr Arg Asp Thr Ser Ile Ser Thr Val Tyr
65   70   75   80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Asp Met Asn Ile Leu Ala Thr Val Pro Phe Asp Ile Trp Gly
            100   105   110

Gln Gly Thr Met Val Thr Val Ser Ser
        115   120

<210> 1132

<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1132
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Val Asn Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Ser Val Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 1133
<211> 1461
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1133

atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactcgttca atccggcgca gaagtcaaga agccaggagc atcagtgaaa 120

gtgtcctgca aagcctcagg ctacatcttc acgggatact acatccactg ggtgcgccag 180

gctccgggcc agggccttga gtggatgggc tggatcaacc ctaactctgg gggaaccaac 240

tacgctcaga agttccaggg gagggtcact atgactcgcg atacctccat ctccactgcg 300

tacatggaac tctcgggact gagatccgac gatcctgccg tgtactactg cgcccgggac 360

atgaacatct tggcgaccgt gccgtttgac atttggggac agggcaccct cgtcactgtg 420

tcgagcggtg gaggaggctc gggggggtggc ggatcaggag ggggaggaag cgacatccag 480

ctgactcaga gcccatcgtc gttgtccgcg tcggtggggg atagagtgac cattacttgc 540

cgcgccagcc agagcatctc atcatatctg aattggtacc agcagaagcc cggaaaggcc 600

ccaaaactgc tgatctacgc tgcaagcagc ctccaatcgg gagtgccgtc acggttctcc 660

gggtccggtt cgggaactga ctttaccctg accgtgaatt cgctgcaacc ggaggatttc 720

gccacgtact actgtcagca aggagactcc gtgccgctga ccttcggtgg aggcaccaag 780

gtcgaaatca agaccactac cccagcaccg aggccaccca ccccggctcc taccatcgcc 840

tcccagcctc tgtccctgcg tccggaggca tgtagacccg cagctggtgg ggccgtgcat 900

acccggggtc ttgacttcgc ctgcgatatc tacatttggg cccctctggc tggtacttgc 960

ggggtcctgc tgctttcact cgtgatcact ctttactgta agcgcggtcg gaagaagctg 1020

ctgtacatct ttaagcaacc cttcatgagg cctgtgcaga ctactcaaga ggaggacggc 1080

tgttcatgcc ggttcccaga ggaggaggaa ggcggctgcg aactgcgcgt gaaattcagc 1140

cgcagcgcag atgctccagc ctacaagcag gggcagaacc agctctacaa cgaactcaat 1200

cttggtcgga gagaggagta cgacgtgctg gacaagcgga gaggacggga cccagaaatg 1260

ggcgggaagc cgcgcagaaa gaatccccaa gagggcctgt acaacgagct ccaaaaggat 1320

aagatggcag aagcctatag cgagattggt atgaaagggg aacgcagaag aggcaaaggc 1380

cacgacggac tgtaccaggg actcagcacc gccaccaagg acacctatga cgctcttcac 1440

atgcaggccc tgccgcctcg g 1461

<210> 1134
<211> 487
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1134
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Ile Phe Thr Gly Tyr Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
65 70 75 80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
85 90 95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Gly Leu Arg Ser Asp Asp Pro
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Asp Met Asn Ile Leu Ala Thr Val Pro
115 120 125

Phe Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly

```
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
145                 150                 155                 160

Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
                165                 170                 175

Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp
            180                 185                 190

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala
        195                 200                 205

Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    210                 215                 220

Gly Thr Asp Phe Thr Leu Thr Val Asn Ser Leu Gln Pro Glu Asp Phe
225                 230                 235                 240

Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Ser Val Pro Leu Thr Phe Gly
                245                 250                 255

Gly Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro
            260                 265                 270

Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro
        275                 280                 285

Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu
    290                 295                 300

Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys
305                 310                 315                 320

Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly
```

325 330 335

Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val
340 345 350

Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu
355 360 365

Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp
370 375 380

Ala Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn
385 390 395 400

Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg
405 410 415

Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly
420 425 430

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
435 440 445

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
450 455 460

Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His
465 470 475 480

Met Gln Ala Leu Pro Pro Arg
485

<210> 1135
<211> 264
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1135

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Ile Phe Thr Gly Tyr Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser
                85                  90                  95

Ile Ser Thr Ala Tyr Met Glu Leu Ser Gly Leu Arg Ser Asp Asp Pro
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Asp Met Asn Ile Leu Ala Thr Val Pro
        115                 120                 125

Phe Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
145                 150                 155                 160

Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
                165                 170                 175
```

```
Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp
            180                 185                 190


Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala
        195                 200                 205


Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    210                 215                 220


Gly Thr Asp Phe Thr Leu Thr Val Asn Ser Leu Gln Pro Glu Asp Phe
225                 230                 235                 240


Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Ser Val Pro Leu Thr Phe Gly
                245                 250                 255


Gly Gly Thr Lys Val Glu Ile Lys
            260


<210> 1136
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1136
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Gly Tyr
            20                  25                  30


Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
```

```
Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Gly Leu Arg Ser Asp Asp Pro Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Asp Met Asn Ile Leu Ala Thr Val Pro Phe Asp Ile Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> 1137
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1137
Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30


Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Val Asn Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Ser Val Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1138
<211> 1467
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1138
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtcc aactccaaca gtcaggcgca gaagtgaaaa agagcggtgc atcggtgaaa 120

gtgtcatgca aagcctcggg ctacaccttc actgactact atatgcactg gctgcggcag 180

gcaccgggac agggacttga gtggatggga tggatcaacc cgaattcagg ggacactaac 240

tacgcgcaga agttccaggg gagagtgacc ctgacgaggg acacctcaat ttcgaccgtc 300

tacatggaat tgtcgcgcct gagatcggac gatactgctg tgtactactg tgcccgcgac 360

atgaacatcc tcgcgactgt gccttttgat atctggggac aggggactat ggtcaccgtt 420

tcctccgctt ccggtggcgg aggctcggga ggccgggcct ccggtggagg aggcagcgac 480

atccagatga ctcagagccc ttcctcgctg agcgcctcag tgggagatcg cgtgaccatc 540

acttgccggg ccagccagtc catttcgtcc tacctcaatt ggtaccagca gaagccggga 600

aaggcgccca agctcttgat ctacgctgcg agctccctgc aaagcggggt gccgagccga 660

ttctcgggtt ccggctcggg aaccgacttc actctgacca tctcatccct gcaaccagag 720

gactttgcca cctactactg ccaacaagga gattctgtcc cactgacgtt cggcggagga 780

accaaggtcg aaatcaagac cactacccca gcaccgaggc cacccacccc ggctcctacc 840

atcgcctccc agcctctgtc cctgcgtccg gaggcatgta gacccgcagc tggtggggcc 900

gtgcataccc ggggtcttga cttcgcctgc gatatctaca tttgggcccc tctggctggt 960

acttgcgggg tcctgctgct ttcactcgtg atcactcttt actgtaagcg cggtcggaag 1020

aagctgctgt acatctttaa gcaacccttc atgaggcctg tgcagactac tcaagaggag 1080

gacggctgtt catgccggtt cccagaggag gaggaaggcg gctgcgaact gcgcgtgaaa 1140

ttcagccgca gcgcagatgc tccagcctac aagcaggggc agaaccagct ctacaacgaa 1200

ctcaatcttg gtcggagaga ggagtacgac gtgctggaca agcggagagg acgggaccca 1260

gaaatgggcg ggaagccgcg cagaaagaat ccccaagagg gcctgtacaa cgagctccaa 1320

aaggataaga tggcagaagc ctatagcgag attggtatga aaggggaacg cagaagaggc 1380

aaaggccacg acggactgta ccagggactc agcaccgcca ccaaggacac ctatgacgct 1440

cttcacatgc aggccctgcc gcctcgg 1467

<210> 1139
<211> 336
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1139
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Ser Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

```
Thr Phe Thr Asp Tyr Tyr Met His Trp Leu Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Asp Thr Asn
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Leu Thr Arg Asp Thr Ser
                85                  90                  95

Ile Ser Thr Val Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Asp Met Asn Ile Leu Ala Thr Val Pro
        115                 120                 125

Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Arg Ala Ser Gly Gly Gly Gly Ser Asp
145                 150                 155                 160

Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
                165                 170                 175

Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu
            180                 185                 190

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
        195                 200                 205

Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
225                 230                 235                 240
```

```
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Ser Val Pro Leu Thr
                245                 250                 255


Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro
            260                 265                 270


Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
        275                 280                 285


Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
    290                 295                 300


Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
305                 310                 315                 320


Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys
                325                 330                 335


<210> 1140
<211> 266
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1140
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val
            20                  25                  30


Lys Lys Ser Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45
```

```
Thr Phe Thr Asp Tyr Tyr Met His Trp Leu Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Trp Ile Asn Pro Asn Ser Gly Asp Thr Asn
65                  70                  75                  80

Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Leu Thr Arg Asp Thr Ser
                85                  90                  95

Ile Ser Thr Val Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Asp Met Asn Ile Leu Ala Thr Val Pro
        115                 120                 125

Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Arg Ala Ser Gly Gly Gly Gly Ser Asp
145                 150                 155                 160

Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
                165                 170                 175

Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu
            180                 185                 190

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
        195                 200                 205

Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    210                 215                 220

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
225                 230                 235                 240
```

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Ser Val Pro Leu Thr
245 250 255

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
260 265

<210> 1141
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1141
Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Lys Lys Ser Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Leu Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Asp Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Arg Asp Thr Ser Ile Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Met Asn Ile Leu Ala Thr Val Pro Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser

115 120

<210> 1142
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1142
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asp Ser Val Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1143
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1143
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agctggtcca gtcgggagcc gaagtcaaga agcccggcgc tagcgtgaaa 120

gtgtcctgca aagcctccgg gtacacattc acctcctact ggatgaattg ggtcagacag 180

gcgcccggcc agggactcga gtggatggga aggattgatc cttacgactc cgaaacccat 240

tacaaccaga agttcaagga ccgcgtgacc atgactgtgg ataagtccac ttccaccgct 300

tacatggagc tgtccagcct gcgctccgag gataccgcag tgtactactg cgcccgggga 360

aactgggacg actattgggg acagggaact accgtgaccg tgtcaagcgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcagggggcg gaggaagcga cgtgcagctc 480

acccagtcgc cctcatttct gtcggcctca gtgggagaca gagtgaccat tacttgtcgg 540

gcctccaaga gcatctccaa ggacctggcc tggtatcagc agaagccagg aaaggcgcct 600

aagttgctca tctactcggg gtcgaccctg caatctggcg tgccgtcccg gttctccggt 660

tcgggaagcg gtaccgaatt cacccttact atctcctccc tgcaaccgga ggacttcgcc 720

acctactact gccaacagca caacaagtac ccgtacactt tcgggggtgg cacgaaggtc 780

gaaatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1144
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1144
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65 70 75 80

Tyr Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser
85 90 95

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln

```
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Gln Leu
145                 150                 155                 160

Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly Asp Arg Val Thr
                165                 170                 175

Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240

Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255

Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
```

305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1145

<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1145

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser
                85                  90                  95

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Gln Leu
145                 150                 155                 160
```

```
Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly Asp Arg Val Thr
                165                 170                 175


Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190


Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205


Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220


Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240


Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255


Gly Thr Lys Val Glu Ile Lys
            260
```

<210> 1146
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1146

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
```

```
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser
        115


<210> 1147
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1147
Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
```

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1148
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1148
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agctggtcca gtcgggagcc gaagtcaaga agcccggcgc tagcgtgaaa 120

gtgtcctgca aagcctccgg gtacacattc acctcctact ggatgaattg ggtcagacag 180

gcgcccggcc agggactcga gtggatggga aggattgatc cttacgactc cgaaacccat 240

tacaaccaga agttcaagga ccgcgtgacc atgactgtgg ataagtccac ttccaccgct 300

tacatggagc tgtccagcct gcgctccgag gataccgcag tgtactactg cgcccgggga 360

aactgggacg actattgggg acagggaact accgtgaccg tgtcaagcgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcagggggcg gaggaagcga agtggtgctg 480

acccagtcgc ccgcaaccct ctctctgtcg ccgggagaac gcgccactct ttcctgtcgg 540

gcgtccaaga gcatctcaaa ggacctcgcc tggtaccagc agaagcctgg tcaagccccg 600

cggctgctga tctactccgg ctccacgctg caatcaggaa tcccagccag attttccggt 660

tcggggtcgg ggactgactt caccttgacc attagctcgc tggaacctga ggacttcgcc 720

gtgtattact gccagcagca caacaagtac ccgtacacct tcggaggcgg tactaaggtc 780

gagatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1149
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1149
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

```
Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser
                85                  90                  95

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Val Leu
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220
```

```
Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225                 230                 235                 240


Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255


Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270


Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285


Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300


Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320


Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335


Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350


Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365


Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380


Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400


Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415
```

```
Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430


Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445


Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485


<210> 1150
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1150
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30


Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45


Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60
```

```
Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80


Tyr Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser
                85                  90                  95


Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110


Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125


Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Val Leu
145                 150                 155                 160


Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175


Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190


Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205


Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220


Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225                 230                 235                 240


Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255
```

Gly Thr Lys Val Glu Ile Lys
260

<210> 1151
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1151
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 1152

<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1152
Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1153
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1153

atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agctggtcca gtcgggagcc gaagtcaaga agcccggcgc tagcgtgaaa 120

gtgtcctgca aagcctccgg gtacacattc acctcctact ggatgaattg ggtcagacag 180

gcgcccggcc agggactcga gtggatggga aggattgatc cttacgactc cgaaacccat 240

tacaaccaga agttcaagga ccgcgtgacc atgactgtgg ataagtccac ttccaccgct 300

tacatggagc tgtccagcct gcgctccgag gataccgcag tgtactactg cgcccgggga 360

aactgggacg actattgggg acagggaact accgtgaccg tgtcaagcgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcagggggcg gaggaagcga cgtcgtgatg 480

acccagtcac cggcattcct gtccgtgact cccggagaaa aggtcacgat tacttgccgg 540

gcgtccaaga gcatctccaa ggacctcgcc tggtaccaac agaagccgga ccaggcccct 600

aagctgttga tctactcggg gtccaccctt caatcgggag tgccatcgcg gtttagcggt 660

tcgggttctg ggaccgactt cactttcacc atctcctcac tggaagccga ggatgccgcc 720

acttactact gtcagcagca caacaagtat ccgtacacct tcggaggcgg taccaaagtg 780

gagatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1154
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1154
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65 70 75 80

Tyr Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser
85 90 95

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
115 120 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly

```
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145                 150                 155                 160

Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly Glu Lys Val Thr
                165                 170                 175

Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala
225                 230                 235                 240

Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255

Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
```

325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1155
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1155

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser
                85                  90                  95

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145                 150                 155                 160

Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly Glu Lys Val Thr
                165                 170                 175
```

```
Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190


Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205


Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220


Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala
225                 230                 235                 240


Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255


Gly Thr Lys Val Glu Ile Lys
            260


<210> 1156
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1156
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
```

```
Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser
        115


<210> 1157
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1157
Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1               5                   10                  15


Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala
65 70 75 80

Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1158
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1158
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agctggtcca gtcgggagcc gaagtcaaga agcccggcgc tagcgtgaaa 120

gtgtcctgca aagcctccgg gtacacattc acctcctact ggatgaattg ggtcagacag 180

gcgcccggcc agggactcga gtggatggga aggattgatc cttacgactc cgaaacccat 240

tacaaccaga agttcaagga ccgcgtgacc atgactgtgg ataagtccac ttccaccgct 300

tacatggagc tgtccagcct gcgctccgag gataccgcag tgtactactg cgcccgggga 360

aactgggacg actattgggg acagggaact accgtgaccg tgtcaagcgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcagggggcg gaggaagcga cgtggtcatg 480

actcagtccc cggactcact cgcggtgtcg cttggagaga gagcgaccat caactgtcgg 540

gcctcaaaga gcatcagcaa ggacctggcc tggtaccagc agaagccggg acagccgcca 600

aagctgctga tctactccgg gtccaccttg caatctggtg tccctgaccg gttctccggt 660

tccgggtcgg gtaccgactt cacgctcact atttcgtcgc tgcaagccga agatgtggcc 720

gtgtactatt gccaacagca caacaagtac ccctacactt ttggcggagg caccaaggtg 780

gaaatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1159
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1159
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

```
Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser
                85                  90                  95

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145                 150                 155                 160

Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175

Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
225                 230                 235                 240
```

```
Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255

Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430
```

```
Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445


Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485


<210> 1160
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1160
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30


Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45


Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60


Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80
```

```
Tyr Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser
                85                  90                  95

Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145                 150                 155                 160

Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175

Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
225                 230                 235                 240

Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255

Gly Thr Lys Val Glu Ile Lys
            260
```

<210> 1161
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1161

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser
        115
```

<210> 1162
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1162
Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1163
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1163
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacgtgc agctcaccca gtcgccctca tttctgtcgg cctcagtggg agacagagtg 120

accattactt gtcgggcctc caagagcatc tccaaggacc tggcctggta tcagcagaag 180

ccaggaaagg cgcctaagtt gctcatctac tcggggtcga ccctgcaatc tggcgtgccg 240

tcccggttct ccggttcggg aagcggtacc gaattcaccc ttactatctc ctccctgcaa 300

ccggaggact tcgccaccta ctactgccaa cagcacaaca agtacccgta cactttcggg 360

ggtggcacga aggtcgaaat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagccaagtg cagctggtcc agtcgggagc cgaagtcaag 480

aagcccggcg ctagcgtgaa agtgtcctgc aaagcctccg ggtacacatt cacctcctac 540

tggatgaatt gggtcagaca ggcgcccggc cagggactcg agtggatggg aaggattgat 600

ccttacgact ccgaaaccca ttacaaccag aagttcaagg accgcgtgac catgactgtg 660

gataagtcca cttccaccgc ttacatggag ctgtccagcc tgcgctccga ggataccgca 720

gtgtactact gcgcccgggg aaactgggac gactattggg gacagggaac taccgtgacc 780

gtgtcaagca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1164
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1164

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu
            20                  25                  30

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys
        35                  40                  45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala
    50                  55                  60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65                  70                  75                  80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
```

145 150 155 160

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
165 170 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
180 185 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
195 200 205

Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr
210 215 220

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala
225 230 235 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln

340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1165
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1165
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1   5   10   15

His Ala Ala Arg Pro Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu
            20   25   30

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys
        35   40   45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala
    50   55   60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65   70   75   80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
                85   90   95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His
            100   105   110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115   120   125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145   150   155   160

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
                165   170   175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
            180   185   190

```
Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205


Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr
    210                 215                 220


Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala
225                 230                 235                 240


Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255


Thr Thr Val Thr Val Ser Ser
            260


<210> 1166
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1166
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60
```

```
Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser
        115


<210> 1167
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1167
Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
```

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1168
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1168
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgg tgctgaccca gtcgcccgca accctctctc tgtcgccggg agaacgcgcc 120

actctttcct gtcgggcgtc caagagcatc tcaaaggacc tcgcctggta ccagcagaag 180

cctggtcaag ccccgcggct gctgatctac tccggctcca cgctgcaatc aggaatccca 240

gccagatttt ccggttcggg gtcggggact gacttcacct tgaccattag ctcgctggaa 300

cctgaggact tcgccgtgta ttactgccag cagcacaaca agtacccgta caccttcgga 360

ggcggtacta aggtcgagat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagccaagtg cagctggtcc agtcgggagc cgaagtcaag 480

aagcccggcg ctagcgtgaa agtgtcctgc aaagcctccg ggtacacatt cacctcctac 540

tggatgaatt gggtcagaca ggcgcccggc cagggactcg agtggatggg aaggattgat 600

ccttacgact ccgaaaccca ttacaaccag aagttcaagg accgcgtgac catgactgtg 660

gataagtcca cttccaccgc ttacatggag ctgtccagcc tgcgctccga ggataccgca 720

gtgtactact gcgcccgggg aaactgggac gactattggg gacagggaac taccgtgacc 780

gtgtcaagca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1169
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1169
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys
35 40 45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

```
Pro Arg Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145                 150                 155                 160

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
            180                 185                 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr
    210                 215                 220

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255
```

```
Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445
```

```
Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485
```

<210> 1170
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1170

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30


Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys
        35                  40                  45


Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60


Pro Arg Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro
65                  70                  75                  80


Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95
```

```
Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145                 150                 155                 160

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
            180                 185                 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr
    210                 215                 220

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser
            260
```

<210> 1171
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1171
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 1172
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1172
Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1173
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1173
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacgtcg tgatgaccca gtcaccggca ttcctgtccg tgactcccgg agaaaaggtc 120

acgattactt gccgggcgtc caagagcatc tccaaggacc tcgcctggta ccaacagaag 180

ccggaccagg cccctaagct gttgatctac tcggggtcca cccttcaatc gggagtgcca 240

tcgcggttta gcggttcggg ttctgggacc gacttcactt tcaccatctc ctcactggaa 300

gccgaggatg ccgccactta ctactgtcag cagcacaaca agtatccgta caccttcgga 360

ggcggtacca aagtggagat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagccaagtg cagctggtcc agtcgggagc cgaagtcaag 480

aagcccggcg ctagcgtgaa agtgtcctgc aaagcctccg ggtacacatt cacctcctac 540

tggatgaatt gggtcagaca ggcgcccggc cagggactcg agtggatggg aaggattgat 600

ccttacgact ccgaaaccca ttacaaccag aagttcaagg accgcgtgac catgactgtg 660

gataagtcca cttccaccgc ttacatggag ctgtccagcc tgcgctccga ggataccgca 720

gtgtactact gcgcccgggg aaactgggac gactattggg gacagggaac taccgtgacc 780

gtgtcaagca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1174
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1174
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu
20 25 30

Ser Val Thr Pro Gly Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys
35 40 45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala
50 55 60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65 70 75 80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
85 90 95

Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His
100 105 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145 150 155 160

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr

```
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
            180                 185                 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr
    210                 215                 220

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
```

355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1175
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1175
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu
            20                  25                  30

Ser Val Thr Pro Gly Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys
        35                  40                  45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala
    50                  55                  60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65                  70                  75                  80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
                85                  90                  95

Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145                 150                 155                 160

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
            180                 185                 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205
```

```
Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr
    210                 215                 220

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser
            260
```

<210> 1176
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1176

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
```

```
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser
        115


<210> 1177
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1177
Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1               5                   10                  15


Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala
65                  70                  75                  80


Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
                85                  90                  95
```

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1178
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1178
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacgtgg tcatgactca gtccccggac tcactcgcgg tgtcgcttgg agagagagcg 120

accatcaact gtcgggcctc aaagagcatc agcaaggacc tggcctggta ccagcagaag 180

ccgggacagc cgccaaagct gctgatctac tccgggtcca ccttgcaatc tggtgtccct 240

gaccggttct ccggttccgg gtcgggtacc gacttcacgc tcactatttc gtcgctgcaa 300

gccgaagatg tggccgtgta ctattgccaa cagcacaaca agtaccccta cacttttggc 360

ggaggcacca aggtggaaat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagccaagtg cagctggtcc agtcgggagc cgaagtcaag 480

aagcccggcg ctagcgtgaa agtgtcctgc aaagcctccg ggtacacatt cacctcctac 540

tggatgaatt gggtcagaca ggcgcccggc cagggactcg agtggatggg aaggattgat 600

ccttacgact ccgaaaccca ttacaaccag aagttcaagg accgcgtgac catgactgtg 660

gataagtcca cttccaccgc ttacatggag ctgtccagcc tgcgctccga ggataccgca 720

gtgtactact gcgcccgggg aaactgggac gactattggg gacagggaac taccgtgacc 780

gtgtcaagca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1179
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1179
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu
20 25 30

Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys
35 40 45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro
50 55 60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65 70 75 80

```
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145                 150                 155                 160

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
            180                 185                 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr
    210                 215                 220

Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270
```

```
Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460
```

```
Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485


<210> 1180
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1180
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu
            20                  25                  30


Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys
        35                  40                  45


Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro
    50                  55                  60


Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65                  70                  75                  80


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95


Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110
```

```
Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140


Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145                 150                 155                 160


Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175


Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
            180                 185                 190


Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205


Asn Gln Lys Phe Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr
    210                 215                 220


Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala
225                 230                 235                 240


Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255


Thr Thr Val Thr Val Ser Ser
            260
```

<210> 1181
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polypeptide"

<400> 1181

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Val Thr Met Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser
        115
```

<210> 1182
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1182

```
Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15
```

```
Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65                  70                  75                  80

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 1183
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1183

```
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg       60

ccccaagtgc agctggtgca gtcaggcagc gaactgaaga agcccggagc ctccgtcaaa      120

gtgtcctgca aagcctcggg atacaccttc acctcctact ggatgaactg ggtccgccag      180

gcacctggac aggggctgga gtggatggga aggatcgatc cctacgattc cgaaacccat      240

tacaatcaga agttcaagga ccggtttgtg ttctccgtgg acaagtccgt gtccaccgcc      300

tacctccaaa ttagcagcct gaaggcggag gatacagctg tctactactg cgctcgcgga      360
```

aactgggatg actattgggg ccagggaact accgtgactg tgtcctccgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcaggggggcg gaggaagcga cgtgcagctc 480

acccagtcgc cctcatttct gtcggcctca gtgggagaca gagtgaccat tacttgtcgg 540

gcctccaaga gcatctccaa ggacctggcc tggtatcagc agaagccagg aaaggcgcct 600

aagttgctca tctactcggg gtcgaccctg caatctggcg tgccgtcccg gttctccggt 660

tcgggaagcg gtaccgaatt cacccttact atctcctccc tgcaaccgga ggacttcgcc 720

acctactact gccaacagca caacaagtac ccgtacactt tcgggggtgg cacgaaggtc 780

gaaatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1184
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polypeptide"

<400> 1184

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser
                85                  90                  95

Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Gln Leu
145                 150                 155                 160

Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly Asp Arg Val Thr
                165                 170                 175

Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
```

180 185 190

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
195 200 205

Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225 230 235 240

Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
245 250 255

Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala

370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1185
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1185
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu
20 25 30

```
Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser
                85                  90                  95

Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Gln Leu
145                 150                 155                 160

Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly Asp Arg Val Thr
                165                 170                 175

Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220
```

```
Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240


Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255


Gly Thr Lys Val Glu Ile Lys
            260


<210> 1186
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1186
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser
        115


<210> 1187
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1187
Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 1188
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1188
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agctggtgca gtcaggcagc gaactgaaga agcccggagc ctccgtcaaa 120

gtgtcctgca aagcctcggg atacaccttc acctcctact ggatgaactg ggtccgccag 180

gcacctggac aggggctgga gtggatggga aggatcgatc cctacgattc cgaaacccat 240

tacaatcaga agttcaagga ccggtttgtg ttctccgtgg acaagtccgt gtccaccgcc 300

tacctccaaa ttagcagcct gaaggcggag gatacagctg tctactactg cgctcgcgga 360

aactgggatg actattgggg ccagggaact accgtgactg tgtcctccgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcaggggcg gaggaagcga agtggtgctg 480

acccagtcgc ccgcaaccct ctctctgtcg ccgggagaac gcgccactct ttcctgtcgg 540

gcgtccaaga gcatctcaaa ggacctcgcc tggtaccagc agaagcctgg tcaagccccg 600

cggctgctga tctactccgg ctccacgctg caatcaggaa tcccagccag attttccggt 660

tcggggtcgg ggactgactt caccttgacc attagctcgc tggaacctga ggacttcgcc 720

gtgtattact gccagcagca caacaagtac ccgtacacct tcggaggcgg tactaaggtc 780

gagatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1189
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1189
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65 70 75 80

Tyr Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser
85 90 95

```
Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Val Leu
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255

Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285
```

```
Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480
```

Gln Ala Leu Pro Pro Arg
485

<210> 1190
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1190
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65 70 75 80

Tyr Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser
85 90 95

Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
115 120 125

```
Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Val Leu
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255

Gly Thr Lys Val Glu Ile Lys
            260
```

<210> 1191
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1191

```
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
```

1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 1192
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1192
Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

```
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> 1193
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polynucleotide"

<400> 1193
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg       60

ccccaagtgc agctggtgca gtcaggcagc gaactgaaga agcccggagc ctccgtcaaa      120

gtgtcctgca aagcctcggg atacaccttc acctcctact ggatgaactg ggtccgccag      180

gcacctggac aggggctgga gtggatggga aggatcgatc cctacgattc cgaaacccat      240

tacaatcaga agttcaagga ccggtttgtg ttctccgtgg acaagtccgt gtccaccgcc      300

tacctccaaa ttagcagcct gaaggcggag gatacagctg tctactactg cgctcgcgga      360

aactgggatg actattgggg ccagggaact accgtgactg tgtcctccgg gggtggcggt      420

agcggaggag ggggctccgg cggcggcggc tcaggggggcg gaggaagcga cgtcgtgatg      480
```

acccagtcac cggcattcct gtccgtgact cccggagaaa aggtcacgat tacttgccgg 540

gcgtccaaga gcatctccaa ggacctcgcc tggtaccaac agaagccgga ccaggcccct 600

aagctgttga tctactcggg gtccaccctt caatcgggag tgccatcgcg gtttagcggt 660

tcgggttctg ggaccgactt cactttcacc atctcctcac tggaagccga ggatgccgcc 720

acttactact gtcagcagca caacaagtat ccgtacacct tcggaggcgg taccaaagtg 780

gagatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1194
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1194
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu

```
1               5                   10                  15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu
            20                  25                  30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser
                85                  90                  95

Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145                 150                 155                 160

Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly Glu Lys Val Thr
                165                 170                 175

Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
```

195 200 205

Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala
225 230 235 240

Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
245 250 255

Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu

385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1195
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1195
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

```
Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
    50                  55                  60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser
                85                  90                  95

Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145                 150                 155                 160

Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly Glu Lys Val Thr
                165                 170                 175

Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala
225                 230                 235                 240
```

```
Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255


Gly Thr Lys Val Glu Ile Lys
            260


<210> 1196
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1196
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110
```

Val Ser Ser
        115

<210> 1197
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1197
Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1   5   10   15

Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala
65   70   75   80

Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 1198
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1198
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

ccccaagtgc agctggtgca gtcaggcagc gaactgaaga agcccggagc ctccgtcaaa 120

gtgtcctgca aagcctcggg atacaccttc acctcctact ggatgaactg ggtccgccag 180

gcacctggac aggggctgga gtggatggga aggatcgatc cctacgattc cgaaacccat 240

tacaatcaga agttcaagga ccggtttgtg ttctccgtgg acaagtccgt gtccaccgcc 300

tacctccaaa ttagcagcct gaaggcggag gatacagctg tctactactg cgctcgcgga 360

aactgggatg actattgggg ccagggaact accgtgactg tgtcctccgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcaggggggcg gaggaagcga cgtggtcatg 480

actcagtccc cggactcact cgcggtgtcg cttggagaga gagcgaccat caactgtcgg 540

gcctcaaaga gcatcagcaa ggacctggcc tggtaccagc agaagccggg acagccgcca 600

aagctgctga tctactccgg gtccaccttg caatctggtg tccctgaccg gttctccggt 660

tccgggtcgg gtaccgactt cacgctcact atttcgtcgc tgcaagccga agatgtggcc 720

gtgtactatt gccaacagca caacaagtac ccctacactt ttggcggagg caccaaggtg 780

gaaatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1199
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1199
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65 70 75 80

Tyr Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser
85 90 95

Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr
100 105 110

```
Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145                 150                 155                 160

Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175

Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
225                 230                 235                 240

Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255

Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300
```

```
Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320


Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335


Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350


Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365


Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380


Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400


Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415


Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430


Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445


Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485
```

<210> 1200
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1200
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu
20 25 30

Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln
50 55 60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65 70 75 80

Tyr Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser
85 90 95

Val Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
115 120 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145 150 155 160

Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
165 170 175

Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
180 185 190

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ser Gly Ser
195 200 205

Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
225 230 235 240

Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
245 250 255

Gly Thr Lys Val Glu Ile Lys
260

<210> 1201
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1201
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr

20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 1202
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1202
Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1203
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1203
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacgtgc agctcaccca gtcgccctca tttctgtcgg cctcagtggg agacagagtg 120

accattactt gtcgggcctc caagagcatc tccaaggacc tggcctggta tcagcagaag 180

ccaggaaagg cgcctaagtt gctcatctac tcggggtcga ccctgcaatc tggcgtgccg 240

tcccggttct ccggttcggg aagcggtacc gaattcaccc ttactatctc ctccctgcaa 300

ccggaggact tcgccaccta ctactgccaa cagcacaaca agtacccgta cactttcggg 360

ggtggcacga aggtcgaaat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagccaagtg cagctggtgc agtcaggcag cgaactgaag 480

aagcccggag cctccgtcaa agtgtcctgc aaagcctcgg gatacacctt cacctcctac 540

tggatgaact gggtccgcca ggcacctgga caggggctgg agtggatggg aaggatcgat 600

ccctacgatt ccgaaaccca ttacaatcag aagttcaagg accggtttgt gttctccgtg 660

gacaagtccg tgtccaccgc ctacctccaa attagcagcc tgaaggcgga ggatacagct 720

gtctactact gcgctcgcgg aaactgggat gactattggg gccagggaac taccgtgact 780

gtgtcctcca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1204
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1204
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu

```
            20                  25                  30

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys
        35                  40                  45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala
    50                  55                  60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65                  70                  75                  80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys
145                 150                 155                 160

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
            180                 185                 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val
```

210 215 220

Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala
225 230 235 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp

405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1205
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1205
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu
20 25 30

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys
35 40 45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala
50 55 60

```
Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65                  70                  75                  80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys
145                 150                 155                 160

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
            180                 185                 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val
    210                 215                 220

Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255
```

Thr Thr Val Thr Val Ser Ser
260

<210> 1206
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1206
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 1207
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1207
Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1208
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

polynucleotide"

<400> 1208

atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgg tgctgaccca gtcgcccgca accctctctc tgtcgccggg agaacgcgcc 120

actctttcct gtcgggcgtc caagagcatc tcaaaggacc tcgcctggta ccagcagaag 180

cctggtcaag ccccgcggct gctgatctac tccggctcca cgctgcaatc aggaatccca 240

gccagatttt ccggttcggg gtcggggact gacttcacct tgaccattag ctcgctggaa 300

cctgaggact tcgccgtgta ttactgccag cagcacaaca agtacccgta caccttcgga 360

ggcggtacta aggtcgagat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagccaagtg cagctggtgc agtcaggcag cgaactgaag 480

aagcccggag cctccgtcaa agtgtcctgc aaagcctcgg gatacacctt cacctcctac 540

tggatgaact gggtccgcca ggcacctgga caggggctgg agtggatggg aaggatcgat 600

ccctacgatt ccgaaaccca ttacaatcag aagttcaagg accggtttgt gttctccgtg 660

gacaagtccg tgtccaccgc ctacctccaa attagcagcc tgaaggcgga ggatacagct 720

gtctactact gcgctcgcgg aaactgggat gactattggg gccagggaac taccgtgact 780

gtgtcctcca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1209
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1209
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys
35 40 45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
85 90 95

Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His
100 105 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
115 120 125

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys
145                 150                 155                 160

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
            180                 185                 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val
    210                 215                 220

Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320
```

```
Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg
                485
```

<210> 1210
<211> 263
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1210

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Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15


His Ala Ala Arg Pro Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30


Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys
        35                  40                  45


Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60


Pro Arg Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro
65                  70                  75                  80


Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95


Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110


Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140


Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys
145                 150                 155                 160
```

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
165 170 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
180 185 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
195 200 205

Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val
210 215 220

Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala
225 230 235 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Thr Val Thr Val Ser Ser
260

<210> 1211
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1211
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 1212
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1212
Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1213
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1213
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacgtcg tgatgaccca gtcaccggca ttcctgtccg tgactcccgg agaaaaggtc 120

acgattactt gccgggcgtc caagagcatc tccaaggacc tcgcctggta ccaacagaag 180

ccggaccagg cccctaagct gttgatctac tcggggtcca cccttcaatc gggagtgcca 240

tcgcggttta gcggttcggg ttctgggacc gacttcactt tcaccatctc ctcactggaa 300

gccgaggatg ccgccactta ctactgtcag cagcacaaca agtatccgta caccttcgga 360

ggcggtacca aagtggagat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagccaagtg cagctggtgc agtcaggcag cgaactgaag 480

aagcccggag cctccgtcaa agtgtcctgc aaagcctcgg gatacacctt cacctcctac 540

tggatgaact gggtccgcca ggcacctgga caggggctgg agtggatggg aaggatcgat 600

ccctacgatt ccgaaaccca ttacaatcag aagttcaagg accggtttgt gttctccgtg 660

gacaagtccg tgtccaccgc ctacctccaa attagcagcc tgaaggcgga ggatacagct 720

gtctactact gcgctcgcgg aaactgggat gactattggg gccagggaac taccgtgact 780

gtgtcctcca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1214
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1214
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu
20 25 30

Ser Val Thr Pro Gly Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys

```
        35                  40                  45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala
    50                  55                  60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65                  70                  75                  80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
                85                  90                  95

Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys
145                 150                 155                 160

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
            180                 185                 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val
    210                 215                 220

Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala
```

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225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
```

420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1215
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1215
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu
20 25 30

Ser Val Thr Pro Gly Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys
35 40 45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala
50 55 60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65 70 75 80

```
Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
                85                  90                  95

Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys
145                 150                 155                 160

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
            180                 185                 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val
    210                 215                 220

Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser
            260
```

<210> 1216
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1216
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 1217
<211> 107
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1217

Asp	Val	Val	Met	Thr	Gln	Ser	Pro	Ala	Phe	Leu	Ser	Val	Thr	Pro	Gly
1				5				10					15		
Glu	Lys	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Lys	Ser	Ile	Ser	Lys	Asp
			20					25					30		
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Asp	Gln	Ala	Pro	Lys	Leu	Leu	Ile
		35					40					45			
Tyr	Ser	Gly	Ser	Thr	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Phe	Thr	Ile	Ser	Ser	Leu	Glu	Ala
65				70					75					80	
Glu	Asp	Ala	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	His	Asn	Lys	Tyr	Pro	Tyr
			85					90					95		
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
		100					105								

<210> 1218
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1218
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacgtgg tcatgactca gtccccggac tcactcgcgg tgtcgcttgg agagagagcg 120

accatcaact gtcgggcctc aaagagcatc agcaaggacc tggcctggta ccagcagaag 180

ccgggacagc cgccaaagct gctgatctac tccgggtcca ccttgcaatc tggtgtccct 240

gaccggttct ccggttccgg gtcgggtacc gacttcacgc tcactatttc gtcgctgcaa 300

gccgaagatg tggccgtgta ctattgccaa cagcacaaca agtaccccta cacttttggc 360

ggaggcacca aggtggaaat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagccaagtg cagctggtgc agtcaggcag cgaactgaag 480

aagcccggag cctccgtcaa agtgtcctgc aaagcctcgg gatacacctt cacctcctac 540

tggatgaact gggtccgcca ggcacctgga caggggctgg agtggatggg aaggatcgat 600

ccctacgatt ccgaaaccca ttacaatcag aagttcaagg accggtttgt gttctccgtg 660

gacaagtccg tgtccaccgc ctacctccaa attagcagcc tgaaggcgga ggatacagct 720

gtctactact gcgctcgcgg aaactgggat gactattggg gccagggaac taccgtgact 780

gtgtcctcca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1219
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1219
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu
20 25 30

Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys
35 40 45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro
50 55 60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65 70 75 80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His
100 105 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

```
Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys
145                 150                 155                 160


Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175


Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
            180                 185                 190


Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205


Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val
    210                 215                 220


Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala
225                 230                 235                 240


Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255


Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270


Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285


Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300


Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320


Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335
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Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg
                485
```

<210> 1220
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1220

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu
            20                  25                  30

Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys
        35                  40                  45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro
    50                  55                  60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65                  70                  75                  80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys
145                 150                 155                 160

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
                165                 170                 175
```

```
Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
            180                 185                 190


Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205


Asn Gln Lys Phe Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val
    210                 215                 220


Ser Thr Ala Tyr Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala
225                 230                 235                 240


Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255


Thr Thr Val Thr Val Ser Ser
            260
```

<210> 1221
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1221

```
Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1               5                   10                  15


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45


Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
```

50 55 60

Lys Asp Arg Phe Val Phe Ser Val Asp Lys Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 1222
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1222
Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1223
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1223
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaggtgc agctggtgca gagcggagcc gaggtcaaga agcctggaga atccctgagg 120

atcagctgca aaggcagcgg gtataccttc acctcctact ggatgaattg ggtccgccag 180

atgcccggaa aaggcctgga gtggatggga cggattgacc cctacgactc ggaaacccat 240

tacaaccaga agttcaagga tcacgtgacc atctccgtgg acaagtccat ttccactgcg 300

tacctccagt ggtcaagcct gaaggcctcc gacactgcta tgtactactg cgcacgcgga 360

aactgggatg attactgggg acagggaaca accgtgactg tgtcctccgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcaggggggcg gaggaagcga cgtgcagctc 480

acccagtcgc cctcatttct gtcggcctca gtgggagaca gagtgaccat tacttgtcgg 540

gcctccaaga gcatctccaa ggacctggcc tggtatcagc agaagccagg aaaggcgcct 600

aagttgctca tctactcggg gtcgaccctg caatctggcg tgccgtcccg gttctccggt 660

tcgggaagcg gtaccgaatt cacccttact atctcctccc tgcaaccgga ggacttcgcc 720

acctactact gccaacagca caacaagtac ccgtacactt tcgggggtgg cacgaaggtc 780

gaaatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1224
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1224
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys

```
    50                  55                  60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser
                85                  90                  95

Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr
            100                 105                 110

Ala Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Gln Leu
145                 150                 155                 160

Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly Asp Arg Val Thr
                165                 170                 175

Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240

Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
```

245 250 255

Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile

435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1225
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1225
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys
50 55 60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65 70 75 80

Tyr Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser
85 90 95

```
Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr
            100                 105                 110

Ala Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Gln Leu
145                 150                 155                 160

Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly Asp Arg Val Thr
                165                 170                 175

Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240

Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255

Gly Thr Lys Val Glu Ile Lys
            260
```

<210> 1226
<211> 115

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1226
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 1227
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1227
Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1228
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1228
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaggtgc agctggtgca gagcggagcc gaggtcaaga agcctggaga atccctgagg 120

atcagctgca aaggcagcgg gtataccttc acctcctact ggatgaattg ggtccgccag 180

atgcccggaa aaggcctgga gtggatggga cggattgacc cctacgactc ggaaacccat 240

tacaaccaga agttcaagga tcacgtgacc atctccgtgg acaagtccat ttccactgcg 300

tacctccagt ggtcaagcct gaaggcctcc gacactgcta tgtactactg cgcacgcgga 360

aactgggatg attactgggg acagggaaca accgtgactg tgtcctccgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcaggggcg gaggaagcga agtggtgctg 480

acccagtcgc ccgcaaccct ctctctgtcg ccgggagaac gcgccactct ttcctgtcgg 540

gcgtccaaga gcatctcaaa ggacctcgcc tggtaccagc agaagcctgg tcaagccccg 600

cggctgctga tctactccgg ctccacgctg caatcaggaa tcccagccag attttccggt 660

tcggggtcgg ggactgactt caccttgacc attagctcgc tggaacctga ggacttcgcc 720

gtgtattact gccagcagca caacaagtac ccgtacacct tcggaggcgg tactaaggtc 780

gagatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1229
<211> 486

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1229

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15


His Ala Ala Arg Pro Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30


Lys Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr
        35                  40                  45


Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys
    50                  55                  60


Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80


Tyr Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser
                85                  90                  95


Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr
            100                 105                 110


Ala Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125


Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Val Leu
145                 150                 155                 160
```

```
Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225                 230                 235                 240

Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255

Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350
```

```
Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365


Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380


Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400


Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415


Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430


Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445


Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485
```

<210> 1230
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1230

N2067-7072WO_SL (1)

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser
                85                  90                  95

Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr
            100                 105                 110

Ala Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Val Leu
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190
```

```
Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205


Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220


Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225                 230                 235                 240


Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255


Gly Thr Lys Val Glu Ile Lys
            260
```

<210> 1231
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1231

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15


Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45


Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
```

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 1232
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1232
Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1233
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1233
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaggtgc agctggtgca gagcggagcc gaggtcaaga agcctggaga atccctgagg 120

atcagctgca aaggcagcgg gtataccttc acctcctact ggatgaattg ggtccgccag 180

atgcccggaa aaggcctgga gtggatggga cggattgacc cctacgactc ggaaacccat 240

tacaaccaga agttcaagga tcacgtgacc atctccgtgg acaagtccat ttccactgcg 300

tacctccagt ggtcaagcct gaaggcctcc gacactgcta tgtactactg cgcacgcgga 360

aactgggatg attactgggg acagggaaca accgtgactg tgtcctccgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcaggggggcg gaggaagcga cgtcgtgatg 480

acccagtcac cggcattcct gtccgtgact cccggagaaa aggtcacgat tacttgccgg 540

gcgtccaaga gcatctccaa ggacctcgcc tggtaccaac agaagccgga ccaggccct 600

aagctgttga tctactcggg gtccaccctt caatcgggag tgccatcgcg gtttagcggt 660

tcgggttctg ggaccgactt cactttcacc atctcctcac tggaagccga ggatgccgcc 720

acttactact gtcagcagca caacaagtat ccgtacacct tcggaggcgg taccaaagtg 780

gagatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1234
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1234
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys
50 55 60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His

65 70 75 80

Tyr Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser
85 90 95

Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr
100 105 110

Ala Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
115 120 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145 150 155 160

Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly Glu Lys Val Thr
165 170 175

Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
180 185 190

Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
195 200 205

Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala
225 230 235 240

Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
245 250 255

Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro

```
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
```

450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1235
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1235
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val
20 25 30

Lys Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys
50 55 60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65 70 75 80

Tyr Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser
85 90 95

Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr
100 105 110

```
Ala Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145                 150                 155                 160

Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly Glu Lys Val Thr
                165                 170                 175

Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala
225                 230                 235                 240

Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255

Gly Thr Lys Val Glu Ile Lys
            260
```

<210> 1236
<211> 115
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1236

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 1237
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1237

```
Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1               5                  10                  15

Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala
65                  70                  75                  80

Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 1238
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1238

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atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg       60

cccgaggtgc agctggtgca gagcggagcc gaggtcaaga agcctggaga atccctgagg      120

atcagctgca aaggcagcgg gtataccttc acctcctact ggatgaattg ggtccgccag      180

atgcccggaa aaggcctgga gtggatggga cggattgacc cctacgactc ggaaacccat      240

tacaaccaga agttcaagga tcacgtgacc atctccgtgg acaagtccat ttccactgcg      300
```

tacctccagt ggtcaagcct gaaggcctcc gacactgcta tgtactactg cgcacgcgga 360

aactgggatg attactgggg acagggaaca accgtgactg tgtcctccgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcaggggggcg gaggaagcga cgtggtcatg 480

actcagtccc cggactcact cgcggtgtcg cttggagaga gagcgaccat caactgtcgg 540

gcctcaaaga gcatcagcaa ggacctggcc tggtaccagc agaagccggg acagccgcca 600

aagctgctga tctactccgg gtccaccttg caatctggtg tccctgaccg gttctccggt 660

tccgggtcgg gtaccgactt cacgctcact atttcgtcgc tgcaagccga agatgtggcc 720

gtgtactatt gccaacagca caacaagtac ccctacactt ttggcggagg caccaaggtg 780

gaaatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1239
<211> 486
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1239

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser
                85                  90                  95

Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr
            100                 105                 110

Ala Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145                 150                 155                 160

Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175
```

```
Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
225                 230                 235                 240

Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255

Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365
```

```
Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480

Gln Ala Leu Pro Pro Arg
                485
```

<210> 1240
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1240

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15
```

```
His Ala Ala Arg Pro Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val
            20                  25                  30

Lys Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser
                85                  90                  95

Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr
            100                 105                 110

Ala Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145                 150                 155                 160

Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175

Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205
```

Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
225 230 235 240

Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
245 250 255

Gly Thr Lys Val Glu Ile Lys
260

<210> 1241
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1241
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 1242
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1242
Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1243
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1243
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacgtgc agctcaccca gtcgccctca tttctgtcgg cctcagtggg agacagagtg 120

accattactt gtcgggcctc caagagcatc tccaaggacc tggcctggta tcagcagaag 180

ccaggaaagg cgcctaagtt gctcatctac tcggggtcga ccctgcaatc tggcgtgccg 240

tcccggttct ccggttcggg aagcggtacc gaattcaccc ttactatctc ctccctgcaa 300

ccggaggact tcgccaccta ctactgccaa cagcacaaca agtacccgta cactttcggg 360

ggtggcacga aggtcgaaat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagcgaggtg cagctggtgc agagcggagc cgaggtcaag 480

aagcctggag aatccctgag gatcagctgc aaaggcagcg ggtatacctt cacctcctac 540

tggatgaatt gggtccgcca gatgcccgga aaaggcctgg agtggatggg acggattgac 600

ccctacgact cggaaaccca ttacaaccag aagttcaagg atcacgtgac catctccgtg 660

gacaagtcca tttccactgc gtacctccag tggtcaagcc tgaaggcctc cgacactgct 720

atgtactact gcgcacgcgg aaactgggat gattactggg gacagggaac aaccgtgact 780

gtgtcctcca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1244
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1244
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu
20 25 30

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys
35 40 45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala
50 55 60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65 70 75 80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile

85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His
100 105 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145 150 155 160

Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr
165 170 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly
180 185 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
195 200 205

Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile
210 215 220

Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala
225 230 235 240

Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu

275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met

465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1245
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1245
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu
20 25 30

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys
35 40 45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala
50 55 60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65 70 75 80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
85 90 95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His
100 105 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
115 120 125

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145                 150                 155                 160

Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile
    210                 215                 220

Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala
225                 230                 235                 240

Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser
            260
```

<210> 1246
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1246
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 1247
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1247
Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1248
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1248
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgg tgctgaccca gtcgcccgca accctctctc tgtcgccggg agaacgcgcc 120

actctttcct gtcgggcgtc caagagcatc tcaaaggacc tcgcctggta ccagcagaag 180

cctggtcaag ccccgcggct gctgatctac tccggctcca cgctgcaatc aggaatccca 240

gccagatttt ccggttcggg gtcggggact gacttcacct tgaccattag ctcgctggaa 300

cctgaggact tcgccgtgta ttactgccag cagcacaaca agtacccgta caccttcgga 360

ggcggtacta aggtcgagat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagcgaggtg cagctggtgc agagcggagc cgaggtcaag 480

aagcctggag aatccctgag gatcagctgc aaaggcagcg ggtatacctt cacctcctac 540

tggatgaatt gggtccgcca gatgcccgga aaaggcctgg agtggatggg acggattgac 600

ccctacgact cggaaaccca ttacaaccag aagttcaagg atcacgtgac catctccgtg 660

gacaagtcca tttccactgc gtacctccag tggtcaagcc tgaaggcctc cgacactgct 720

atgtactact gcgcacgcgg aaactgggat gattactggg gacagggaac aaccgtgact 780

gtgtcctcca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1249
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1249

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys
        35                  40                  45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145                 150                 155                 160

Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly
            180                 185                 190
```

```
Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile
    210                 215                 220

Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala
225                 230                 235                 240

Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380
```

```
Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400


Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415


Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430


Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445


Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485


<210> 1250
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1250
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30
```

```
Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys
        35                  40                  45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

Pro Arg Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145                 150                 155                 160

Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile
    210                 215                 220
```

Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala
225 230 235 240

Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Thr Val Thr Val Ser Ser
260

<210> 1251
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1251
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr

100 105 110

Val Ser Ser
115

<210> 1252
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1252
Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1253
<211> 1458

<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1253
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacgtcg tgatgaccca gtcaccggca ttcctgtccg tgactcccgg agaaaaggtc 120

acgattactt gccgggcgtc caagagcatc tccaaggacc tcgcctggta ccaacagaag 180

ccggaccagg cccctaagct gttgatctac tcggggtcca cccttcaatc gggagtgcca 240

tcgcggttta gcggttcggg ttctgggacc gacttcactt tcaccatctc ctcactggaa 300

gccgaggatg ccgccactta ctactgtcag cagcacaaca agtatccgta caccttcgga 360

ggcggtacca aagtggagat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagcgaggtg cagctggtgc agagcggagc cgaggtcaag 480

aagcctggag aatccctgag gatcagctgc aaaggcagcg ggtatacctt cacctcctac 540

tggatgaatt gggtccgcca gatgcccgga aaaggcctgg agtggatggg acggattgac 600

ccctacgact cggaaaccca ttacaaccag aagttcaagg atcacgtgac catctccgtg 660

gacaagtcca tttccactgc gtacctccag tggtcaagcc tgaaggcctc cgacactgct 720

atgtactact gcgcacgcgg aaactgggat gattactggg gacagggaac aaccgtgact 780

gtgtcctcca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1254
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1254
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu
20 25 30

Ser Val Thr Pro Gly Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys
35 40 45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala
50 55 60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65 70 75 80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
85 90 95

Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His

100 105 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

Gly Gly Gly Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145 150 155 160

Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr
165 170 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly
180 185 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
195 200 205

Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile
210 215 220

Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala
225 230 235 240

Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp

290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg

485

<210> 1255
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1255
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu
20 25 30

Ser Val Thr Pro Gly Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys
35 40 45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala
50 55 60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65 70 75 80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
85 90 95

Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His
100 105 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
130 135 140

```
Gly Gly Gly Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145                 150                 155                 160


Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr
                165                 170                 175


Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly
            180                 185                 190


Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205


Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile
    210                 215                 220


Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala
225                 230                 235                 240


Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255


Thr Thr Val Thr Val Ser Ser
            260


<210> 1256
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1256
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15
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```
Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45


Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser
        115


<210> 1257
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1257
Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1               5                   10                  15


Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20                  25                  30
```

Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala
65 70 75 80

Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1258
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1258
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacgtgg tcatgactca gtccccggac tcactcgcgg tgtcgcttgg agagagagcg 120

accatcaact gtcgggcctc aaagagcatc agcaaggacc tggcctggta ccagcagaag 180

ccgggacagc cgccaaagct gctgatctac tccgggtcca ccttgcaatc tggtgtccct 240

gaccggttct ccggttccgg gtcgggtacc gacttcacgc tcactatttc gtcgctgcaa 300

gccgaagatg tggccgtgta ctattgccaa cagcacaaca agtaccccta cacttttggc 360

ggaggcacca aggtggaaat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagcgaggtg cagctggtgc agagcggagc cgaggtcaag 480

aagcctggag aatccctgag gatcagctgc aaaggcagcg ggtatacctt cacctcctac 540

tggatgaatt gggtccgcca gatgcccgga aaaggcctgg agtggatggg acggattgac 600

ccctacgact cggaaaccca ttacaaccag aagttcaagg atcacgtgac catctccgtg 660

gacaagtcca tttccactgc gtacctccag tggtcaagcc tgaaggcctc cgacactgct 720

atgtactact gcgcacgcgg aaactgggat gattactggg gacagggaac aaccgtgact 780

gtgtcctcca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1259
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1259
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu
            20                  25                  30

Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys
        35                  40                  45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro
    50                  55                  60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65                  70                  75                  80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145                 150                 155                 160

Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205
```

```
Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile
    210                 215                 220

Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala
225                 230                 235                 240

Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400
```

```
Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415


Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430


Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445


Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485
```

<210> 1260
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1260

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu
            20                  25                  30


Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys
        35                  40                  45
```

```
Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro
    50                  55                  60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65                  70                  75                  80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
145                 150                 155                 160

Lys Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly
            180                 185                 190

Leu Glu Trp Met Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile
    210                 215                 220

Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala
225                 230                 235                 240
```

Met Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
245 250 255

Thr Thr Val Thr Val Ser Ser
260

<210> 1261
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1261
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp His Val Thr Ile Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser

115

<210> 1262
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1262
Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1263
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1263
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agctcgtcga gagcggaggg ggactggtgc agcccggagg aagcctgagg 120

ctgtcctgcg ctgcctccgg ctacaccttc acctcctact ggatgaactg ggtcagacag 180

gcacctggaa agggactggt ctgggtgtcg cgcattgacc cctacgactc cgaaacccat 240

tacaatcaga aattcaagga ccgcttcacc atctccgtgg acaaagccaa gagcaccgcg 300

tacctccaaa tgaactccct gcgcgctgag gatacagcag tgtactattg cgcccgggga 360

aactgggatg attactgggg ccagggaact actgtgactg tgtcatccgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcagggggcg gaggaagcga cgtgcagctc 480

acccagtcgc cctcatttct gtcggcctca gtgggagaca gagtgaccat tacttgtcgg 540

gcctccaaga gcatctccaa ggacctggcc tggtatcagc agaagccagg aaaggcgcct 600

aagttgctca tctactcggg gtcgaccctg caatctggcg tgccgtcccg gttctccggt 660

tcgggaagcg gtaccgaatt cacccttact atctcctccc tgcaaccgga ggacttcgcc 720

acctactact gccaacagca caacaagtac ccgtacactt tcgggggtgg cacgaaggtc 780

gaaatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1264
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1264
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65 70 75 80

Tyr Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala
85 90 95

Lys Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln

115 120 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
130 135 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Gln Leu
145 150 155 160

Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly Asp Arg Val Thr
165 170 175

Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
180 185 190

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
195 200 205

Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
210 215 220

Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225 230 235 240

Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
245 250 255

Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
260 265 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
275 280 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
290 295 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly

305 310 315 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1265

<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1265

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala
                85                  90                  95

Lys Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Gln Leu
145                 150                 155                 160
```

```
Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly Asp Arg Val Thr
                165                 170                 175


Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190


Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205


Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220


Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
225                 230                 235                 240


Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255


Gly Thr Lys Val Glu Ile Lys
            260
```

<210> 1266
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1266

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30
```

```
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val
        35                  40                  45


Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser
        115


<210> 1267
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1267
Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
```

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1268
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1268
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agctcgtcga gagcggaggg ggactggtgc agcccggagg aagcctgagg 120

ctgtcctgcg ctgcctccgg ctacaccttc acctcctact ggatgaactg ggtcagacag 180

gcacctggaa agggactggt ctgggtgtcg cgcattgacc cctacgactc cgaaacccat 240

tacaatcaga aattcaagga ccgcttcacc atctccgtgg acaaagccaa gagcaccgcg 300

tacctccaaa tgaactccct gcgcgctgag gatacagcag tgtactattg cgcccgggga 360

aactgggatg attactgggg ccagggaact actgtgactg tgtcatccgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcagggggcg gaggaagcga agtggtgctg 480

acccagtcgc ccgcaaccct ctctctgtcg ccgggagaac gcgccactct ttcctgtcgg 540

gcgtccaaga gcatctcaaa ggacctcgcc tggtaccagc agaagcctgg tcaagccccg 600

cggctgctga tctactccgg ctccacgctg caatcaggaa tcccagccag attttccggt 660

tcggggtcgg ggactgactt caccttgacc attagctcgc tggaacctga ggacttcgcc 720

gtgtattact gccagcagca caacaagtac ccgtacacct tcggaggcgg tactaaggtc 780

gagatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1269
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1269
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

```
Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala
                85                  90                  95

Lys Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Val Leu
145                 150                 155                 160

Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175

Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220
```

```
Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225                 230                 235                 240


Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255


Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270


Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285


Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300


Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320


Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335


Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350


Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365


Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380


Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400


Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415
```

```
Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430


Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445


Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485


<210> 1270
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1270
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30


Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr
        35                  40                  45


Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60
```

```
Gly Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80


Tyr Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala
                85                  90                  95


Lys Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110


Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125


Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Val Leu
145                 150                 155                 160


Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr
                165                 170                 175


Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190


Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205


Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220


Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
225                 230                 235                 240


Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255
```

Gly Thr Lys Val Glu Ile Lys
            260

<210> 1271
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1271
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val
        35   40   45

Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50   55   60

Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys Ser Thr Ala Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100   105   110

Val Ser Ser
        115

<210> 1272

<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1272
Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5   10   15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35   40   45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
                85   90   95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 1273
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1273

atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agctcgtcga gagcggaggg ggactggtgc agcccggagg aagcctgagg 120

ctgtcctgcg ctgcctccgg ctacaccttc acctcctact ggatgaactg ggtcagacag 180

gcacctggaa agggactggt ctgggtgtcg cgcattgacc cctacgactc cgaaacccat 240

tacaatcaga aattcaagga ccgcttcacc atctccgtgg acaaagccaa gagcaccgcg 300

tacctccaaa tgaactccct gcgcgctgag gatacagcag tgtactattg cgcccgggga 360

aactgggatg attactgggg ccagggaact actgtgactg tgtcatccgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcagggggcg gaggaagcga cgtcgtgatg 480

acccagtcac cggcattcct gtccgtgact cccggagaaa aggtcacgat tacttgccgg 540

gcgtccaaga gcatctccaa ggacctcgcc tggtaccaac agaagccgga ccaggcccct 600

aagctgttga tctactcggg gtccaccctt caatcgggag tgccatcgcg gtttagcggt 660

tcgggttctg ggaccgactt cactttcacc atctcctcac tggaagccga ggatgccgcc 720

acttactact gtcagcagca caacaagtat ccgtacacct tcggaggcgg taccaaagtg 780

gagatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1274
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1274
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr
35 40 45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys
50 55 60

Gly Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65 70 75 80

Tyr Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala
85 90 95

Lys Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
100 105 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
115 120 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly

```
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145                 150                 155                 160

Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly Glu Lys Val Thr
                165                 170                 175

Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala
225                 230                 235                 240

Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255

Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
```

325 330 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1275
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1275

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr
        35                  40                  45

Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala
                85                  90                  95

Lys Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145                 150                 155                 160

Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly Glu Lys Val Thr
                165                 170                 175
```

```
Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190


Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205


Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220


Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala
225                 230                 235                 240


Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255


Gly Thr Lys Val Glu Ile Lys
            260


<210> 1276
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1276
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val
        35                  40                  45
```

```
Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser
        115


<210> 1277
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1277
Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1               5                   10                  15


Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala
65 70 75 80

Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1278
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1278
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgc agctcgtcga gagcggaggg ggactggtgc agcccggagg aagcctgagg 120

ctgtcctgcg ctgcctccgg ctacaccttc acctcctact ggatgaactg ggtcagacag 180

gcacctggaa agggactggt ctgggtgtcg cgcattgacc cctacgactc cgaaacccat 240

tacaatcaga aattcaagga ccgcttcacc atctccgtgg acaaagccaa gagcaccgcg 300

tacctccaaa tgaactccct gcgcgctgag gatacagcag tgtactattg cgcccgggga 360

aactgggatg attactgggg ccagggaact actgtgactg tgtcatccgg gggtggcggt 420

agcggaggag ggggctccgg cggcggcggc tcagggggcg gaggaagcga cgtggtcatg 480

actcagtccc cggactcact cgcggtgtcg cttggagaga gagcgaccat caactgtcgg 540

gcctcaaaga gcatcagcaa ggacctggcc tggtaccagc agaagccggg acagccgcca 600

aagctgctga tctactccgg gtccaccttg caatctggtg tccctgaccg gttctccggt 660

tccgggtcgg gtaccgactt cacgctcact atttcgtcgc tgcaagccga agatgtggcc 720

gtgtactatt gccaacagca caacaagtac ccctacactt ttggcggagg caccaaggtg 780

gaaatcaaga ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1279
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1279
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
20 25 30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr
35 40 45

```
Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60

Gly Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80

Tyr Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala
                85                  90                  95

Lys Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145                 150                 155                 160

Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175

Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
225                 230                 235                 240
```

```
Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255

Gly Thr Lys Val Glu Ile Lys Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430
```

```
Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445


Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485


<210> 1280
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1280
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
            20                  25                  30


Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr
        35                  40                  45


Thr Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys
    50                  55                  60


Gly Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His
65                  70                  75                  80
```

```
Tyr Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala
                85                  90                  95

Lys Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
            100                 105                 110

Ala Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met
145                 150                 155                 160

Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr
                165                 170                 175

Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp Leu Ala Trp Tyr
            180                 185                 190

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Ser Gly Ser
        195                 200                 205

Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly
    210                 215                 220

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala
225                 230                 235                 240

Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr Thr Phe Gly Gly
                245                 250                 255

Gly Thr Lys Val Glu Ile Lys
            260
```

<210> 1281
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1281
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val
        35   40   45

Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50   55   60

Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys Ser Thr Ala Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100   105   110

Val Ser Ser
        115

<210> 1282
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1282
Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1283
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1283
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacgtgc agctcaccca gtcgccctca tttctgtcgg cctcagtggg agacagagtg 120

accattactt gtcgggcctc caagagcatc tccaaggacc tggcctggta tcagcagaag 180

ccaggaaagg cgcctaagtt gctcatctac tcggggtcga ccctgcaatc tggcgtgccg 240

tcccggttct ccggttcggg aagcggtacc gaattcaccc ttactatctc ctccctgcaa 300

ccggaggact tcgccaccta ctactgccaa cagcacaaca agtacccgta cactttcggg 360

ggtggcacga aggtcgaaat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagcgaagtg cagctcgtcg agagcggagg gggactggtg 480

cagcccggag gaagcctgag gctgtcctgc gctgcctccg gctacacctt cacctcctac 540

tggatgaact gggtcagaca ggcacctgga aagggactgg tctgggtgtc gcgcattgac 600

ccctacgact ccgaaaccca ttacaatcag aaattcaagg accgcttcac catctccgtg 660

gacaaagcca agagcaccgc gtacctccaa atgaactccc tgcgcgctga ggatacagca 720

gtgtactatt gcgcccgggg aaactgggat gattactggg gccagggaac tactgtgact 780

gtgtcatcca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1284
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1284

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15


His Ala Ala Arg Pro Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu
            20                  25                  30


Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys
        35                  40                  45


Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala
    50                  55                  60


Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65                  70                  75                  80


Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
                85                  90                  95


Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His
            100                 105                 110


Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140


Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
```

```
145                 150                 155                 160

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly
            180                 185                 190

Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys
    210                 215                 220

Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
```

340 345 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1285
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1285
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1   5   10   15

His Ala Ala Arg Pro Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu
            20   25   30

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys
        35   40   45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala
    50   55   60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65   70   75   80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
                85   90   95

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His
            100   105   110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115   120   125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130   135   140

Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
145   150   155   160

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr
                165   170   175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly
            180   185   190

```
Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205


Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys
    210                 215                 220


Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
225                 230                 235                 240


Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255


Thr Thr Val Thr Val Ser Ser
            260


<210> 1286
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1286
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val
        35                  40                  45


Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60
```

```
Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser
        115


<210> 1287
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1287
Asp Val Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
```

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1288
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1288
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgaagtgg tgctgaccca gtcgcccgca accctctctc tgtcgccggg agaacgcgcc 120

actctttcct gtcgggcgtc caagagcatc tcaaaggacc tcgcctggta ccagcagaag 180

cctggtcaag ccccgcggct gctgatctac tccggctcca cgctgcaatc aggaatccca 240

gccagatttt ccggttcggg gtcggggact gacttcacct tgaccattag ctcgctggaa 300

cctgaggact tcgccgtgta ttactgccag cagcacaaca agtacccgta caccttcgga 360

ggcggtacta aggtcgagat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagcgaagtg cagctcgtcg agagcggagg gggactggtg 480

cagcccggag gaagcctgag gctgtcctgc gctgcctccg gctacacctt cacctcctac 540

tggatgaact gggtcagaca ggcacctgga aagggactgg tctgggtgtc gcgcattgac 600

ccctacgact ccgaaaccca ttacaatcag aaattcaagg accgcttcac catctccgtg 660

gacaaagcca agagcaccgc gtacctccaa atgaactccc tgcgcgctga ggatacagca 720

gtgtactatt gcgcccgggg aaactgggat gattactggg gccagggaac tactgtgact 780

gtgtcatcca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1289
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1289
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu
20 25 30

Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys
35 40 45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

```
Pro Arg Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro
65                  70                  75                  80

Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
145                 150                 155                 160

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly
            180                 185                 190

Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys
    210                 215                 220

Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255
```

```
Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445
```

```
Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460


Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485
```

<210> 1290
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1290

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu
            20                  25                  30


Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys
        35                  40                  45


Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60


Pro Arg Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro
65                  70                  75                  80


Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95
```

```
Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
145                 150                 155                 160

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly
            180                 185                 190

Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys
    210                 215                 220

Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser
            260
```

<210> 1291
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1291
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val
35 40 45

Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys Ser Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 1292
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1292
Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1293
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1293
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacgtcg tgatgaccca gtcaccggca ttcctgtccg tgactcccgg agaaaaggtc 120

acgattactt gccgggcgtc caagagcatc tccaaggacc tcgcctggta ccaacagaag 180

ccggaccagg cccctaagct gttgatctac tcggggtcca cccttcaatc gggagtgcca 240

tcgcggttta gcggttcggg ttctgggacc gacttcactt tcaccatctc ctcactggaa 300

gccgaggatg ccgccactta ctactgtcag cagcacaaca agtatccgta caccttcgga 360

ggcggtacca aagtggagat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagcgaagtg cagctcgtcg agagcggagg gggactggtg 480

cagcccggag gaagcctgag gctgtcctgc gctgcctccg gctacacctt cacctcctac 540

tggatgaact gggtcagaca ggcacctgga aagggactgg tctgggtgtc gcgcattgac 600

ccctacgact ccgaaaccca ttacaatcag aaattcaagg accgcttcac catctccgtg 660

gacaaagcca agagcaccgc gtacctccaa atgaactccc tgcgcgctga ggatacagca 720

gtgtactatt gcgcccgggg aaactgggat gattactggg gccagggaac tactgtgact 780

gtgtcatcca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1294
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1294

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                  10                  15


His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu
            20                  25                  30


Ser Val Thr Pro Gly Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys
        35                  40                  45


Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala
    50                  55                  60


Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65                  70                  75                  80


Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
                85                  90                  95


Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His
            100                 105                 110


Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140


Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
145                 150                 155                 160


Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr
```

```
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly
            180                 185                 190

Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys
    210                 215                 220

Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270

Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
```

355 360 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
370 375 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385 390 395 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
405 410 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
420 425 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
435 440 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
450 455 460

Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465 470 475 480

Gln Ala Leu Pro Pro Arg
485

<210> 1295
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1295
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

```
His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu
            20                  25                  30

Ser Val Thr Pro Gly Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys
        35                  40                  45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala
    50                  55                  60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65                  70                  75                  80

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile
                85                  90                  95

Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
145                 150                 155                 160

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly
            180                 185                 190

Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205
```

```
Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys
    210                 215                 220

Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser
            260
```

<210> 1296
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1296

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val
        35                  40                  45

Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys Ser Thr Ala Tyr
65                  70                  75                  80
```

```
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser
        115


<210> 1297
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1297
Asp Val Val Met Thr Gln Ser Pro Ala Phe Leu Ser Val Thr Pro Gly
1               5                   10                  15


Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala
65                  70                  75                  80


Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
                85                  90                  95
```

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 1298
<211> 1458
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1298
atggccctcc ctgtcaccgc cctgctgctt ccgctggctc ttctgctcca cgccgctcgg 60

cccgacgtgg tcatgactca gtccccggac tcactcgcgg tgtcgcttgg agagagagcg 120

accatcaact gtcgggcctc aaagagcatc agcaaggacc tggcctggta ccagcagaag 180

ccgggacagc cgccaaagct gctgatctac tccgggtcca ccttgcaatc tggtgtccct 240

gaccggttct ccggttccgg gtcgggtacc gacttcacgc tcactatttc gtcgctgcaa 300

gccgaagatg tggccgtgta ctattgccaa cagcacaaca agtaccccta cacttttggc 360

ggaggcacca aggtggaaat caaggggggt ggcggtagcg gaggaggggg ctccggcggc 420

ggcggctcag ggggcggagg aagcgaagtg cagctcgtcg agagcggagg gggactggtg 480

cagcccggag gaagcctgag gctgtcctgc gctgcctccg gctacacctt cacctcctac 540

tggatgaact gggtcagaca ggcacctgga aagggactgg tctgggtgtc gcgcattgac 600

ccctacgact ccgaaaccca ttacaatcag aaattcaagg accgcttcac catctccgtg 660

gacaaagcca agagcaccgc gtacctccaa atgaactccc tgcgcgctga ggatacagca 720

gtgtactatt gcgcccgggg aaactgggat gattactggg gccagggaac tactgtgact 780

gtgtcatcca ccactacccc agcaccgagg ccacccaccc cggctcctac catcgcctcc 840

cagcctctgt ccctgcgtcc ggaggcatgt agacccgcag ctggtggggc cgtgcatacc 900

cggggtcttg acttcgcctg cgatatctac atttgggccc ctctggctgg tacttgcggg 960

gtcctgctgc tttcactcgt gatcactctt tactgtaagc gcggtcggaa gaagctgctg 1020

tacatcttta agcaaccctt catgaggcct gtgcagacta ctcaagagga ggacggctgt 1080

tcatgccggt tcccagagga ggaggaaggc ggctgcgaac tgcgcgtgaa attcagccgc 1140

agcgcagatg ctccagccta caagcagggg cagaaccagc tctacaacga actcaatctt 1200

ggtcggagag aggagtacga cgtgctggac aagcggagag gacgggaccc agaaatgggc 1260

gggaagccgc gcagaaagaa tccccaagag ggcctgtaca acgagctcca aaaggataag 1320

atggcagaag cctatagcga gattggtatg aaaggggaac gcagaagagg caaaggccac 1380

gacggactgt accagggact cagcaccgcc accaaggaca cctatgacgc tcttcacatg 1440

caggccctgc cgcctcgg 1458

<210> 1299
<211> 486
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1299
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1 5 10 15

His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu
20 25 30

Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys
35 40 45

Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro
50 55 60

Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65 70 75 80

```
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110

Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
145                 150                 155                 160

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr
                165                 170                 175

Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly
            180                 185                 190

Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205

Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys
    210                 215                 220

Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
225                 230                 235                 240

Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255

Thr Thr Val Thr Val Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro
            260                 265                 270
```

```
Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
        275                 280                 285

Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
    290                 295                 300

Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
305                 310                 315                 320

Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg
                325                 330                 335

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
            340                 345                 350

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
        355                 360                 365

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
    370                 375                 380

Pro Ala Tyr Lys Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
385                 390                 395                 400

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
                405                 410                 415

Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu
            420                 425                 430

Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile
        435                 440                 445

Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr
    450                 455                 460
```

```
Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met
465                 470                 475                 480


Gln Ala Leu Pro Pro Arg
                485
```

<210> 1300
<211> 263
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1300

```
Met Ala Leu Pro Val Thr Ala Leu Leu Leu Pro Leu Ala Leu Leu Leu
1               5                   10                  15


His Ala Ala Arg Pro Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu
            20                  25                  30


Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys
        35                  40                  45


Ser Ile Ser Lys Asp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro
    50                  55                  60


Pro Lys Leu Leu Ile Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro
65                  70                  75                  80


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95


Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His
            100                 105                 110
```

```
Asn Lys Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    130                 135                 140


Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
145                 150                 155                 160


Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr
                165                 170                 175


Phe Thr Ser Tyr Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly
            180                 185                 190


Leu Val Trp Val Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr
        195                 200                 205


Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys
    210                 215                 220


Ser Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
225                 230                 235                 240


Val Tyr Tyr Cys Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly
                245                 250                 255


Thr Thr Val Thr Val Ser Ser
            260


<210> 1301
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
```

polypeptide"

<400> 1301

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val
        35                  40                  45


Ser Arg Ile Asp Pro Tyr Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Phe Thr Ile Ser Val Asp Lys Ala Lys Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Asn Trp Asp Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser
        115
```

<210> 1302
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1302

```
Asp Val Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1               5                   10                  15
```

```
Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Asp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Val Pro Asp Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65                  70                  75                  80

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln His Asn Lys Tyr Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> 1303
<211> 514
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"

<400> 1303
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45
```

```
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
    50                  55                  60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65                  70                  75                  80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95

Tyr Tyr Cys Ala Arg Asp Leu Gly Trp Ile Ala Val Ala Gly Thr Phe
            100                 105                 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160

Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp
            180                 185                 190

Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys
        195                 200                 205

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220

Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Leu Asn His
225                 230                 235                 240
```

```
Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Thr Gly Gly Gly Gly
                245                 250                 255

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
            260                 265                 270

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
        275                 280                 285

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
    290                 295                 300

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
305                 310                 315                 320

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
                325                 330                 335

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
            340                 345                 350

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
        355                 360                 365

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
    370                 375                 380

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Glu
385                 390                 395                 400

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
                405                 410                 415

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
            420                 425                 430
```

```
Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser
        435                 440                 445


Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser
    450                 455                 460


Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr
465                 470                 475                 480


Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
                485                 490                 495


Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            500                 505                 510


Ser Ser
```

<210> 1304
<211> 737
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1304

```
Glu Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15


Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30


Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45
```

```
Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
    50                  55                  60

Val Ser Val Lys Ser Arg Ile Thr Ile Asn Pro Asp Thr Ser Lys Asn
65                  70                  75                  80

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95

Tyr Tyr Cys Ala Arg Asp Leu Gly Trp Ile Ala Val Ala Gly Thr Phe
            100                 105                 110

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140

Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160

Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175

Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp
            180                 185                 190

Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys
        195                 200                 205

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220

Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser Ser Leu Asn His
225                 230                 235                 240
```

```
Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Thr Gly Gly Gly Gly
                245                 250                 255

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
            260                 265                 270

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
        275                 280                 285

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
    290                 295                 300

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
305                 310                 315                 320

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
                325                 330                 335

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
            340                 345                 350

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
        355                 360                 365

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
    370                 375                 380

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Glu
385                 390                 395                 400

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
                405                 410                 415

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
            420                 425                 430
```

```
Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser
        435                 440                 445

Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser
    450                 455                 460

Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr
465                 470                 475                 480

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
                485                 490                 495

Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            500                 505                 510

Ser Ser Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
        515                 520                 525

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
    530                 535                 540

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
545                 550                 555                 560

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
                565                 570                 575

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr
            580                 585                 590

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
        595                 600                 605

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
    610                 615                 620
```

```
Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln
625                 630                 635                 640


Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
                645                 650                 655


Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
            660                 665                 670


Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
        675                 680                 685


Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
    690                 695                 700


Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
705                 710                 715                 720


Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
                725                 730                 735


Arg
```

<210> 1305
<211> 1542
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1305
gaagtgcagc tccaacagtc aggaccagga ctcgtcaaac cctcccaaac cctcagcctt 60

acttgtgcca tttccgggga ttccgtgtcg agcaattccg ccgcctggaa ctggatcagg 120

cagtccccgt cgcgcgggct cgaatggctg ggacgcactt actaccggtc caagtggtac 180

aacgactacg ccgtcagcgt gaagtcgcgg atcaccatta accccgacac ctccaagaac 240

cagttcagcc tccaactgaa ctccgtgacc cctgaggata ccgcggtcta ctattgtgcc 300

cgggacctgg gttggattgc cgtggccggg accttcgatt actggggcca gggaactctc 360

gtcaccgtgt cctcgggagg gggtggctca gggggtggtg gatcgggtgg tggcggctcc 420

cagtccgctc tgactcagcc cgcgtccgtg tccggttccc cgggacagtc gatcacaatc 480

agctgcactg gcacctcctc cgacgtcggc gggtacaact acgtgtcgtg gtaccaacag 540

caccctggaa aagccccgaa gctgatgatc tacgacgtgt ccaagaggcc aagcggagtg 600

tcaaatcgct tttccggctc gaagtcggga aacaccgcca gcctgactat ctcgggactg 660

caggccgagg acgaggccga ctactactgc tcgtcttaca cctcctcatc cttgaaccac 720

gtgttcggaa ccggaaccaa ggtcaccgtg ctgactggag ggggaggctc cggtggcggc 780

ggctctggag gaggagggtc cggcggagga ggatcggaaa tcgtgatgac ccagtccccc 840

gcaaccctgt ccctgagccc gggcgaaaga gctaccctgt cgtgccgggc gtcgcaggac 900

atctccaagt acctgaactg gtaccagcag aagcccggcc aggcaccgag actgctgatc 960

taccacacta gccgcctgca ttccggtatc cccgcacggt tcagcggcag cgggagcgga 1020

accgattaca cgctcactat ttcctcactg caacccgagg atttcgctgt gtacttctgc 1080

caacaaggaa acaccctgcc ttataccttc ggacagggta caaagctgga gattaaggga 1140

ggagggggct ccggcggcgg gggcagcggg ggcggcggaa gccaggtcca gctgcaggaa 1200

tccggtccgg gactcgtgaa gccctccgaa actctctccc ttacgtgcac cgtgtcaggg 1260

gtgtccctgc cggactacgg agtgtcctgg attcggcaac ctccggggaa gggactggag 1320

tggatcggag tgatctgggg ctccgaaact acctactacc agtcatcatt gaagtcaaga 1380

gtgaccattt cgaaggacaa cagcaagaac caggtgtccc ttaaactgtc cagcgtgacc 1440

gcggcggata ctgccgtcta ctactgcgcc aagcactatt actacggcgg aagctatgcg 1500

atggactact ggggacaggg caccttggtc actgtgtcct cc 1542

<210> 1306
<211> 2211
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1306
gaagtgcagc tccaacagtc aggaccagga ctcgtcaaac cctcccaaac cctcagcctt 60

acttgtgcca tttccgggga ttccgtgtcg agcaattccg ccgcctggaa ctggatcagg 120

cagtccccgt cgcgcgggct cgaatggctg ggacgcactt actaccggtc caagtggtac 180

aacgactacg ccgtcagcgt gaagtcgcgg atcaccatta accccgacac ctccaagaac 240

cagttcagcc tccaactgaa ctccgtgacc cctgaggata ccgcggtcta ctattgtgcc 300

cgggacctgg gttggattgc cgtggccggg accttcgatt actggggcca gggaactctc 360

gtcaccgtgt cctcgggagg gggtggctca gggggtggtg gatcgggtgg tggcggctcc 420

cagtccgctc tgactcagcc cgcgtccgtg tccggttccc cgggacagtc gatcacaatc 480

agctgcactg gcacctcctc cgacgtcggc gggtacaact acgtgtcgtg gtaccaacag 540

caccctggaa aagccccgaa gctgatgatc tacgacgtgt ccaagaggcc aagcggagtg 600

tcaaatcgct tttccggctc gaagtcggga aacaccgcca gcctgactat ctcgggactg 660

caggccgagg acgaggccga ctactactgc tcgtcttaca cctcctcatc cttgaaccac 720

gtgttcggaa ccggaaccaa ggtcaccgtg ctgactggag ggggaggctc cggtggcggc 780

ggctctggag gaggagggtc cggcggagga ggatcggaaa tcgtgatgac ccagtccccc 840

gcaaccctgt ccctgagccc gggcgaaaga gctaccctgt cgtgccgggc gtcgcaggac 900

atctccaagt acctgaactg gtaccagcag aagcccggcc aggcaccgag actgctgatc 960

taccacacta gccgcctgca ttccggtatc cccgcacggt tcagcggcag cgggagcgga 1020

accgattaca cgctcactat ttcctcactg caacccgagg atttcgctgt gtacttctgc 1080

caacaaggaa acaccctgcc ttataccttc ggacagggta caaagctgga gattaaggga 1140

ggaggggct ccggcggcgg gggcagcggg ggcggcggaa gccaggtcca gctgcaggaa 1200

tccggtccgg gactcgtgaa gccctccgaa actctctccc ttacgtgcac cgtgtcaggg 1260

gtgtccctgc cggactacgg agtgtcctgg attcggcaac ctccggggaa gggactggag 1320

tggatcggag tgatctgggg ctccgaaact acctactacc agtcatcatt gaagtcaaga 1380

gtgaccattt cgaaggacaa cagcaagaac caggtgtccc ttaaactgtc cagcgtgacc 1440

gcggcggata ctgccgtcta ctactgcgcc aagcactatt actacggcgg aagctatgcg 1500

atggactact ggggacaggg caccttggtc actgtgtcct ccaccactac cccagcaccg 1560

aggccaccca ccccggctcc taccatcgcc tcccagcctc tgtccctgcg tccggaggca 1620

tgtagacccg cagctggtgg ggccgtgcat acccggggtc ttgacttcgc ctgcgatatc 1680

tacatttggg cccctctggc tggtacttgc ggggtcctgc tgctttcact cgtgatcact 1740

ctttactgta agcgcggtcg gaagaagctg ctgtacatct ttaagcaacc cttcatgagg 1800

cctgtgcaga ctactcaaga ggaggacggc tgttcatgcc ggttcccaga ggaggaggaa 1860

ggcggctgcg aactgcgcgt gaaattcagc cgcagcgcag atgctccagc ctacaagcag 1920

gggcagaacc agctctacaa cgaactcaat cttggtcgga gagaggagta cgacgtgctg 1980

gacaagcgga gaggacggga cccagaaatg ggcgggaagc cgcgcagaaa gaatccccaa 2040

gagggcctgt acaacgagct ccaaaaggat aagatggcag aagcctatag cgagattggt 2100

atgaaagggg aacgcagaag aggcaaaggc cacgacggac tgtaccaggg actcagcacc 2160

gccaccaagg acacctatga cgctcttcac atgcaggccc tgccgcctcg g 2211

<210> 1307
<211> 514
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1307

```
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                  10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Glu
        115                 120                 125

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
    130                 135                 140

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145                 150                 155                 160

Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser
                165                 170                 175

Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser
            180                 185                 190
```

```
Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr
        195                 200                 205

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
    210                 215                 220

Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
225                 230                 235                 240

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
                245                 250                 255

Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Gly
            260                 265                 270

Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly
        275                 280                 285

Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser
    290                 295                 300

Pro Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys
305                 310                 315                 320

Trp Tyr Asn Asp Tyr Ala Val Ser Val Lys Ser Arg Ile Thr Ile Asn
                325                 330                 335

Pro Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr
            340                 345                 350

Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Leu Gly Trp Ile
        355                 360                 365

Ala Val Ala Gly Thr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
    370                 375                 380
```

```
Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
385                 390                 395                 400


Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro
                405                 410                 415


Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly
            420                 425                 430


Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro
        435                 440                 445


Lys Leu Met Ile Tyr Asp Val Ser Lys Arg Pro Ser Gly Val Ser Asn
    450                 455                 460


Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser
465                 470                 475                 480


Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr
                485                 490                 495


Ser Ser Ser Leu Asn His Val Phe Gly Thr Gly Thr Lys Val Thr Val
            500                 505                 510


Leu Thr
```

<210> 1308
<211> 737
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1308

```
Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                  10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr His Thr Ser Arg Leu His Ser Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Glu
        115                 120                 125

Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys
    130                 135                 140

Thr Val Ser Gly Val Ser Leu Pro Asp Tyr Gly Val Ser Trp Ile Arg
145                 150                 155                 160

Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile Trp Gly Ser
                165                 170                 175

Glu Thr Thr Tyr Tyr Gln Ser Ser Leu Lys Ser Arg Val Thr Ile Ser
            180                 185                 190
```

```
Lys Asp Asn Ser Lys Asn Gln Val Ser Leu Lys Leu Ser Ser Val Thr
        195                 200                 205

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr Tyr Tyr Gly
    210                 215                 220

Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
225                 230                 235                 240

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
                245                 250                 255

Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Gln Gln Ser Gly Pro Gly
            260                 265                 270

Leu Val Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly
        275                 280                 285

Asp Ser Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser
    290                 295                 300

Pro Ser Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys
305                 310                 315                 320

Trp Tyr Asn Asp Tyr Ala Val Ser Val Lys Ser Arg Ile Thr Ile Asn
                325                 330                 335

Pro Asp Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr
            340                 345                 350

Pro Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Leu Gly Trp Ile
        355                 360                 365

Ala Val Ala Gly Thr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
    370                 375                 380
```

```
Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
385                 390                 395                 400

Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro
                405                 410                 415

Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly
            420                 425                 430

Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro
        435                 440                 445

Lys Leu Met Ile Tyr Asp Val Ser Lys Arg Pro Ser Gly Val Ser Asn
    450                 455                 460

Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser
465                 470                 475                 480

Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr
                485                 490                 495

Ser Ser Ser Leu Asn His Val Phe Gly Thr Gly Thr Lys Val Thr Val
            500                 505                 510

Leu Thr Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
        515                 520                 525

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
    530                 535                 540

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
545                 550                 555                 560

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
                565                 570                 575
```

Leu Val Ile Thr Leu Tyr Cys Lys Arg Gly Arg Lys Lys Leu Leu Tyr
580 585 590

Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu
595 600 605

Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu
610 615 620

Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln
625 630 635 640

Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu
645 650 655

Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly
660 665 670

Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
675 680 685

Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
690 695 700

Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
705 710 715 720

Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
725 730 735

Arg

<210> 1309
<211> 1542
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1309
gaaatcgtga tgacccagtc ccccgcaacc ctgtccctga gcccgggcga aagagctacc 60

ctgtcgtgcc gggcgtcgca ggacatctcc aagtacctga actggtacca gcagaagccc 120

ggccaggcac cgagactgct gatctaccac actagccgcc tgcattccgg tatccccgca 180

cggttcagcg gcagcgggag cggaaccgat tacacgctca ctatttcctc actgcaaccc 240

gaggatttcg ctgtgtactt ctgccaacaa ggaaacaccc tgccttatac cttcggacag 300

ggtacaaagc tggagattaa gggaggaggg ggctccggcg gcgggggcag cgggggcggc 360

ggaagccagg tccagctgca ggaatccggt ccgggactcg tgaagccctc cgaaactctc 420

tcccttacgt gcaccgtgtc aggggtgtcc ctgccggact acggagtgtc ctggattcgg 480

caacctccgg ggaagggact ggagtggatc ggagtgatct ggggctccga aactacctac 540

taccagtcat cattgaagtc aagagtgacc atttcgaagg acaacagcaa gaaccaggtg 600

tcccttaaac tgtccagcgt gaccgcggcg gatactgccg tctactactg cgccaagcac 660

tattactacg gcggaagcta tgcgatggac tactggggac agggcacctt ggtcactgtg 720

tcctccggag ggggaggctc cggtggcggc ggctctggag gaggagggtc cggcggagga 780

ggatcggaag tgcagctcca acagtcagga ccaggactcg tcaaaccctc ccaaaccctc 840

agccttactt gtgccatttc cggggattcc gtgtcgagca attccgccgc ctggaactgg 900

atcaggcagt ccccgtcgcg cgggctcgaa tggctgggac gcacttacta ccggtccaag 960

tggtacaacg actacgccgt cagcgtgaag tcgcggatca ccattaaccc cgacacctcc 1020

aagaaccagt tcagcctcca actgaactcc gtgaccctg aggataccgc ggtctactat 1080

tgtgcccggg acctgggttg gattgccgtg gccgggacct tcgattactg gggccaggga 1140

actctcgtca ccgtgtcctc gggaggggt ggctcagggg gtggtggatc gggtggtggc 1200

ggctcccagt ccgctctgac tcagcccgcg tccgtgtccg gttccccggg acagtcgatc 1260

acaatcagct gcactggcac ctcctccgac gtcggcgggt acaactacgt gtcgtggtac 1320

caacagcacc ctggaaaagc cccgaagctg atgatctacg acgtgtccaa gaggccaagc 1380

ggagtgtcaa atcgcttttc cggctcgaag tcgggaaaca ccgccagcct gactatctcg 1440

ggactgcagg ccgaggacga ggccgactac tactgctcgt cttacacctc ctcatccttg 1500

aaccacgtgt tcggaaccgg aaccaaggtc accgtgctga ct 1542

<210> 1310
<211> 2211
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1310
gaaatcgtga tgacccagtc ccccgcaacc ctgtccctga gcccgggcga aagagctacc 60

ctgtcgtgcc gggcgtcgca ggacatctcc aagtacctga actggtacca gcagaagccc 120

ggccaggcac cgagactgct gatctaccac actagccgcc tgcattccgg tatccccgca 180

cggttcagcg gcagcgggag cggaaccgat tacacgctca ctatttcctc actgcaaccc 240

gaggatttcg ctgtgtactt ctgccaacaa ggaaacaccc tgccttatac cttcggacag 300

ggtacaaagc tggagattaa gggaggaggg ggctccggcg gcgggggcag cgggggcggc 360

ggaagccagg tccagctgca ggaatccggt ccgggactcg tgaagccctc cgaaactctc 420

tcccttacgt gcaccgtgtc aggggtgtcc ctgccggact acggagtgtc ctggattcgg 480

caacctccgg ggaagggact ggagtggatc ggagtgatct ggggctccga aactacctac 540

taccagtcat cattgaagtc aagagtgacc atttcgaagg acaacagcaa gaaccaggtg 600

tcccttaaac tgtccagcgt gaccgcggcg gatactgccg tctactactg cgccaagcac 660

tattactacg gcggaagcta tgcgatggac tactggggac agggcacctt ggtcactgtg 720

tcctccggag ggggaggctc cggtggcggc ggctctggag gaggagggtc cggcggagga 780

ggatcggaag tgcagctcca acagtcagga ccaggactcg tcaaaccctc ccaaaccctc 840

agccttactt gtgccatttc cggggattcc gtgtcgagca attccgccgc ctggaactgg 900

atcaggcagt ccccgtcgcg cgggctcgaa tggctgggac gcacttacta ccggtccaag 960

tggtacaacg actacgccgt cagcgtgaag tcgcggatca ccattaaccc cgacacctcc 1020

aagaaccagt tcagcctcca actgaactcc gtgacccctg aggataccgc ggtctactat 1080

tgtgcccggg acctgggttg gattgccgtg gccgggacct tcgattactg gggccaggga 1140

actctcgtca ccgtgtcctc gggagggggt ggctcagggg gtggtggatc gggtggtggc 1200

ggctcccagt ccgctctgac tcagcccgcg tccgtgtccg gttccccggg acagtcgatc 1260

acaatcagct gcactggcac ctcctccgac gtcggcgggt acaactacgt gtcgtggtac 1320

caacagcacc ctggaaaagc cccgaagctg atgatctacg acgtgtccaa gaggccaagc 1380

ggagtgtcaa atcgcttttc cggctcgaag tcgggaaaca ccgccagcct gactatctcg 1440

ggactgcagg ccgaggacga ggccgactac tactgctcgt cttacacctc ctcatccttg 1500

aaccacgtgt tcggaaccgg aaccaaggtc accgtgctga ctaccactac cccagcaccg 1560

aggccaccca ccccggctcc taccatcgcc tcccagcctc tgtccctgcg tccggaggca 1620

tgtagacccg cagctggtgg ggccgtgcat acccggggtc ttgacttcgc ctgcgatatc 1680

tacatttggg cccctctggc tggtacttgc ggggtcctgc tgctttcact cgtgatcact 1740

ctttactgta agcgcggtcg gaagaagctg ctgtacatct ttaagcaacc cttcatgagg 1800

cctgtgcaga ctactcaaga ggaggacggc tgttcatgcc ggttcccaga ggaggaggaa 1860

ggcggctgcg aactgcgcgt gaaattcagc cgcagcgcag atgctccagc ctacaagcag 1920

gggcagaacc agctctacaa cgaactcaat cttggtcgga gagaggagta cgacgtgctg 1980

gacaagcgga gaggacggga cccagaaatg ggcgggaagc cgcgcagaaa gaatccccaa 2040

gagggcctgt acaacgagct ccaaaaggat aagatggcag aagcctatag cgagattggt 2100

atgaaagggg aacgcagaag aggcaaaggc cacgacggac tgtaccaggg actcagcacc 2160

gccaccaagg acacctatga cgctcttcac atgcaggccc tgccgcctcg g 2211

<210> 1311
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 1311
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser
20

<210> 1312
<211> 5
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<400> 1312
ggaaa 5

<210> 1313
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
oligonucleotide"

<220>
<221> modified_base

<222> (7)..(7)
<223> a, c, t, g, unknown or other

<220>
<221> modified_base
<222> (9)..(9)
<223> a, c, t, g, unknown or other

<400> 1313
wggaaanhn 9

<210> 1314
<211> 6
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic oligonucleotide"

<400> 1314
gggact 6

<210> 1315
<211> 120
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1315
agcttggatc caagaggaaa atttgtttca tacagaaggc gttaagagga aaatttgttt 60

catacagaag gcgttaagag gaaaatttgt ttcatacaga aggcgttcaa gcttgtcgac 120

<210> 1316
<211> 4
<212> PRT
<213> Artificial Sequence

<220>

<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1316
Arg Gly Asp Ser
1

<210> 1317
<211> 41
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1317
Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
1   5   10   15

Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
            20   25   30

Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        35   40

<210> 1318
<211> 123
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1318
aggagtaaga ggagcaggct cctgcacagt gactacatga acatgactcc ccgccgcccc 60

gggcccaccc gcaagcatta ccagccctat gccccaccac gcgacttcgc agcctatcgc 120

tcc 123

<210> 1319
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polypeptide"

<400> 1319
Thr Lys Lys Lys Tyr Ser Ser Ser Val His Asp Pro Asn Gly Glu Tyr
1 5 10 15

Met Phe Met Arg Ala Val Asn Thr Ala Lys Lys Ser Arg Leu Thr Asp
20 25 30

Val Thr Leu
35

<210> 1320
<211> 105
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
polynucleotide"

<400> 1320
acaaaaaaga agtattcatc cagtgtgcac gaccctaacg gtgaatacat gttcatgaga 60

gcagtgaaca cagccaaaaa atccagactc acagatgtga cccta 105

<210> 1321
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1321
Thr Lys Lys Lys Tyr Ser Ser Ser Val His Asp Pro Asn Gly Glu Phe
1 5 10 15

Met Phe Met Arg Ala Val Asn Thr Ala Lys Lys Ser Arg Leu Thr Asp
20 25 30

Val Thr Leu
35

<210> 1322
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1322
Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr
1 5 10 15

Lys Gly

<210> 1323
<211> 521
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1323
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ccgaacgtct tacgccttgt ggcgcgcccg tccttgtccc gggtgtgatg gcggggtgtg 120

gggcggaggg cgtggcgggg aagggccggc gacgagagcc gcgcgggacg actcgtcggc 180

gataaccggt gtcgggtagc gccagccgcg cgacggtaac gagggaccgc gacaggcaga 240

cgctcccatg atcactctgc acgccgaagg caaatagtgc aggccgtgcg gcgcttggcg 300

ttccttggaa gggctgaatc cccgcctcgt ccttcgcagc ggccccccgg gtgttcccat 360

cgccgcttct aggcccactg cgacgcttgc ctgcacttct tacacgctct gggtcccagc 420

cgcggcgacg caaagggcct tggtgcgggt ctcgtcggcg cagggacgcg tttgggtccc 480

gacggaacct tttccgcgtt ggggttgggg caccataagc t 521

<210> 1324
<211> 118
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1324
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ccgaacgtct tacgccttgt ggcgcgcccg tccttgtccc gggtgtgatg gcggggtg 118

<210> 1325
<211> 221
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1325
acccctctct ccagccacta agccagttgc tccctcggct gacggctgca cgcgaggcct 60

ccgaacgtct tacgccttgt ggcgcgcccg tccttgtccc gggtgtgatg gcggggtgtg 120

gggcggaggg cgtggcgggg aagggccggc gacgagagcc gcgcgggacg actcgtcggc 180

gataaccggt gtcgggtagc gccagccgcg cgacggtaac g 221

<210> 1326
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1326
acccctctct ccagccacta agccagttgc tccctcggct gacggctgca cgcgaggcct 60

ccgaacgtct tacgccttgt ggcgcgcccg tccttgtccc gggtgtgatg gcggggtgtg 120

gggcggaggg cgtggcgggg aagggccggc gacgagagcc gcgcgggacg actcgtcggc 180

gataaccggt gtcgggtagc gccagccgcg cgacggtaac gagggaccgc gacaggcaga 240

cgctcccatg atcactctgc acgccgaagg caaatagtgc aggccgtgcg gcgcttggcg 300

ttccttggaa gggctgaatc cccg 324

<210> 1327
<211> 422
<212> DNA
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polynucleotide"

<400> 1327
acccctctct ccagccacta agccagttgc tccctcggct gacggctgca cgcgaggcct 60

ccgaacgtct tacgccttgt ggcgcgcccg tccttgtccc gggtgtgatg gcggggtgtg 120

gggcggaggg cgtggcgggg aagggccggc gacgagagcc gcgcgggacg actcgtcggc 180

gataaccggt gtcgggtagc gccagccgcg cgacggtaac gagggaccgc gacaggcaga 240

cgctcccatg atcactctgc acgccgaagg caaatagtgc aggccgtgcg gcgcttggcg 300

ttccttggaa gggctgaatc cccgcctcgt ccttcgcagc ggccccccgg gtgttcccat 360

cgccgcttct aggcccactg cgacgcttgc ctgcacttct tacacgctct gggtcccagc 420

cg 422

<210> 1328
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
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<222> (1)..(3)
<223> /replace=" "

<220>
<221> misc_feature
<222> (1)..(21)
<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 1328
Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu
1 5 10 15

Glu Asn Pro Gly Pro
20

<210> 1329
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>
<221> VARIANT
<222> (1)..(3)
<223> /replace=" "

<220>
<221> misc_feature
<222> (1)..(22)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 1329
Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val
1 5 10 15

Glu Glu Asn Pro Gly Pro
20

<210> 1330
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>
<221> VARIANT
<222> (1)..(3)
<223> /replace=" "

<220>
<221> misc_feature
<222> (1)..(23)
<223> /note="Variant residues given in the sequence have no
preference with respect to those in the annotations
for variant positions"

<400> 1330
Gly Ser Gly Gln Cys Thr Asn Tyr Ala Leu Leu Lys Leu Ala Gly Asp
1 5 10 15

Val Glu Ser Asn Pro Gly Pro
20

<210> 1331
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
<221> VARIANT
<222> (1)..(3)
<223> /replace=" "

<220>
<221> misc_feature
<222> (1)..(25)
<223> /note="Variant residues given in the sequence have no preference with respect to those in the annotations for variant positions"

<400> 1331
Gly Ser Gly Val Lys Gln Thr Leu Asn Phe Asp Leu Leu Lys Leu Ala
1 5 10 15

Gly Asp Val Glu Ser Asn Pro Gly Pro
20 25

<210> 1332
<211> 1132
<212> PRT
<213> Homo sapiens

<400> 1332
Met Pro Arg Ala Pro Arg Cys Arg Ala Val Arg Ser Leu Leu Arg Ser

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1               5                   10                  15

His Tyr Arg Glu Val Leu Pro Leu Ala Thr Phe Val Arg Arg Leu Gly
            20                  25                  30

Pro Gln Gly Trp Arg Leu Val Gln Arg Gly Asp Pro Ala Ala Phe Arg
        35                  40                  45

Ala Leu Val Ala Gln Cys Leu Val Cys Val Pro Trp Asp Ala Arg Pro
    50                  55                  60

Pro Pro Ala Ala Pro Ser Phe Arg Gln Val Ser Cys Leu Lys Glu Leu
65                  70                  75                  80

Val Ala Arg Val Leu Gln Arg Leu Cys Glu Arg Gly Ala Lys Asn Val
                85                  90                  95

Leu Ala Phe Gly Phe Ala Leu Leu Asp Gly Ala Arg Gly Gly Pro Pro
            100                 105                 110

Glu Ala Phe Thr Thr Ser Val Arg Ser Tyr Leu Pro Asn Thr Val Thr
        115                 120                 125

Asp Ala Leu Arg Gly Ser Gly Ala Trp Gly Leu Leu Leu Arg Arg Val
    130                 135                 140

Gly Asp Asp Val Leu Val His Leu Leu Ala Arg Cys Ala Leu Phe Val
145                 150                 155                 160

Leu Val Ala Pro Ser Cys Ala Tyr Gln Val Cys Gly Pro Pro Leu Tyr
                165                 170                 175

Gln Leu Gly Ala Ala Thr Gln Ala Arg Pro Pro Pro His Ala Ser Gly
            180                 185                 190

Pro Arg Arg Arg Leu Gly Cys Glu Arg Ala Trp Asn His Ser Val Arg
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195 200 205

Glu Ala Gly Val Pro Leu Gly Leu Pro Ala Pro Gly Ala Arg Arg Arg
210 215 220

Gly Gly Ser Ala Ser Arg Ser Leu Pro Leu Pro Lys Arg Pro Arg Arg
225 230 235 240

Gly Ala Ala Pro Glu Pro Glu Arg Thr Pro Val Gly Gln Gly Ser Trp
245 250 255

Ala His Pro Gly Arg Thr Arg Gly Pro Ser Asp Arg Gly Phe Cys Val
260 265 270

Val Ser Pro Ala Arg Pro Ala Glu Glu Ala Thr Ser Leu Glu Gly Ala
275 280 285

Leu Ser Gly Thr Arg His Ser His Pro Ser Val Gly Arg Gln His His
290 295 300

Ala Gly Pro Pro Ser Thr Ser Arg Pro Pro Arg Pro Trp Asp Thr Pro
305 310 315 320

Cys Pro Pro Val Tyr Ala Glu Thr Lys His Phe Leu Tyr Ser Ser Gly
325 330 335

Asp Lys Glu Gln Leu Arg Pro Ser Phe Leu Leu Ser Ser Leu Arg Pro
340 345 350

Ser Leu Thr Gly Ala Arg Arg Leu Val Glu Thr Ile Phe Leu Gly Ser
355 360 365

Arg Pro Trp Met Pro Gly Thr Pro Arg Arg Leu Pro Arg Leu Pro Gln
370 375 380

Arg Tyr Trp Gln Met Arg Pro Leu Phe Leu Glu Leu Leu Gly Asn His

385 390 395 400

Ala Gln Cys Pro Tyr Gly Val Leu Leu Lys Thr His Cys Pro Leu Arg
405 410 415

Ala Ala Val Thr Pro Ala Ala Gly Val Cys Ala Arg Glu Lys Pro Gln
420 425 430

Gly Ser Val Ala Ala Pro Glu Glu Glu Asp Thr Asp Pro Arg Arg Leu
435 440 445

Val Gln Leu Leu Arg Gln His Ser Ser Pro Trp Gln Val Tyr Gly Phe
450 455 460

Val Arg Ala Cys Leu Arg Arg Leu Val Pro Pro Gly Leu Trp Gly Ser
465 470 475 480

Arg His Asn Glu Arg Arg Phe Leu Arg Asn Thr Lys Lys Phe Ile Ser
485 490 495

Leu Gly Lys His Ala Lys Leu Ser Leu Gln Glu Leu Thr Trp Lys Met
500 505 510

Ser Val Arg Gly Cys Ala Trp Leu Arg Arg Ser Pro Gly Val Gly Cys
515 520 525

Val Pro Ala Ala Glu His Arg Leu Arg Glu Glu Ile Leu Ala Lys Phe
530 535 540

Leu His Trp Leu Met Ser Val Tyr Val Val Glu Leu Leu Arg Ser Phe
545 550 555 560

Phe Tyr Val Thr Glu Thr Thr Phe Gln Lys Asn Arg Leu Phe Phe Tyr
565 570 575

Arg Lys Ser Val Trp Ser Lys Leu Gln Ser Ile Gly Ile Arg Gln His

580 585 590

Leu Lys Arg Val Gln Leu Arg Glu Leu Ser Glu Ala Glu Val Arg Gln
595 600 605

His Arg Glu Ala Arg Pro Ala Leu Leu Thr Ser Arg Leu Arg Phe Ile
610 615 620

Pro Lys Pro Asp Gly Leu Arg Pro Ile Val Asn Met Asp Tyr Val Val
625 630 635 640

Gly Ala Arg Thr Phe Arg Arg Glu Lys Arg Ala Glu Arg Leu Thr Ser
645 650 655

Arg Val Lys Ala Leu Phe Ser Val Leu Asn Tyr Glu Arg Ala Arg Arg
660 665 670

Pro Gly Leu Leu Gly Ala Ser Val Leu Gly Leu Asp Asp Ile His Arg
675 680 685

Ala Trp Arg Thr Phe Val Leu Arg Val Arg Ala Gln Asp Pro Pro Pro
690 695 700

Glu Leu Tyr Phe Val Lys Val Asp Val Thr Gly Ala Tyr Asp Thr Ile
705 710 715 720

Pro Gln Asp Arg Leu Thr Glu Val Ile Ala Ser Ile Ile Lys Pro Gln
725 730 735

Asn Thr Tyr Cys Val Arg Arg Tyr Ala Val Val Gln Lys Ala Ala His
740 745 750

Gly His Val Arg Lys Ala Phe Lys Ser His Val Ser Thr Leu Thr Asp
755 760 765

Leu Gln Pro Tyr Met Arg Gln Phe Val Ala His Leu Gln Glu Thr Ser

770 775 780

Pro Leu Arg Asp Ala Val Val Ile Glu Gln Ser Ser Ser Leu Asn Glu
785 790 795 800

Ala Ser Ser Gly Leu Phe Asp Val Phe Leu Arg Phe Met Cys His His
805 810 815

Ala Val Arg Ile Arg Gly Lys Ser Tyr Val Gln Cys Gln Gly Ile Pro
820 825 830

Gln Gly Ser Ile Leu Ser Thr Leu Leu Cys Ser Leu Cys Tyr Gly Asp
835 840 845

Met Glu Asn Lys Leu Phe Ala Gly Ile Arg Arg Asp Gly Leu Leu Leu
850 855 860

Arg Leu Val Asp Asp Phe Leu Leu Val Thr Pro His Leu Thr His Ala
865 870 875 880

Lys Thr Phe Leu Arg Thr Leu Val Arg Gly Val Pro Glu Tyr Gly Cys
885 890 895

Val Val Asn Leu Arg Lys Thr Val Val Asn Phe Pro Val Glu Asp Glu
900 905 910

Ala Leu Gly Gly Thr Ala Phe Val Gln Met Pro Ala His Gly Leu Phe
915 920 925

Pro Trp Cys Gly Leu Leu Leu Asp Thr Arg Thr Leu Glu Val Gln Ser
930 935 940

Asp Tyr Ser Ser Tyr Ala Arg Thr Ser Ile Arg Ala Ser Leu Thr Phe
945 950 955 960

Asn Arg Gly Phe Lys Ala Gly Arg Asn Met Arg Arg Lys Leu Phe Gly

965 970 975

Val Leu Arg Leu Lys Cys His Ser Leu Phe Leu Asp Leu Gln Val Asn
980 985 990

Ser Leu Gln Thr Val Cys Thr Asn Ile Tyr Lys Ile Leu Leu Leu Gln
995 1000 1005

Ala Tyr Arg Phe His Ala Cys Val Leu Gln Leu Pro Phe His Gln
1010 1015 1020

Gln Val Trp Lys Asn Pro Thr Phe Phe Leu Arg Val Ile Ser Asp
1025 1030 1035

Thr Ala Ser Leu Cys Tyr Ser Ile Leu Lys Ala Lys Asn Ala Gly
1040 1045 1050

Met Ser Leu Gly Ala Lys Gly Ala Ala Gly Pro Leu Pro Ser Glu
1055 1060 1065

Ala Val Gln Trp Leu Cys His Gln Ala Phe Leu Leu Lys Leu Thr
1070 1075 1080

Arg His Arg Val Thr Tyr Val Pro Leu Leu Gly Ser Leu Arg Thr
1085 1090 1095

Ala Gln Thr Gln Leu Ser Arg Lys Leu Pro Gly Thr Thr Leu Thr
1100 1105 1110

Ala Leu Glu Ala Ala Ala Asn Pro Ala Leu Pro Ser Asp Phe Lys
1115 1120 1125

Thr Ile Leu Asp
1130

<210> 1333

<211> 4027
<212> DNA
<213> Homo sapiens

<400> 1333
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cgcgcgctcc ccgctgccga gccgtgcgct ccctgctgcg cagccactac cgcgaggtgc 120

tgccgctggc cacgttcgtg cggcgcctgg ggccccaggg ctggcggctg gtgcagcgcg 180

gggacccggc ggctttccgc gcgctggtgg cccagtgcct ggtgtgcgtg ccctgggacg 240

cacggccgcc ccccgccgcc ccctccttcc gccaggtgtc ctgcctgaag gagctggtgg 300

cccgagtgct gcagaggctg tgcgagcgcg gcgcgaagaa cgtgctggcc ttcggcttcg 360

cgctgctgga cggggcccgc gggggccccc ccgaggcctt caccaccagc gtgcgcagct 420

acctgcccaa cacggtgacc gacgcactgc gggggagcgg ggcgtggggg ctgctgttgc 480

gccgcgtggg cgacgacgtg ctggttcacc tgctggcacg ctgcgcgctc tttgtgctgg 540

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cctggaacca tagcgtcagg gaggccgggg tccccctggg cctgccagcc ccgggtgcga 720

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ctgcccctga gccggagcgg acgcccgttg ggcaggggtc ctgggcccac ccgggcagga 840

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ccccggtgta cgccgagacc aagcacttcc tctactcctc aggcgacaag gagcagctgc 1080

ggccctcctt cctactcagc tctctgaggc ccagcctgac tggcgctcgg aggctcgtgg 1140

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cagccggtgt ctgtgcccgg gagaagcccc agggctctgt ggcggccccc gaggaggagg 1380

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acggcttcgt gcgggcctgc ctgcgccggc tggtgccccc aggcctctgg ggctccaggc 1500

acaacgaacg ccgcttcctc aggaacacca agaagttcat ctccctgggg aagcatgcca 1560

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gcaagtccta cgtccagtgc caggggatcc cgcagggctc catcctctcc acgctgctct 2580

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acaagatcct cctgctgcag gcgtacaggt ttcacgcatg tgtgctgcag ctcccatttc 3120

atcagcaagt ttggaagaac cccacatttt tcctgcgcgt catctctgac acggcctccc 3180

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gccctgtaca caggcgagga ccctgcacct ggatgggggt ccctgtgggt caaattgggg 3960

ggaggtgctg tgggagtaaa atactgaata tatgagtttt tcagttttga aaaaaaaaaa 4020

aaaaaaa 4027

<210> 1334
<211> 14

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
<221> MOD_RES
<222> (3)..(5)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (9)..(12)
<223> Any amino acid

<400> 1334
Thr Gly Xaa Xaa Xaa Asp Xaa Gly Xaa Xaa Xaa Xaa Val Ser
1 5 10

<210> 1335
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
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<222> (1)..(1)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (3)..(3)

<223> Any amino acid

<400> 1335
Xaa Val Xaa Asn Arg Pro Ser
1 5

<210> 1336
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
<221> MOD_RES
<222> (3)..(11)
<223> Any amino acid

<400> 1336
Ser Ser Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 1337
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1337
Asn Asn Asn Ala Ala Trp Asn
1 5

<210> 1338
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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peptide"

<400> 1338
Ser Asn Ser Ala Ala Trp Asn
1 5

<210> 1339
<211> 7
<212> PRT
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<220>
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peptide"

<400> 1339
Ser Asn Ser Asp Thr Trp Asn
1 5

<210> 1340
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<220>
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<400> 1340
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<210> 1341
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<220>
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<400> 1341
Ser Asn Ser Asp Thr Trp Asn
1 5

<210> 1342
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<400> 1342
Ser Asn Ser Asp Thr Trp Asn
1 5

<210> 1343
<211> 7
<212> PRT
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<220>
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<400> 1343
Ser Asn Ser Asp Thr Trp Asn
1 5

<210> 1344
<211> 7
<212> PRT
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1344

Ser Asn Ser Asp Thr Trp Asn
1 5

<210> 1345
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1345
Ser Asn Ser Asp Thr Trp Asn
1 5

<210> 1346
<211> 18
<212> PRT
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1346
Arg Thr Tyr His Arg Ser Thr Trp Tyr Asn Asp Tyr Val Gly Ser Val
1 5 10 15

Lys Ser

<210> 1347
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1347
Arg Thr Phe Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Gly

<210> 1348
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1348
Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala Ser Ser Val
1 5 10 15

Arg Gly

<210> 1349
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1349
Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala Ser Ser Val
1 5 10 15

Arg Gly

<210> 1350

<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1350
Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala Ser Ser Val
1 5 10 15

Arg Gly

<210> 1351
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1351
Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala Ser Ser Val
1 5 10 15

Arg Gly

<210> 1352
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1352

Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala Ser Ser Val
1 5 10 15

Arg Gly

<210> 1353
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1353
Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala Ser Ser Val
1 5 10 15

Arg Gly

<210> 1354
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala Ser Ser Val
1 5 10 15

Arg Gly

<210> 1355
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<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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<210> 1356
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<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1356
Gly Asp Tyr Tyr Tyr Gly Leu Asp Val
1 5

<210> 1357
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1357
Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp Ala Phe Asp Val
1 5 10 15

<210> 1358
<211> 15
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1358
Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp Ala Phe Asp Val
1 5 10 15

<210> 1359
<211> 15
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<213> Artificial Sequence

<220>
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<400> 1359
Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp Ala Phe Asp Val
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<210> 1360
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1360
Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp Ala Phe Asp Val
1 5 10 15

<210> 1361
<211> 15
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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 1361
Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp Ala Phe Asp Val
1 5 10 15

<210> 1362
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1362
Val Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp Ala Phe Asp Val
1 5 10 15

<210> 1363
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1363
Val Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp Ala Phe Asp Val
1 5 10 15

<210> 1364
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1364

Ser Asn Ser Ala Ala Trp Asn
1 5

<210> 1365
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1365
Ser Asn Tyr Met Ser
1 5

<210> 1366
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<400> 1366
Ser Asn Ser Ala Ala Trp Asn
1 5

<210> 1367
<211> 7
<212> PRT
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<220>
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<400> 1367
Ser Asn Ser Asp Thr Trp Asn
1 5

<210> 1368
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1368
Asp Tyr Ala Met His
1 5

<210> 1369
<211> 5
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1369
Asp Tyr Ala Met His
1 5

<210> 1370
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

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1 5

<210> 1371
<211> 5

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1371
Gly Tyr Tyr Met His
1 5

<210> 1372
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1372
Ser Tyr Gly Ile Ser
1 5

<210> 1373
<211> 5
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1373
Asn Ala Trp Met Asn
1 5

<210> 1374
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1374
Ser Asn Ser Asp Thr Trp Asn
1 5

<210> 1375
<211> 7
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1375
Ser Asn Ser Ala Ala Trp Asn
1 5

<210> 1376
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1376
Ser Asn Ser Asp Thr Trp Asn
1 5

<210> 1377
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 1377
Ser Ser Ser Tyr Tyr Trp Gly
1 5

<210> 1378
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1378
Ser Tyr Tyr Met His
1 5

<210> 1379
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1379
Ser Tyr Ala Met His
1 5

<210> 1380
<211> 5
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1380

Ser Tyr Tyr Met His
1 5

<210> 1381
<211> 5
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1381
Ser Tyr Ala Met Ser
1 5

<210> 1382
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1382
Ser Tyr Tyr Met His
1 5

<210> 1383
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1383
Ser Tyr Tyr Met His
1 5

<210> 1384
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1384
Ser Tyr Tyr Met His
1 5

<210> 1385
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1385
Ser Tyr Tyr Met His
1 5

<210> 1386
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1386
Ser Tyr Ala Ile Ser
1 5

<210> 1387
<211> 5

<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1387
Ser Tyr Tyr Met His
1 5

<210> 1388
<211> 5
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1388
Ser Tyr Ala Met Ser
1 5

<210> 1389
<211> 5
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1389
Ser Tyr Tyr Met His
1 5

<210> 1390
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1390
Gly Ser Trp Ile Gly
1 5

<210> 1391
<211> 5
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1391
Ser Tyr Tyr Trp Ser
1 5

<210> 1392
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1392
Asp Tyr Tyr Met Ser
1 5

<210> 1393
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 1393
Ser Tyr Tyr Met His
1 5

<210> 1394
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1394
Gly Tyr Tyr Met His
1 5

<210> 1395
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1395
Ser Tyr Asp Ile Asn
1 5

<210> 1396
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1396

Ser Tyr Gly Ile Ser
1 5

<210> 1397
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1397
Thr Phe Gly Met Ser Val Ser
1 5

<210> 1398
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1398
Thr Ser Arg His Trp Trp Asn
1 5

<210> 1399
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1399
Ser Tyr Tyr Met His
1 5

<210> 1400
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1400
Ser Tyr Tyr Met His
1 5

<210> 1401
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1401
Ser Tyr Tyr Met His
1 5

<210> 1402
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1402
Ser Tyr Tyr Met His
1 5

<210> 1403
<211> 18

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1403
Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 1404
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1404
Val Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> 1405
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1405
Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 1406
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1406
Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala Ser Ser Val
1 5 10 15

Arg Gly

<210> 1407
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1407
Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1408
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 1408
Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1409
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 1409
Arg Thr Tyr Tyr Arg Ser Thr Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 1410
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 1410
Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1411
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1411
Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> 1412
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1412
Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr Ala Asp Tyr Ala Ala Pro
1 5 10 15

Val Lys Gly

<210> 1413
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 1413
Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala Ser Ser Val
1 5 10 15

Arg Gly

<210> 1414
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1414
Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 1415
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1415
Arg Thr Tyr His Arg Ser Thr Trp Tyr Asp Asp Tyr Ala Ser Ser Val
1 5 10 15

Arg Gly

<210> 1416
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1416
Ser Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 1417
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1417
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1418
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1418
Ala Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asn Ser Val Lys
1 5 10 15

Asp

<210> 1419
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1419
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1420
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1420
Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1421
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1421
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1422
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1422
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1423
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1423
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1424
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1424
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1425
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1425
Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1426
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1426
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1427
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1427
Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1428
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1428
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1429
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1429
Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 1430
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1430
Phe Thr Ser His Ser Gly Asn Val Lys Tyr Asn Pro Ser Leu Thr Gly
1 5 10 15

<210> 1431
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1431
Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1432
<211> 17
<212> PRT
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<400> 1432
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1433
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1433
Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1434

<211> 17
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1434
Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1435
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1435
Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> 1436
<211> 16
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<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1436

Leu Ile Asp Trp Asp Asp Asp Lys Tyr Tyr Ser Thr Ser Leu Arg Thr
1 5 10 15

<210> 1437
<211> 16
<212> PRT
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1437
Gln Ile Tyr His Ser Gly Thr Thr Thr Tyr Asn Pro Ser Leu Gly Ser
1 5 10 15

<210> 1438
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1438
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1439
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1439
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1440
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1440
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1441
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1441
Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 1442

<211> 12
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1442
Glu Val Thr Gly Asp Leu Glu Asp Ala Phe Asp Ile
1 5 10

<210> 1443
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1443
Gln Ser Thr Pro Tyr Asp Ser Ser Gly Tyr Tyr Ser Gly Asp Ala Phe
1 5 10 15

Asp Ile

<210> 1444
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1444
Asp Leu Gly Trp Ile Ala Val Ala Gly Thr Phe Asp Tyr
1 5 10

<210> 1445
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1445
Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp Ala Phe Asp Val
1 5 10 15

<210> 1446
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1446
Gly Leu Ser Ser Trp His Phe His Asp Ala Leu Asp Ile
1 5 10

<210> 1447
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1447
Asp Lys Gly Gly Gly Tyr Tyr Asp Phe Trp Ser Gly Ser Asp Tyr
1 5 10 15

<210> 1448
<211> 9
<212> PRT

<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1448
Glu Gly Ser Gly Ser Tyr Tyr Ala Tyr
1 5

<210> 1449
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1449
Asp Tyr Trp Gly Tyr Tyr Gly Ser Gly Thr Leu Asp Tyr
1 5 10

<210> 1450
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1450
Ala Gly Leu Ala Leu Tyr Ser Asn Tyr Val Pro Tyr Tyr Tyr Tyr Gly
1 5 10 15

Met Asp Val

<210> 1451
<211> 5

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1451
Gly Ala Thr Asp Val
1 5

<210> 1452
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1452
Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp Ala Phe Asp Val
1 5 10 15

<210> 1453
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1453
Glu Glu Ser Ser Ser Gly Trp Tyr Glu Gly Asn Trp Phe Asp Pro
1 5 10 15

<210> 1454
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1454
Asp Arg Leu Gln Asp Gly Asn Ser Trp Ser Asp Ala Phe Asp Val
1 5 10 15

<210> 1455
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1455
Gly Arg Met Asp Thr Ala Met Ala Gln Ile
1 5 10

<210> 1456
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1456
Asp Leu Asp Val Ser Leu Asp Ile
1 5

<210> 1457
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

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<400> 1457
Val His Ser Ser Gly Tyr Tyr His Pro Gly Pro Asn Asp Tyr
1 5 10

<210> 1458
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1458
Glu Ala Gly Val Val Ala Val Asp Tyr
1 5

<210> 1459
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1459
Glu Pro Leu Phe Gly Val Val Glu Glu Asp Val Asp Tyr
1 5 10

<210> 1460
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1460

Gly Ser Gly Ser Leu Gly Asp Ala Phe Asp Ile
1 5 10

<210> 1461
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1461
Asp Gly Phe Gly Glu Leu Ser Gly Ala Phe Asp Ile
1 5 10

<210> 1462
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1462
Gly Pro Ile Gly Cys Ser Gly Gly Ser Cys Leu Asp Tyr
1 5 10

<210> 1463
<211> 12
<212> PRT
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<400> 1463
Gly Ser Tyr Gly Asp Tyr Gly Asp Ala Phe Asp Ile
1 5 10

<210> 1464
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1464
Asp His Lys Val Val Arg Phe Gly Tyr
1 5

<210> 1465
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1465
Gly Asp Tyr Tyr Met Asp Val
1 5

<210> 1466
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1466
Asp Gly Pro Ile Arg Tyr Phe Asp His Ser Lys Ala Phe Asp Ile
1 5 10 15

<210> 1467
<211> 10

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1467
Glu Met Asp Asp Ser Ser Gly Pro Asp Tyr
1 5 10

<210> 1468
<211> 14
<212> PRT
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1468
Gly Phe Leu Arg Gly Gly Asp Cys Cys Gly Ala Leu Asp Ile
1 5 10

<210> 1469
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1469
Gly Leu Asp Pro Leu Phe Ala Tyr Asp Ala Phe Glu Ile
1 5 10

<210> 1470
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1470
Asp Asp Phe Trp Ser Gly Ser Val Asp Tyr
1 5 10

<210> 1471
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1471
Glu Asp Asp Ser Ser Gly Tyr Thr Ser Pro Phe Asp Tyr
1 5 10

<210> 1472
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1472
Glu Pro Ala Ser Ser Ser Trp Tyr Gly Tyr Tyr Tyr Tyr Met Asp Val
1 5 10 15

<210> 1473
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 1473
Gly Asp Ser Asn Tyr Trp Ser Tyr Tyr Gly Met Asp Val
1 5 10

<210> 1474
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1474
Phe Ser Ser Ser Asp Ser Tyr Asp Tyr
1 5

<210> 1475
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1475
Ile Tyr Gly Gly Asp Arg Thr Asn Thr Gln Ala Pro Tyr Phe Phe Asp
1 5 10 15

Leu

<210> 1476
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1476
Asp Tyr Leu Glu Leu Ala Thr Tyr Tyr Gly Met Asp Val
1 5 10

<210> 1477
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1477
Asp Leu Ala Ala Ala Gly Asn Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 1478
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1478
Asp Asp Asp Phe Trp Ser Gly Ser Gly Ala Phe Asp Ile
1 5 10

<210> 1479
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1479
Pro Glu Gly Val Ser Tyr Tyr Asp Ser Ser Val Leu Asp Tyr
1 5 10

<210> 1480
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1480
Gly Gly Tyr Gly Asp Tyr Leu Asp Ala Phe Asp Ile
1 5 10

<210> 1481
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1481
Asp Tyr Ala Phe His
1 5

<210> 1482
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1482
Lys Tyr Gly Met Asn
1 5

<210> 1483
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1483
Asp Tyr Tyr Met Ala
1 5

<210> 1484
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1484
Thr Tyr Gly Met Ser Val Gly
1 5

<210> 1485
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1485
Ser Ser Gly Met Gln
1 5

<210> 1486

<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1486
Thr His Gly Met Gly Val Gly
1 5

<210> 1487
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1487
Thr Ser Gly Met Val Val Ser
1 5

<210> 1488
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1488
Gly Tyr Ala Met His
1 5

<210> 1489
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1489
Asp Tyr Tyr Met Ala
1 5

<210> 1490
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1490
Ser Ser Gly Met Gln
1 5

<210> 1491
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1491
Asp Tyr Ala Phe His
1 5

<210> 1492
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1492
Lys Tyr Gly Met Asn
1 5

<210> 1493
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1493
Thr Tyr Gly Met Ser Val Gly
1 5

<210> 1494
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1494
Thr His Gly Met Gly Val Gly
1 5

<210> 1495
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1495
Thr Ser Gly Met Val Val Ser
1 5

<210> 1496
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1496
Gly Tyr Ala Met His
1 5

<210> 1497
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1497
Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gly

<210> 1498
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1498
Ser Ile Ser Ser Thr Ser Ile Tyr Ile Tyr Tyr Ala Asp Thr Val Lys
1 5 10 15

Gly

<210> 1499
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1499
Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys Gly
1 5 10 15

<210> 1500
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1500
Asp Ile Trp Trp Asp Asp Asp Lys His Tyr Asn Pro Ser Leu Lys Asn
1 5 10 15

<210> 1501
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 1501
Gly Ile Tyr Tyr Asp Ser Tyr Lys Lys Ser Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1502
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1502
Asn Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Asn
1 5 10 15

<210> 1503
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1503
Ala Ile Ala Trp Asp Gly Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 1504
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 1504
Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gly

<210> 1505
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 1505
Ser Ile Ser Tyr Glu Gly Asn Pro Tyr Tyr Gly Asp Ser Val Lys Gly
1 5 10 15

<210> 1506
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 1506
Gly Ile Tyr Tyr Asp Ser Tyr Lys Lys Ser Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 1507
<211> 17

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1507
Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gly

<210> 1508
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1508
Ser Ile Ser Ser Thr Ser Ile Tyr Ile Tyr Tyr Ala Asp Thr Val Lys
1 5 10 15

Gly

<210> 1509
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1509
Asp Ile Trp Trp Asp Asp Asp Lys His Tyr Asn Pro Ser Leu Lys Asn

1 5 10 15

<210> 1510
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1510
Asn Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Asn
1 5 10 15

<210> 1511
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1511
Ala Ile Ala Trp Asp Gly Asp Lys Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 1512
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1512
Trp Ile Asn Thr Tyr Ser Gly Lys Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gly

<210> 1513
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1513
Gly Ala Tyr Tyr Gly Tyr Arg Asp Trp Phe Thr Tyr
1 5 10

<210> 1514
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1514
His Asp Tyr Ser Ser Tyr Ser Tyr
1 5

<210> 1515
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1515
His Asp His Asn Asn Val Asp Trp Phe Ala Tyr
1 5 10

<210> 1516
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
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<400> 1516
Ser Ser Thr Thr Asp Gly Ile Val Thr Tyr Val Met Asp Val
1 5 10

<210> 1517
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1517
Ser Ala Tyr Tyr Gly Tyr Lys Asp Tyr Phe Asp Tyr
1 5 10

<210> 1518
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1518
Ile Glu Gly Ser Pro Val Val Thr Thr Val Phe Asp Tyr
1 5 10

<210> 1519
<211> 12

<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1519
Arg Asp Tyr Asp Val Gly Tyr Tyr Tyr Phe Asp Phe
1 5 10

<210> 1520
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1520
Ser Thr Tyr Tyr Gly Tyr Lys Asp Trp Phe Ala Tyr
1 5 10

<210> 1521
<211> 11
<212> PRT
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1521
His Asp His Asn Asn Val Asp Trp Phe Ala Tyr
1 5 10

<210> 1522
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1522
Ser Ala Tyr Tyr Gly Tyr Lys Asp Tyr Phe Asp Tyr
1 5 10

<210> 1523
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1523
Gly Ala Tyr Tyr Gly Tyr Arg Asp Trp Phe Thr Tyr
1 5 10

<210> 1524
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 1524
His Asp Tyr Ser Ser Tyr Ser Tyr
1 5

<210> 1525
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic

peptide"

<400> 1525
Ser Ser Thr Thr Asp Gly Ile Val Thr Tyr Val Met Asp Val
1 5 10

<210> 1526
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
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1 5 10

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<212> PRT
<213> Artificial Sequence

<220>
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<400> 1527
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<210> 1528
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<213> Artificial Sequence

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<400> 1528

Ser Thr Tyr Tyr Gly Tyr Lys Asp Trp Phe Ala Tyr
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<210> 1529
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<212> PRT
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<220>
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<400> 1529
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1 5 10

TERAPIAS CD20, TERAPIAS CD22 Y TERAPIAS DE COMBINACIÓN CON UNA CÉLULA QUE EXPRESA UN RECEPTOR QUIMÉRICO DE ANTÍGENO (CAR) DE CD19

Esta solicitud reivindica la prioridad de la solicitud de Estados Unidos de Nº Serial 62/144.615 presentada el 8 de abril de de 2015, Estados Unidos Nº Serial 62/144.497 presentada el 8 de abril del año 2015 Estados Unidos Nº Serial 62/144.639 presentada el 8 de abril de 2015, Estados Unidos Nº Serial 62/207.255 presentada el 19 de agosto de 2015, Estados Unidos Nº Serial 62/263.423 presentada el 04 de diciembre 2015, los contenidos de las cuales se incorporan en el presente documento por referencia en su totalidad.

CAMPO DE LA INVENCIÓN

La presente invención se refiere en general al uso de células T modificadas para expresar un Receptor Quimérico de Antígeno (CAR) opcionalmente en combinación con un inhibidor de células B, por ejemplo, uno o más inhibidores de CD10, CD19, CD20, CD22, CD34, CD123, FLT- 3, ROR1, CD79b, CD179b, o CD79a, para tratar una enfermedad asociada con la expresión de la proteína del grupo de diferenciación 19 (CD19).

FUNDAMENTO DE LA INVENCIÓN

Muchos pacientes con tumores malignos de células B no pueden ser curados con terapia estándar. Además, las opciones de tratamiento tradicionales a menudo tienen efectos secundarios graves. Se han hecho intentos en inmunoterapia del cáncer; sin embargo, varios obstáculos hacen que lograr la eficacia clínica en relación con este objetivo sea muy difícil. Aunque se han identificado cientos de presuntos antígenos tumorales, estos se derivan generalmente de uno mismo y por lo tanto son poco inmunogénicos. Por otra parte, los tumores utilizan diversos mecanismos para volverse hostiles a la iniciación y propagación de ataques inmunes.

Desarrollos recientes usando terapia con células T autólogas modificadas (TCAR) con receptores quiméricos de antígeno (CAR), los cuales se basan en la reorientación de las células T a una molécula de la superficie celular adecuada en células cancerosas, tales como tumores

malignos de células B, muestran resultados prometedores en el aprovechamiento de la capacidad del sistema inmunitario para tratar tumores malignos de células B y otros tipos de cáncer (véase, por ejemplo, Sadelain et al., Cancer Discovery 3: 388-398 (2013)). Los resultados clínicos de células TCAR19 murinas (es decir, "CTL019") han demostrado ser prometedores en el establecimiento de remisiones completas en pacientes que sufren de LLC, así como en LLA infantil (véase, por ejemplo, Kalos et al., Sci Transl Med 3: 95ra73 (2011), Porter et al., NEJM 365: 725-733 (2011), Grupp et al., NEJM 368: 1509-1518 (2013)). Además de la capacidad que tiene el receptor quimérico de antígeno en las células T modificadas genéticamente para reconocer y destruir las células blanco, una terapia con células T terapéuticas exitosa requiere tener la capacidad de proliferar y persistir en el tiempo con el fin de identificar la recaída de leucemia. La calidad variable de las células T, que resulta de la anergia, supresión o agotamiento, tendrá efectos sobre el desempeño de las células T transformadas con CAR, sobre las cuales los profesionales calificados tienen control limitado en este momento. Para ser eficaces, las células T de pacientes transformadas con CAR deben persistir y mantener la capacidad de proliferar en respuesta al antígeno cognado. Se ha demostrado que las células T de pacientes con LLA pueden hacer esto con TCAR19 que comprende un scFv murino (véase, por ejemplo, Grupp et al., NEJM 368: 1509-1518 (2013)).

BREVE DESCRIPCIÓN DE LA INVENCIÓN

La divulgación presenta, al menos parcialmente, un método para tratar un trastorno asociado con la expresión de la proteína del grupo de diferenciación 19 (CD19) (por ejemplo, No. de Acc. OMIM 107265, Swiss Prot. P15391). En ciertas modalidades, la enfermedad es un cáncer, por ejemplo, un cáncer hematológico. En algunas modalidades, el método comprende la administración de una molécula de Receptor Quimérico de Antígeno (CAR) que une a CD19 en combinación con un inhibidor de células B, por ejemplo, uno o más (por ejemplo, uno, dos, tres o más) inhibidores de células B. En algunas modalidades, el inhibidor de células B se selecciona de entre un inhibidor de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3 o ROR1, o una combinación de los mismos. En algunas modalidades, la combinación mantiene o tiene mejor eficacia clínica en comparación con cualquiera de las terapias administradas individualmente. En algunas modalidades, los métodos del presente documento implican el uso de células modificadas, por ejemplo, células T, para expresar una molécula de CAR que une a CD19, en

combinación con un inhibidor de células B (por ejemplo, un anticuerpo (por ejemplo, un anticuerpo mono o biespecífico), a un segundo blanco B, por ejemplo, CD10, CD19, CD20, CD22, CD34, CD123, FLT-3 o ROR1) o una célula que expresa CAR, por ejemplo, una célula efectora inmune que expresa CAR, que se une al segundo blanco de células B, o a una combinación de los mismos) para tratar la condición asociada a la expresión de CD19. La divulgación también caracterizadominios novedosos de unión a antígeno y moléculas de CAR dirigidas a CD20 y CD22, y usos, por ejemplo como monoterapias o terapias de combinación.

En consecuencia, en un aspecto, la invención se refiere a un método para tratar un sujeto (por ejemplo, un mamífero) que tiene una enfermedad asociada con la expresión de CD19. El método comprende la administración al sujeto de un inhibidor de CD19, por ejemplo, una molécula de CAR que une a CD19 descrita en el presente documento, en combinación con un inhibidor de células B. Por ejemplo, el método comprende administrar al sujeto una cantidad eficaz de una o más células que expresan una molécula de CAR que une a CD19, por ejemplo, una molécula de CAR que une CD19 descrita en el presente documento (por ejemplo, CD19 de tipo silvestre o mutante), en combinación con un inhibidor de células B. En ciertas modalidades, el inhibidor de células B se selecciona de entre un inhibidor de CD10, por ejemplo, uno o más inhibidores de CD10 descritos en el presente documento; un inhibidor de CD20, por ejemplo, uno o más inhibidores de CD20 descritos en el presente documento; un inhibidor de CD22, por ejemplo, uno o más inhibidores de CD22 descritos en el presente documento; un inhibidor de CD34, por ejemplo, uno o más inhibidores de CD34 descritos en el presente documento; un inhibidor de CD123, por ejemplo, uno o más inhibidores de CD123 descritos en el presente documento; un inhibidor de FLT-3, por ejemplo, uno o más inhibidores de FLT-3 descritos en el presente documento; un inhibidor de ROR1, por ejemplo, uno o más inhibidores de ROR1; un inhibidor de CD79b, por ejemplo, uno o más inhibidores de CD79b descritos en el presente documento; descritos en el presente documento; un inhibidor de CD179b, por ejemplo, uno o más inhibidores de CD179b descritos en el presente documento; un inhibidor de CD79a, por ejemplo, uno o más inhibidores de CD79a descritos en el presente documento; o cualquier combinación de los mismos. En ciertos aspectos, se divulga un método para tratar un sujeto que tiene una leucemia de células B o un linfoma de células B, el cual comprende administrar al sujeto una cantidad eficaz de una o más células que expresan una molécula de CAR que une a CD19, en combinación con uno o más inhibidores de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, or CD79a.

En un aspecto relacionado, la presente descripción proporciona un método para reducir la proliferación de células que expresan CD19, por ejemplo, administrando a un sujeto, por ejemplo, un paciente que lo necesita, una terapia de combinación como se describe en el presente documento, por ejemplo, un inhibidor de CD19 en combinación con un inhibidor de células B, por ejemplo, uno o más inhibidores de células B tal como se describen en el presente documento. En otro aspecto, la presente descripción proporciona un método para eliminar de manera selectiva células que expresan CD19, por ejemplo, administrando a un sujeto, por ejemplo, un paciente que lo necesita, una terapia de combinación como se describe en el presente documento, por ejemplo, un inhibidor de CD19 en combinación con un inhibidor de células B, por ejemplo, uno o más inhibidores de células B tal como se describen en el presente documento. En ciertos aspectos, la descripción proporciona un método para proporcionar una inmunidad anti-tumoral en un sujeto, por ejemplo, un mamífero, el cual comprende administrar al mamífero una cantidad eficaz de una combinación (por ejemplo, una o más células que expresan CAR) tal como se describe en el presente documento.

En un aspecto, la divulgación proporciona un método para prevenir una recaída negativa para CD19 en un mamífero, el cual comprende administrar al mamífero una o más inhibidores de células B, donde el inhibidor de células B comprende un inhibidor de una o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a.

En otro aspecto, la descripción proporciona un método para tratar un sujeto que tiene una enfermedad asociada con la expresión de CD19, por ejemplo, DLBCL (por ejemplo, DLBCL primario). El método comprende administrar al sujeto una cantidad eficaz de una o más células que expresan una molécula de CAR que une a CD19, por ejemplo, un CAR de CD19, opcionalmente en combinación con un inhibidor de PD1.

Opcionalmente, el sujeto tiene, o se identifica por tener, al menos 5 %, 6 %, 7 %, 8 %, 9 %, 10 %, 20 %, 30 %, 40 %, 50 %, 60 %, 70 %, 80 % o 90 % de células cancerosas, por ejemplo, células DLBCL, que son CD3+/PD1+.

En un aspecto, la descripción proporciona un método para tratar un sujeto que tiene una enfermedad asociada con la expresión de CD19, por ejemplo, DLBCL. El método comprende administrar al sujeto una cantidad eficaz de una o más células que expresan una molécula de CAR que une a CD19, por ejemplo, un CAR de CD19, en combinación con un inhibidor de PD-

L1. Opcionalmente, el sujeto tiene, o se identifica por tener, menos de 20 %, 10 %, 9 %, 8 %, 7 %, 6 %, 5 %, 4 %, 3 %, 2 % o 1 % de células en el cáncer, por ejemplo, microambiente del cáncer, que son doble positivas para CD19 y PD-L1.

En un aspecto, la descripción proporciona uno o más inhibidores de células B, en donde el inhibidor de células B comprende un inhibidor de uno o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a, para su uso en el tratamiento de un sujeto que tiene una enfermedad asociada con la expresión de CD19, y en el que dicho sujeto ha recibido, recibe o está a punto de recibir una célula que expresa una molécula de CAR que se une a CD19, por ejemplo, un CAR CD19.

PROGRAMACIÓN Y DOSIS DE LA ADMINISTRACIÓN EN COMBINACIÓN

La una o más terapias descritas en el presente documento se pueden administrar al sujeto sustancialmente al mismo tiempo o en cualquier orden. Por ejemplo, un inhibidor de CD19, una célula que expresa un CAR descrita en el presente documento, el uno o más inhibidor de células B y/o opcionalmente el al menos uno agente terapéutico adicional se pueden administrar simultáneamente, en la misma composición o en composiciones separadas, o de manera secuencial.

Para la administración secuencial, la célula que expresa un CAR descrita en el presente documento (por ejemplo, una célula que expresa un CAR de CD19, una célula que expresa un CAR de CD20, una célula que expresa un CAR de CD22) se puede administrar primero y luego se puede administrar el agente adicional, o el orden de administración puede ser invertido. En algunas modalidades, la primera terapia (por ejemplo, una célula que expresa un CAR tal como una célula TCAR de CD19, una célula TCAR de CD20, una célula TCAR de CD22) se continúa cuando se introduce la segunda terapia, y en otras modalidades la primera terapia se interrumpe antes, después o simultáneamente cuando se introduce la segunda terapia. En casos de administración secuencial, en algunas modalidades, la segunda terapia se inicia después de un período de tiempo predeterminado, o después de que el sujeto muestra uno o más indicios de que ha ocurrido una recaída o de que es probable que ocurra. El indicio puede ser, por ejemplo, la presencia de células cancerosas que tienen una alteración en el blanco de la primera terapia, por ejemplo, CD19, CD20 o CD22. La alteración puede ser, por ejemplo, una mutación de desplazamiento del marco y/o un codón prematuro de terminación.

En otras modalidades, las dos o más terapias (por ejemplo, una célula que expresa un CAR de CD19 y un inhibidor de células B) se administran simultáneamente. Al margen de las limitaciones que impone la teoría, en algunas modalidades, la administración simultánea de las terapias puede reducir la probabilidad de recaída y/o retrasar la recaída.

Cuando se administran en combinación, la primera terapia (por ejemplo, la terapia con CAR, por ejemplo, una célula que expresa un CAR dirigida contra CD19, CD20 o CD22) y el agente adicional (por ejemplo, un segundo o tercer agente, por ejemplo, un inhibidor de células B), o todos, se pueden administrar en una cantidad o dosis mayor, menor o igual a la cantidad o dosis de cada agente usado de manera individual, por ejemplo, como una monoterapia. En ciertas modalidades, la cantidad o la dosis administrada de la primera terapia, la segunda terapia, opcionalmente una tercera terapia, o todas, es menor (por ejemplo, al menos 20 %, al menos 30 %, al menos 40 % o al menos 50 % menor) a la cantidad o la dosis de cada agente cuando se usa individualmente, por ejemplo, como una monoterapia. En otras modalidades, la cantidad o la dosis administrada de la primera terapia, la segunda terapia, opcionalmente una tercera terapia, o todas, que produce un efecto deseado (por ejemplo, tratamiento del cáncer) es menor (por ejemplo, al menos 20%, al menos 30 %, al menos 40 % o al menos 50 % menor) a la cantidad o la dosis requerida de cada agente cuando se usa de manera individual, por ejemplo, como una monoterapia, para conseguir el mismo efecto terapéutico. En ciertas modalidades, la dosis más baja produce una reducción en los efectos secundarios en comparación con aquellos que se observan cuando se administra la dosis regular (monoterapia).

En una modalidad, la terapia comprende una población de células. En modalidades, las células son células inmunes efectoras, por ejemplo, células que expresan CAR.

Alternativamente, o en combinación con los métodos descritos en el presente documento, se describen métodos que comprenden una etapa de diagnóstico o una etapa de selección del paciente, por ejemplo, tal como se describe a continuación.

En un aspecto, la invención proporciona un método para evaluar un sujeto, por ejemplo, un paciente, para determinar su estado recidivante (por ejemplo, recidivante o no recidivante después de una terapia con CAR). En una modalidad, el método identifica un sujeto, por ejemplo, un paciente, que ha sufrido una recaída ("recidivante") o que probablemente sufrirá una

recaída, o que no ha sufrido una recaída ("no recidivante"), o que probablemente no sufrirá una recaída, después de un tratamiento con CAR (por ejemplo, una terapia con TCAR de CD19, por ejemplo, tal como se describe en el presente documento, por ejemplo, una terapia con CTL019). En una modalidad, el estado recidivante (por ejemplo, recidivante o no recidivante después de una terapia con TCAR) se determina sometiendo a ensayo una o más características de CD19.

En una modalidad, la una o más características de CD19 incluyen una alteración en una secuencia de ácido nucleico (por ejemplo, una mutación tal como una inserción, una deleción o una sustitución, o una combinación de las mismas), una alteración en un nivel de ácido nucleico, una alteración en una secuencia de proteína, o una alteración en un nivel de proteína, o una combinación de las mismas. En una modalidad, un sujeto recidivante tiene una o más mutaciones en CD19, por ejemplo, una o más mutaciones (por ejemplo, inserciones o deleciones) en el exón 2 de CD19. En una modalidad, un sujeto recidivante tiene una o más mutaciones en el exón 1, exón 2, exón 3, exón 4, exón 5, exón 6 o exón 7 de CD19. En una modalidad, la mutación produce un codón de terminación prematuro, por ejemplo, por una inserción o deleción que conduce a un desplazamiento del marco, por ejemplo, en el exón 2 de CD19. En una modalidad, la mutación es una mutación de la **Tabla 31**.

En una modalidad, la característica de CD19 se compara con una característica de referencia. Por ejemplo, cuando la característica es una secuencia (por ejemplo, secuencia de ácido nucleico o proteína de una muestra biológica), la característica de referencia puede ser una secuencia de tipo silvestre (por ejemplo, secuencia de ácido nucleico o proteína) de CD19. La característica puede ser el porcentaje de células de la muestra que tienen una secuencia mutante. Cuando la característica es un nivel (por ejemplo, nivel de ácido nucleico o proteína), la característica de referencia puede ser un nivel de tipo silvestre (por ejemplo, nivel de ácido nucleico o proteína) de CD19. La característica puede ser el nivel de ácido nucleico o proteína de la muestra. La característica puede ser el porcentaje de células de la muestra que tiene un nivel de ácido nucleico o proteína que está por encima de un umbral dado.

En una modalidad, se proporcionan métodos para identificar un sujeto que tiene cáncer, por ejemplo, un cáncer hematológico, tal como, por ejemplo, LLC o LLA, como recidivante o no recidivante después de un tratamiento que comprende una terapia con CAR, por ejemplo, una terapia con TCAR de CD19. El método comprende: (1) adquirir una muestra del sujeto (por ejemplo, una muestra de aféresis obtenida a partir de la sangre del sujeto; y/o, por ejemplo, una

muestra de producto fabricado, por ejemplo, células T genéticamente modificadas obtenidas a partir de la sangre del sujeto); (2) determinar una característica de CD19, por ejemplo, una secuencia o nivel tal como se describe en el presente documento; y (3) (opcionalmente) comparar la característica determinada de CD19 con una característica de referencia; donde la diferencia, por ejemplo, una diferencia estadísticamente significativa, entre la característica determinada con respecto a la característica de referencia, es predictiva de recaída frente a la terapia con CAR; y (4) identificar al sujeto como recidivante o no recidivante frente a la terapia con CAR, por ejemplo, con base a la característica determinada de CD19. En una modalidad, la presencia o ausencia de la característica de CD19 es la presencia o ausencia de un codón de terminación prematuro, por ejemplo, por una inserción o deleción que conduce a un desplazamiento del marco. En una modalidad, la presencia de la característica de CD19 es una mutación de la **Tabla 31**.

En una modalidad, los métodos proporcionados comprenden (1) adquirir una muestra del sujeto (por ejemplo, una muestra de aféresis obtenida a partir de la sangre del sujeto; y/o, por ejemplo, una muestra de producto fabricado, por ejemplo, células T genéticamente modificadas obtenidas a partir de la sangre del sujeto, por ejemplo, un producto de TCAR19 fabricado); (2) determinar una característica de CD19, por ejemplo, una secuencia o nivel tal como se describe en el presente documento; y (3) (opcionalmente) comparar la característica determinada de CD19 con una característica de referencia; donde la presencia de la característica de CD19 (por ejemplo, la diferencia, por ejemplo, una diferencia estadísticamente significativa, entre la característica determinada con respecto a la característica de referencia) es predictiva de recaída frente a la terapia con CAR. En una modalidad, la presencia de la característica de CD19 es la presencia de un codón de terminación prematuro, por ejemplo, por una inserción o deleción que conduce a un desplazamiento del marco. En una modalidad, la presencia de la característica de CD19 es una mutación de la **Tabla 31**.

En una modalidad, se proporcionan métodos para determinar la recaída de un sujeto que tiene cáncer, por ejemplo, un cáncer hematológico tal como LLC o LLA, después de un tratamiento que comprende una terapia con CAR, por ejemplo, una terapia con CAR de CD19 tal como se describe en el presente documento. El método comprende determinar una característica de CD19 en una muestra obtenida antes de la recaída. En una modalidad, la presencia de la característica de CD19 (por ejemplo, la diferencia, por ejemplo, una diferencia

estadísticamente significativa entre la característica determinada en comparación con la característica de referencia) es indicativa de la recaída después de la terapia con CAR. En una modalidad, la presencia de la característica de CD19 es la presencia de un codón de terminación prematuro, por ejemplo, por una inserción o deleción que conduce a un desplazamiento del marco. En una modalidad, la presencia de la característica de CD19 es una mutación de la **Tabla 31**.

En una modalidad, se proporcionan métodos para evaluar a un sujeto que tiene cáncer, por ejemplo, un cáncer hematológico tal como LLC o LLA. El método comprende adquirir un valor de estado recidivante para el sujeto, que comprende una medición de una o más características de CD19, por ejemplo, una o más de las características de CD19 descritas en el presente documento, evaluando de esta manera al sujeto.

En una modalidad, se proporcionan métodos para evaluar o monitorear la eficacia de una terapia con CAR, por ejemplo, una terapia con TCAR de CD19, en un sujeto que tiene cáncer, que comprende adquirir un valor de estado recidivante para el sujeto, que comprende una medición de una o más características de CD19, por ejemplo, una o más de las características de CD19 descritas en el presente documento, evaluando o monitoreando de este modo la eficacia de la terapia con CAR en el sujeto.

En una modalidad, se proporcionan métodos para obtener una predicción de la tasa de éxito de una terapia con CAR, por ejemplo, una terapia con TCAR de CD19, por ejemplo, tal como la que se describe en el presente documento, en un sujeto que tiene cáncer. Dicho método comprende las etapas de proporcionar una muestra biológica del sujeto, determinar una o más características de CD19, por ejemplo, una o más de las características de CD19 descritas en el presente documento y, con base en la característica determinada, proporcionar un pronóstico para el sujeto.

En algunos aspectos, la presente divulgación proporciona, por ejemplo, un método, o un ensayo, para identificar un sujeto que tiene cáncer con una probabilidad mayor o menor de responder a un tratamiento que comprende una terapia con un receptor quimérico de antígeno (CAR), donde el método comprende:

(1) adquirir una muestra del sujeto;

(2) determinar un valor para uno o más de:

(i) un nivel de uno o más marcadores enumerados en la **Tabla 29** en la muestra;

(ii) una característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de terminación prematuro o ambos, o

(iii) un nivel o actividad de células T_{REG}; y

(3) (opcionalmente) comparar el valor determinado, por ejemplo, el nivel, la actividad o la característica de (i), (ii) o (iii), o una combinación de los mismos, con un valor de referencia, donde la diferencia, por ejemplo, una diferencia estadísticamente significativa, entre el valor determinado en comparación con el valor de referencia puede predecir la capacidad de respuesta del sujeto a la terapia con CAR; y

(4) identificar al sujeto como con respuesta completa, respuesta parcial o sin respuesta, o recidivante o no recidivante a la terapia con CAR, con base en el valor determinado.

En ciertas modalidades, cualquiera de los métodos antes mencionados puede incluir, además, lo siguiente:

(i) administrar al sujeto una dosis terapéuticamente eficaz de una terapia con CAR, por ejemplo, una terapia que comprende una célula que expresa CD19, si no se detecta ninguna diferencia, por ejemplo, ninguna diferencia estadísticamente significativa, en el valor de uno, dos o más (todos) de (i) el nivel o la actividad de uno o más marcadores enumerados en la **Tabla 29**; (ii) la característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de terminación prematuro o ambos, o (iii) el nivel de células T_{REG} de una muestra biológica;

(ii) administrar al sujeto una dosis terapéuticamente eficaz de una terapia con CAR, por ejemplo, una terapia que comprende una célula que expresa CD19 y uno o más inhibidores de células B (por ejemplo, uno o más inhibidores de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1, tal como se describen en el presente documento) si se detecta ninguna diferencia, por ejemplo, una diferencia estadísticamente significativa, en el valor de uno, dos o más (todos) de (i) el nivel o la actividad de uno o más marcadores enumerados en la **Tabla 29**; (ii) la característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de terminación prematuro o ambos, o (iii) el nivel de células T_{REG} de una muestra biológica; o

(iii) interrumpir una primera terapia, por ejemplo, una terapia que comprende una célula que expresa CD19, y administrar una segunda terapia, por ejemplo, uno o más inhibidores de células B (por ejemplo, uno o más inhibidores de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1, tal como se describen en el presente documento) si se detecta ninguna diferencia, por ejemplo, una diferencia estadísticamente significativa, en el valor de uno, dos o más (o todos) de (i) el nivel o la actividad de uno o más marcadores enumerados en la **Tabla 29**; (ii) la característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de terminación prematuro o ambos, o (iii) el nivel de células T_{REG} de una muestra biológica.

Los pasos de administración (i)-(iii) se pueden realizar antes o después de las etapas de evaluación del paciente, tal como se describe en modalidades de ejemplo más adelante.

En ciertos aspectos, se divulga un método para tratar un sujeto que tiene cáncer. El método comprende:

(a) adquirir, por ejemplo, determinar si el sujeto tiene, un valor de uno, dos o más (todos) de:

(i) un nivel de uno o más marcadores enumerados en la **Tabla 29**;

(ii) una característica de CD19, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de terminación prematuro o ambos, o

(iii) un nivel o actividad de células T_{REG} de una muestra biológica, y

(b) una respuesta a dicho valor, incluye además lo siguiente:

(i) administrar al sujeto una dosis terapéuticamente eficaz de una terapia con CAR, por ejemplo, una terapia que comprende una célula que expresa CD19, si no se detecta ninguna diferencia, por ejemplo, ninguna diferencia estadísticamente significativa, en uno, dos o más (o todos) de (i) el nivel o la actividad de uno o más marcadores enumerados en la **Tabla 29**; (ii) la característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de terminación prematuro o ambos, o (iii) el nivel de células T_{REG} de una muestra biológica;

(ii) administrar al sujeto una dosis terapéuticamente eficaz de una terapia con CAR, por ejemplo, una terapia que comprende una célula que expresa CD19 y uno o más inhibidores

de células B (por ejemplo, uno o más inhibidores de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1, tal como se describen en el presente documento) si se detecta ninguna diferencia, por ejemplo, una diferencia estadísticamente significativa, en uno, dos o más (o todos) de (i) el nivel o la actividad de uno o más marcadores enumerados en la **Tabla 29**; (ii) la característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de terminación prematuro o ambos, o (iii) el nivel de células T_{REG} de una muestra biológica; o

(iii) interrumpir una primera terapia, por ejemplo, una terapia que comprende una célula que expresa CD19, y administrar una segunda terapia, por ejemplo, uno o más inhibidores de células B (por ejemplo, uno o más inhibidores de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1, tal como se describen en el presente documento) si se detecta ninguna diferencia, por ejemplo, una diferencia estadísticamente significativa, en uno o más de (i) el nivel o la actividad de uno o más marcadores enumerados en la **Tabla 29**; (ii) la característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de terminación prematuro o ambos, o (iii) el nivel de células T_{REG} de una muestra biológica.

En otro aspecto, se proporciona un método para tratar un sujeto que tiene cáncer. El método incluye:

(a) administrar a un sujeto una dosis terapéuticamente eficaz de una terapia con CAR, por ejemplo, una terapia que comprende una célula que expresa CD19,

(b) adquirir un valor para (por ejemplo, determinar si el sujeto tiene) uno, dos o más (todos) de:

(i) un nivel de uno o más marcadores enumerados en la **Tabla 29**;

(ii) una característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de terminación prematuro o ambos, o

(iii) un nivel o actividad de células T_{REG} de una muestra biológica, y

(c) en respuesta al valor o determinación en la etapa (b) (I-III), realizar una o más de lo siguiente:

(i) administrar al sujeto una dosis terapéuticamente eficaz de una terapia con CAR,

por ejemplo, una terapia que comprende una célula que expresa CD19, si no se detecta ninguna diferencia, por ejemplo, ninguna diferencia estadísticamente significativa, en uno o más de (i) el nivel o la actividad de uno o más marcadores enumerados en la **Tabla 29**; (ii) la característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de terminación prematuro o ambos, o (iii) el nivel de células T $_{REG}$ de muestra biológica;

(ii) administrar al sujeto una dosis terapéuticamente eficaz de una terapia con CAR, por ejemplo, una terapia que comprende una célula que expresa CD19 y uno o más inhibidores de células B (por ejemplo, uno o más inhibidores de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1, tal como se describen en el presente documento) si se detecta ninguna diferencia, por ejemplo, una diferencia estadísticamente significativa, en uno o dos de (i) el nivel o la actividad de uno o más marcadores enumerados en la **Tabla 29**; (ii) la característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de terminación prematuro o ambos, o (iii) el nivel de células T $_{REG}$ de muestra biológica; o

(iii) interrumpir una primera terapia, por ejemplo, una terapia que comprende una célula que expresa CD19, y administrar una segunda terapia, por ejemplo, uno o más inhibidores de células B (por ejemplo, uno o más inhibidores de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1, tal como se describen en el presente documento) si se detecta ninguna diferencia, por ejemplo, una diferencia estadísticamente significativa, en uno o más de (i) el nivel o la actividad de uno o más marcadores enumerados en la **Tabla 29**; (ii) la característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de terminación prematuro o ambos, o (iii) el nivel de células T_{REG} de muestra biológica.

En algunas modalidades de cualquiera de los métodos antes mencionados, la muestra es una muestra biológica seleccionada de una muestra de sangre, plasma o suero. En una modalidad particular, una muestra biológica es una muestra de sangre. En una modalidad, la muestra es una muestra de aféresis, por ejemplo, células T obtenidas de la sangre del sujeto. En una modalidad, la muestra es una muestra de producto fabricado, por ejemplo, células T genéticamente modificadas obtenidas de la sangre del sujeto, por ejemplo, un producto de CAR fabricado, por ejemplo, un producto de TCAR19 fabricado.

En una modalidad, los métodos de este documento se pueden usar para determinar si es

probable que un paciente responda a la terapia con CAR (por ejemplo, TCAR de CD19), por ejemplo, si es probable que un paciente que no ha recibido terapia con CAR responda a la terapia con CAR, o si es probable que un paciente que ha recibido terapia con CAR responda a la terapia con CAR continuada. En general, las mismas características de CD19 que predicen la recaída predicen que un paciente tiene una menor probabilidad de responder a la terapia con CAR de CD19. A un paciente que se identifica como menos propenso a responder a una terapia con CAR de CD19, se puede administrar un tipo diferente de terapia, tal como un inhibidor de células B (por ejemplo, uno o más inhibidores de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a, tal como se describen en el presente documento).

En otro aspecto, se proporciona un método para tratar un sujeto que tiene cáncer, por ejemplo, un cáncer hematológico. En una modalidad, el método incluye determinar si un sujeto tiene una diferencia, por ejemplo, una diferencia estadísticamente significativa, en una característica de CD19 en relación con una característica de referencia, y si hay una diferencia, por ejemplo, una diferencia estadísticamente significativa entre la característica determinada y la característica de referencia, administrar al sujeto una dosis terapéuticamente eficaz de una terapia con CAR, por ejemplo, TCAR, tratando de este modo al sujeto. En una modalidad, la característica es la secuencia de CD19, por ejemplo, secuencia de ácido nucleico o proteína. En una modalidad, el método comprende realizar ensayos para detectar la presencia o la ausencia de CD19 con desplazamiento del marco, por ejemplo, CD19 que comprende un codón de terminación prematuro.

En modalidades de cualquiera de los métodos anteriormente mencionados, el tratamiento consiste en la administración de una célula que expresa un CAR de CD19, opcionalmente en combinación con uno o más inhibidores de células B. En una modalidad, la terapia con CAR de CD19 se administra de manera simultánea con el uno o más inhibidores de células B (por ejemplo, uno o más inhibidores de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a, tal como se describen en el presente documento). En una modalidad, la terapia con CAR de CD19 se administra antes del uno más inhibidores de células B. En una modalidad, la terapia con CAR de CD19 se administra después del uno o más inhibidores de células B.

En una modalidad, en la que hay una diferencia entre la característica determinada y la característica de referencia, el método comprende modificar el producto de CAR antes de la

infusión en el sujeto. En una modalidad, en la que hay una diferencia entre la característica determinada y la característica de referencia, el método comprende modificar la fabricación de un producto de CAR antes de la infusión en el sujeto. En una modalidad, si hay una diferencia entre la característica determinada y la característica de referencia, el procedimiento comprende ajustar la dosis de infusión de CAR para lograr un efecto anticancerígeno.

En una modalidad, los métodos de tratamiento comprenden determinar si un sujeto tiene una mayor probabilidad de responder a una terapia con CAR, por ejemplo, una terapia con CAR de CD19, por ejemplo, una terapia con CAR de CD19 descrita en el presente documento, comparando una característica de CD19 en una muestra del sujeto con respecto a una característica de referencia, donde una diferencia en la característica con respecto a la característica de referencia indica una mayor probabilidad de respuesta; y administrar al sujeto una dosis terapéuticamente eficaz de una terapia con CAR, tratando de este modo al sujeto.

En una modalidad, los métodos de tratamiento comprenden obtener una muestra de un sujeto; determinar una característica de CD19 (por ejemplo, la presencia o ausencia de un desplazamiento del marco o un codón de terminación prematuro), con respecto a una característica de referencia; y la administración de una dosis terapéuticamente eficaz de una célula que expresa CAR, si se identifica que el sujeto tiene una diferencia estadísticamente significativa entre la característica de CD19 de la muestra y una característica de referencia de la muestra.

La característica de CD19 se puede usar para diseñar un tratamiento para el paciente. Por ejemplo, en una modalidad, cuando una muestra de un paciente comprende CD19 de tipo silvestre, se administra al paciente un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD19, por ejemplo, una célula TCAR de CD19. En una modalidad, cuando una muestra de un paciente comprende CD19 mutante, por ejemplo, CD19 con desplazamiento de marco, por ejemplo, CD19 que comprende un codón de terminación prematuro, se administra al paciente una terapia diferente de un inhibidor de CD19, por ejemplo, se administra al paciente otro inhibidor de células B. En una modalidad, cuando una muestra de un paciente comprende al menos niveles normales de CD19, se administra al paciente un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD19, por ejemplo, una célula TCAR de CD19. En una modalidad, cuando una muestra de un paciente comprende niveles más bajos que los niveles normales de CD19, se administra al paciente una terapia diferente a un inhibidor de CD19, por

ejemplo, se administra al paciente otro inhibidor de células B (por ejemplo, uno o más inhibidores de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a,tal como se describen en el presente documento).

En una modalidad, los métodos de tratamiento comprenden la adquisición de un valor de estado recidivante para el sujeto, que comprende una medición de una característica de CD19, y una respuesta a una determinación de la condición recidivante, a través de uno, dos, tres, cuatro o más de: (1) identificar al sujeto como recidivante o no recidivante; (2) administrar una terapia con CAR; (3) seleccionar o alterar una dosificación de una terapia con CAR; (4) seleccionar o alterar el esquema o la programación de una terapia con CAR; (5) administrar, por ejemplo, a un paciente recidivante, un agente adicional en combinación con la terapia con CAR, por ejemplo, administrar uno o más inhibidores de células B; o un inhibidor de punto de control, por ejemplo, un inhibidor de punto de control descrito en el presente documento, o un inhibidor de la quinasa, por ejemplo, un inhibidor de la quinasa descrito en el presente documento; (6) administrar a un paciente recidivante una terapia que aumenta el número de células T inalteradas en el sujeto antes del tratamiento con una terapia con CAR; modificar un proceso de fabricación de una terapia con CAR, por ejemplo, incrementar las células T inalteradas antes de introducir un ácido nucleico que codifica un CAR, por ejemplo, para un sujeto identificado como recidivante; o (7) seleccionar una terapia alternativa, por ejemplo, un tratamiento estándar para un cáncer particular (por ejemplo, tal como se describe en el presente documento), por ejemplo, para un paciente recidivante; tratando de este modo el cáncer en el sujeto.

En algunas modalidades, el método comprende la administración de uno, dos, tres o más inhibidores de células B (por ejemplo, uno o más inhibidores de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1, tal como se describen en el presente documento). Por ejemplo, en una modalidad, el método incluye la administración de un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD19, en combinación con un inhibidor de CD10, o cualquier combinación de un inhibidor de CD10 y un inhibidor de CD20, CD22, CD34, CD123, FLT-3 o ROR1, tal como se describe en el presente documento. En otra modalidad, el método incluye la administración de un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD20, en combinación con un inhibidor de CD20, o cualquier combinación de un inhibidor de CD20 y un inhibidor de CD10, CD22, CD34, CD123, FLT-3 o ROR1, tal como se describe en el presente documento. En otra modalidad, el método incluye la administración de un inhibidor de

CD19, por ejemplo, una célula que expresa un CAR de CD22, en combinación con un inhibidor de CD22, o cualquier combinación de un inhibidor de CD22 y un inhibidor de CD10, CD20, CD34, CD123, FLT-3 o ROR1, tal como se describe en el presente documento. En otra modalidad, el método incluye la administración de un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD34, en combinación con un inhibidor de CD34, o cualquier combinación de un inhibidor de CD34 y un inhibidor de CD20, CD22, CD123, CD123, FLT-3 o ROR1, tal como se describe en el presente documento. En otra modalidad, el método incluye la administración de un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD123, en combinación con un inhibidor de CD123, o cualquier combinación de un inhibidor de CD123 y un inhibidor de CD10, CD20, CD34, CD22, FLT-3 o ROR1, tal como se describe en el presente documento. En otra modalidad, el método incluye la administración de un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de FLT-3, en combinación con un inhibidor de FLT-3, o cualquier combinación de un inhibidor de FLT-3 y un inhibidor de CD10, CD20, CD34, CD123 o ROR1, tal como se describe en el presente documento. En otra modalidad, el método incluye la administración de un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de ROR1, en combinación con un inhibidor de ROR1, o cualquier combinación de un inhibidor de ROR1 y un inhibidor de CD10, CD20, CD34, CD123, FLT-3 o ROR1, tal como se describe en el presente documento. En algunas modalidades, el método comprende administrar una, dos, tres o más inhibidores de células B (por ejemplo, uno o más inhibidores de CD10, CD20, CD22, CD34, CD123, FLT-3, or ROR1, CD79b, CD179b, o CD79a como se describen en el presente documento).

En algunas realizaciones, los métodos de tratamiento descrito en este documento comprenden además uno o ambos de: determinar un nivel de una molécula de puesto de control inmune (por ejemplo, PD-L1, PD1, LAG3, o TIM3) en una muestra del paciente; y la administración de un inhibidor de punto de control inmune (por ejemplo, un inhibidor de uno o más de PD-L1, PD1, LAG3, y TIM3) al paciente. Por ejemplo, el método puede comprender el tratamiento de un paciente con una o más células CAR-expresión descritos en este documento (por ejemplo, CD19 CAR en combinación con un inhibidor de células B, CAR CD20, o CAR CD22) y determinar el nivel de una molécula de puesto de control inmunológico en el paciente antes o después del tratamiento. En algunas realizaciones, el método comprende administrar el inhibidor de punto de control inmune a un paciente que tiene niveles elevados de la molécula de puesto de control inmune en comparación con un nivel de referencia, por ejemplo, la

administración de un inhibidor de PD-L1 en respuesta a niveles elevados de PD-L1, la administración de un PD1 inhibidor en respuesta a niveles elevados PD1, la administración de un inhibidor de LAG3 en respuesta a niveles elevados de LAG3, o la administración de un inhibidor de TIM3 en respuesta a niveles elevados de TIM3. En algunas realizaciones, el método comprende la administración de un inhibidor de punto de control inmune a un paciente que ha recibido, está recibiendo, o está a punto de recibir el tratamiento con una o más células CAR-expresión descritos en este documento (por ejemplo, CD19 CAR en combinación con una célula B inhibidor, CD20 CAR, o CD22 CAR), en el que el paciente tiene, o se identifica por tener niveles elevados de la molécula inmune puesto de control en comparación con un nivel de referencia.

COMPOSICIONES

En algunos aspectos, la presente divulgación proporciona, por ejemplo, una composición que comprende: (i) una o más células que expresan una molécula de CAR que une a CD19, por ejemplo, una molécula de CAR que une a CD19 descrita en el presente documento, por ejemplo, un CAR de CD19, y (ii) un inhibidor de células B, por ejemplo, uno o más inhibidores de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1. En algunas modalidades, (i) y (ii) se proporcionan por separado, y en algunas modalidades, (i) y (ii) se mezclan.

En algunos aspectos, la presente divulgación proporciona, por ejemplo, un ácido nucleico que codifica: (i) una molécula de CAR que une a CD19, por ejemplo, una molécula de CAR que une a CD19 descrita en el presente documento, por ejemplo, un CAR de CD19, y (ii) uno o más inhibidores de células B, por ejemplo, inhibidores de una o más de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1. En algunos aspectos, la presente divulgación proporciona, por ejemplo, un ácido nucleico que codifica: (i) una molécula de CAR que une a CD19, por ejemplo, una molécula de CAR que une a CD19 descrita en el presente documento, por ejemplo, un CAR de CD19, y (ii) una molécula de CAR que une un antígeno de células B, por ejemplo, una o más de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1. En algunas modalidades, el ácido nucleico comprende ARN o ADN.

En algunos aspectos, la presente descripción proporciona, por ejemplo, un ácido nucleico que codifica: (i) una molécula de CAR que se une a CD19, por ejemplo, una molécula de CAR

que se une CD19 descrita en el presente documento, por ejemplo, un CARde CD19, y (ii) una molécula de CAR que se une a un antígeno de células B, por ejemplo, uno o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a. En formas de realización, el ácido nucleico comprende ARN o ADN. En formas de realización, las secuencias de ácido nucleico que codifica (i) y (ii) están situados en la misma orientación, por ejemplo, la transcripción de las secuencias de ácido nucleico que codifica (i) y (ii) el producto en la misma dirección. En formas de realización, las secuencias de ácido nucleico que codifica (i) y (ii) están situados en diferentes orientaciones. En formas de realización, un único promotor controla la expresión de las secuencias de ácido nucleico que codifica (i) y (ii). En formas de realización, un ácido nucleico que codifica un sitio de escisión de la proteasa (como un T2A, P2A, E2A, o sitio de escisión F2A) está situado entre las secuencias de ácido nucleico que codifica (i) y (ii). En formas de realización, el sitio de escisión de la proteasa se coloca de tal manera que una célula puede expresar una proteína de fusión que comprende (i) y (ii), que la proteína es posteriormente procesada en dos péptidos por escisión proteolítica. En algunas realizaciones, las secuencias de ácido nucleico que codifica (i) es aguas arriba de las secuencias de ácido nucleico que codifica (ii), o las secuencias de ácido nucleico que codifica (ii) está aguas arriba de las secuencias de ácido nucleico que codifica (i). En formas de realización, un primer promotor controla la expresión de la secuencia de ácido nucleico que codifica (i) y un segundo de expresión controla promotor de la secuencia de ácido nucleico que codifica (ii). En formas de realización, el ácido nucleico es un plásmido. En formas de realización, el ácido nucleico comprende un elemento de embalaje viral. En algunos aspectos, la presente descripción proporciona una célula, por ejemplo, una célula efectora inmune, que comprende el ácido nucleico descrito en el presente documento, por ejemplo, que comprende un ácido nucleico (i) y (ii) como se describe anteriormente. La célula puede comprender una proteasa (por ejemplo, endógeno o exógeno) que escinde una T2A, P2A, E2A, o sitio de escisión F2A.

En algunos aspectos, la presente divulgación proporciona, por ejemplo, una composición que comprende: (i) un primer ácido nucleico que codifica una molécula de CAR que une a CD19, por ejemplo, una molécula de CAR que une a CD19 descrita en el presente documento, por ejemplo, un CAR de CD19, y (ii) un segundo ácido nucleico que codifica uno o más inhibidores de células B, por ejemplo, inhibidores de una o más de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1. En algunos aspectos, la presente divulgación proporciona, por ejemplo, una composición que comprende: (i) un primer ácido nucleico que codifica una molécula de

CAR que une a CD19, por ejemplo, una molécula de CAR que une a CD19 descrita en el presente documento, por ejemplo, un CAR de CD19, y (ii) una molécula de CAR que une un antígeno de células B, por ejemplo, una o más de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1. En algunas modalidades, el primer ácido nucleico y el segundo ácido nucleico comprenden cada uno ARN o ADN.

En algunos aspectos, la presente divulgación proporciona, por ejemplo, un vector que comprende un ácido nucleico o ácidos nucleicos tal como se describe en el presente documento. La presente divulgación también proporciona, en ciertos aspectos, una célula que comprende un vector o ácido nucleico tal como se describe en el presente documento.

Esta divulgación también proporciona, en ciertos aspectos, una composición que comprende una o más células efectoras inmunes: (i) un primer ácido nucleico que codifica, o un primer polipéptido que comprende, una molécula de CAR que une a CD19, por ejemplo, una molécula de CAR que une a CD19 descrita en el presente documento, por ejemplo, un CAR de CD19, y (ii) un segundo ácido nucleico que codifica, o un segundo polipéptido que comprende, una molécula de CAR que une un antígeno de células B, por ejemplo, una o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a. En algunas modalidades, el primer ácido nucleico o primer polipéptido y el segundo ácido nucleico o segundo polipéptido están cada uno contenidos dentro de, por ejemplo, expresados por, una primera célula efectora inmune. En algunas modalidades, la composición comprende una primera célula efectora inmune que contiene, por ejemplo, que expresa el primer ácido nucleico o el primer polipéptido y una segunda célula efectora inmune que contiene, por ejemplo, que expresa el segundo ácido nucleico o el segundo polipéptido. En algunas modalidades, la composición no comprende una célula que contiene, por ejemplo, que expresan tanto de la primera de ácido nucleico o polipéptido primero y el segundo ácido nucleico o segundo polipéptido.

FABRICACIÓN

En ciertos aspectos, la descripción proporciona un método de fabricación de una célula, que comprende transducir una célula efectora inmune, por ejemplo, una célula T o una célula NK, con un vector tal como se describe en el presente documento, por ejemplo, un vector que

codifica un CAR. En ciertos aspectos, la descripción proporciona un método de fabricación de una célula, que comprende introducir un ácido nucleico tal como se describe en el presente documento (por ejemplo, un ácido nucleico que codifica un CAR) en una célula efectora inmune, por ejemplo, una célula T o una célula NK. En ciertos aspectos, la divulgación proporciona un método de generación de una población de células con ARN modificado, que comprende la introducción de un ARN transcrito in vitro o ARN sintético en una célula, donde el ARN comprende un ácido nucleico tal como se describe en el presente documento, por ejemplo, un ácido nucleico que codifica un CAR.

En algunas modalidades, los métodos de fabricación descrito en la presente invención comprenden además poner en contacto la población de células (por ejemplo, que expresan CAR de CD19, que expresan CAR de CD20, que expresan CAR de CD22, células inhibidoras de células B, o ambas de una célula que expresa CAR de CD19 y células inhibidoras de células B), con un ácido nucleico que codifica una subunidad de telomerasa, por ejemplo, hTERT. El ácido nucleico que codifica la subunidad de telomerasa puede ser ADN.

En algunas modalidades, el método de fabricación divulgado en el presente documento comprende además cultivar la población de células (por ejemplo, que expresan CAR de CD19, que expresan CAR de CD20, que expresan CAR de CD22, células inhibidoras de células B, o ambas de una célula que expresa CAR de CD19 y células inhibidoras de células B), en suero que comprende suero hAB al 2 %.

INDICACIONES

En una modalidad, la enfermedad asociada con la expresión de CD19 se selecciona de una enfermedad proliferativa tal como un cáncer o tumor maligno, o una condición pre-cancerosa tal como una mielodisplasia, un síndrome mielodisplásico o una preleucemia, o es una indicación no oncológica asociada con la expresión de CD19. En una modalidad, la enfermedad es un tumor sólido o un tumor líquido. En una modalidad, el cáncer es un cáncer de páncreas. En una modalidad, la enfermedad es un cáncer hematológico. En una modalidad, el cáncer hematológico es una leucemia. En una modalidad, el cáncer se selecciona del grupo que consiste en una o más leucemias agudas, incluyendo, de manera enunciativa mas no limitativa, leucemia linfoide aguda de células B (LLA B), leucemia linfoide aguda de células T (LLA T), linfoma

linfocítico de células pequeñas (LLCP), leucemia linfoide aguda (LLA) (por ejemplo, LLA recidivante y refractaria); una o más leucemias crónicas, incluyendo, de manera enunciativa mas no limitativa, leucemia mielógena crónica (LMC) y leucemia linfocítica crónica (LLC). Enfermedades o cánceres hematológicos adicionales incluyen, de manera enunciativa mas no limitativa, linfoma de células del manto (LCM), leucemia prolinfocítica de células B, neoplasia blástica de células dendríticas plasmocitoides, linfoma de Burkitt, linfoma difuso de células B grandes, linfoma folicular, leucemia de células pilosas, linfoma folicular de células pequeñas o células grandes, enfermedades linfoproliferativas malignas, linfoma MALT, linfoma de zona marginal, mieloma múltiple, mielodisplasia y síndrome mielodisplásico, linfoma no Hodgkin, linfoma de Hodgkin, linfoma plasmablástico, neoplasia de células dendríticas plasmocitoides, macroglobulinemia de Waldenstrom y "pre-leucemia". La preleucemia abarca una diversa colección de enfermedades hematológicas unidas por la producción ineficaz (o displasia) de glóbulos mieloides. En algunas modalidades, una enfermedad asociada con la expresión de CD19 incluye, de manera enunciativa más no limitativa, cánceres atípicos y/o no clásicos, tumores malignos, enfermedades precancerosas o enfermedades proliferativas que expresan CD19; y cualquier combinación de las mismas.

En una modalidad, la enfermedad asociada con la expresión de CD19 es un linfoma, por ejemplo, LCM o linfoma de Hodgkin. En una modalidad, la enfermedad asociada con la expresión de CD19 es leucemia, por ejemplo, LLCP, LLC y/o LLA.

En una realización, la enfermedad asociada con un antígeno de tumor, por ejemplo, un antígeno tumoral se describe en la presente, se selecciona de una enfermedad proliferativa, tal como un cáncer o tumor maligno o una afección precancerosa tal como una mielodisplasia, un síndrome mielodisplásico o una preleucemia, o es una indicación no relacionada con el cáncer asociada con la expresión de un antígeno tumoral que se describe en el presente documento. En una realización, la enfermedad asociada con un antígeno tumoral que se describe aquí es un tumor sólido, por ejemplo, un tumor sólido descrito en este documento, por ejemplo, cáncer de próstata, colorrectal, pancreático, cervical, gástrico, de ovario, cabeza o cáncer de pulmón.

En una modalidad, el cáncer se selecciona de entre LMA, LLA, LLA B, LLA T, leucemia prolinfocítica de células B, leucemia linfocítica crónica, LMC, leucemia de células pilosas, linfoma de Hodgkin, enfermedad de mastocitos, síndrome mielodisplásico, neoplasia

mieloproliferativa, mieloma de células plasmáticas, neoplasia de células dendríticas plasmocitoides, o una combinación de las mismas.

En una modalidad, el sujeto (por ejemplo, un sujeto que será tratado con un CAR de CD19, opcionalmente en combinación con un segundo agente tal como un inhibidor de PD1 o un inhibidor de PD-L1) tiene, o se identifica por tener, al menos 5 %, 6 %, 7 %, 8 %, 9 %, 10 %, 20 %, 30 %, 40 %, 50 %, 60 %, 70 %, 80 % o 90 % de células cancerosas, por ejemplo, células DLBCL, que son CD3+/PD1+.

En una realización, el sujeto ha recaído o se identifica por tener una recaída después del tratamiento con una o más células que expresan una molécula de CAR que se une a CD19, por ejemplo, un CAR CD19. En una realización, el sujeto ha recaído o se identifica por tener una recaída basado en uno o más de, reaparición de blastos en la sangre, médula ósea (> 5%), o cualquier sitio extramedular, después de una respuesta completa. En una realización, el sujeto ha recaído o se identifica por tener una recaída basado en la detección de blastocitos de CD19- por encima de un umbral predeterminado, por ejemplo, más de 1%, 2%, 3%, 4%, 5%, o 10%.

TERAPIAS CON CAR

En ciertas modalidades, el método de tratamiento comprende una terapia con CAR, por ejemplo, la administración de una o más células que expresan una o más moléculas de CAR. Una célula que expresa una o más moléculas de CAR puede ser una célula efectora inmune, por ejemplo, una célula T o una célula NK. En una modalidad, el sujeto es un humano.

En una modalidad, la célula que expresa la molécula de CAR comprende un vector que incluye una secuencia de ácido nucleico que codifica la molécula de CAR. En una modalidad, el vector se selecciona del grupo que consiste en un ADN, un ARN, un plásmido, un vector lentivirus, un vector adenoviral o un vector retrovirus. En una modalidad, el vector es un vector lentivirus. En una modalidad, el vector comprende además un promotor. En una modalidad, el promotor es un promotor EF-1. En una modalidad, el promotor EF-1 comprende una secuencia de SEQ ID NO.: 100. *En una modalidad, el vector es un vector transcrito* in vitro, por ejemplo, un vector que transcribe el ARN de una molécula de ácido nucleico que se describe en el presente documento. En una modalidad, la secuencia de ácido nucleico en el vector *in vitro* comprende además una cola poli(A) o ejemplo, una cola poli A descrita en el presente documento, por ejemplo, que comprende aproximadamente 150 bases de adenosina. En una

modalidad, la secuencia de ácido nucleico en el vector *in vitro* comprende además un 3'-UTR, por ejemplo, un 3'-UTR descrito en el presente documento, por ejemplo, que comprende al menos una repetición de un 3'-UTR derivado de beta-globulina humana. En una modalidad, la secuencia de ácido nucleico en el vector *in vitro* comprende además un promotor. En una modalidad, la secuencia de ácido nucléico comprende una secuencia T2A.

En una modalidad, la célula que expresa la molécula de CAR es una célula descrita en el presente documento, por ejemplo, una célula T humana o una célula NK humana, por ejemplo, una célula T humana descrita en el presente documento o una célula NK humana descrita en el presente documento. En una modalidad, la célula T humana es una célula T CD8+. En una modalidad, la célula T humana es una célula T CD4+. En una modalidad, la célula T humana es una célula T CD4+/CD8+. En una modalidad, la célula T humana es una mezcla de células T CD8+ y células T CD4+. En una modalidad, la célula es una célula T autóloga. En una modalidad, la célula es una célula T alogénica. En una modalidad, la célula es una célula T y la célula T es deficiente de diacilglicerol quinasa (DGK). En una modalidad, la célula es una célula T y la célula T es deficiente de Ikaros. En una modalidad, la célula es una célula T y la célula T es deficiente de diacilglicerol quinasa (DGK) y deficiente de Ikaros.

En otra modalidad, la célula que expresa la molécula CAR, por ejemplo, tal como se describe en el presente documento, puede expresar adicionalmente otro agente, por ejemplo, un agente que aumenta la actividad de una célula que expresa CAR.

En una modalidad, el método incluye la administración de una célula que expresa la molécula de CAR, tal como se describe en el presente documento, en combinación con un agente que incrementa la actividad de una célula que expresa CAR, donde el agente es una citoquina, por ejemplo, IL-7, IL-15, IL-21, o una combinación de las mismas. La citoquina se puede entregar en combinación con, por ejemplo, simultáneamente o poco después de, la administración de la célula que expresa CAR. Alternativamente, la citoquina se puede entregar después de un período prolongado de tiempo después de la administración de la célula que expresa CAR, por ejemplo, después de la evaluación de la respuesta del sujeto a la célula que expresa CAR.

Por ejemplo, en una modalidad, el agente que incrementa la actividad de una célula que expresa un CAR puede ser un agente que inhibe una molécula inhibidora inmunitaria. Ejemplos de moléculas inhibidoras inmunitarias incluyen PD1, PD-L1, CTLA4, TIM3, CEACAM (por

ejemplo, CEACAM-1, CEACAM-3 y/o CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 y TGFR beta. En una modalidad, el agente que inhibe una molécula inhibidora inmunitaria comprende un primer polipéptido, por ejemplo, una molécula inhibidora, asociado a un segundo polipéptido que proporciona una señal positiva a la célula, por ejemplo, un dominio de señalización intracelular descrito en el presente documento. En una modalidad, el agente comprende un primer polipéptido, por ejemplo, de una molécula inhibidora inmunitaria tal como PD1, PD-L1, CTLA4, TIM3, CEACAM (por ejemplo, CEACAM-1, CEACAM-3 y/o CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 o TGFR beta, o un fragmento de cualquiera de estas (por ejemplo, al menos una porción del dominio extracelular de cualquiera de estas), y un segundo polipéptido que es un dominio de señalización intracelular descrito en el presente documento (por ejemplo, que comprende un dominio coestimulador (por ejemplo, 41BB, CD27 o CD28, por ejemplo, como se describe en el presente documento) y/o un dominio primario de señalización (por ejemplo, un dominio de señalización de CD3 zeta descrito en el presente documento). En una modalidad, el agente comprende un primer polipéptido de PD1 o un fragmento de la misma (por ejemplo, al menos una porción del dominio extracelular de PD1), y un segundo polipéptido de un dominio de señalización intracelular descrito en el presente documento (por ejemplo, un dominio de señalización de CD28 descrito en el presente documento y/o un dominio de señalización de CD3 zeta descrito en el presente documento).

En una modalidad, una infusión de linfocitos, por ejemplo, una infusión de linfocitos alogénicos, se usa en el tratamiento de cáncer, donde la infusión de linfocitos comprende al menos una célula que expresa un CAR de CD19 descrita en el presente documento y, opcionalmente, al menos una célula que expresa un CAR dirigida contra un antígeno de células B. En una modalidad, una infusión de linfocitos autólogos se usa en el tratamiento de cáncer, donde la infusión de linfocitos autólogos comprende al menos una célula que expresa CD19 y, opcionalmente, al menos una célula que expresa un CAR dirigida contra un antígeno de células B.

En una modalidad, la célula que expresa CAR, por ejemplo, célula T, se administra a un sujeto que ha recibido un trasplante de células madre previamente, por ejemplo, un trasplante de células madre autólogas, o un sujeto que ha recibido una dosis de melfalán previamente.

En una modalidad, la célula que expresa la molécula de CAR, por ejemplo, una molécula

de CAR descrita en el presente documento, se administra en combinación con un agente que disminuye uno o más efectos secundarios asociados con la administración de una célula que expresa una molécula de CAR, o con administración de un inhibidor de células B, por ejemplo, un agente descrito en el presente documento.

En una modalidad, la célula que expresa la molécula de CAR, por ejemplo, una molécula de CAR de CD19 descrita en el presente documento, y el inhibidor de células B se administran en combinación con un agente adicional que trata la enfermedad asociada con CD19, por ejemplo, un agente adicional descrito en el presente documento.

En una modalidad, las células que expresan una molécula de CAR, por ejemplo, una molécula de CAR descrita en el presente documento, se administran a una dosis y/o programas de dosificación descritos en el presente documento.

En una modalidad, la molécula de CAR se introduce en células T, por ejemplo, usando transcripción *in vitro*, y el sujeto (por ejemplo, humano) recibe una administración inicial de células que comprenden una molécula de CAR, y una o más administraciones subsiguientes de células que comprenden una molécula de CAR, donde se llevan a cabo una o más administraciones posteriores menos de 15 días, por ejemplo, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3 o 2 días, después de la administración anterior. En una modalidad, se realiza más de una administración de células que comprenden una molécula de CAR al sujeto (por ejemplo, humano) por semana, por ejemplo, se realizan 2, 3 o 4 administraciones de células que comprenden una molécula de CAR por semana. En una modalidad, el sujeto (por ejemplo, sujeto humano) recibe más de una administración de células que comprenden una molécula de CAR por semana (por ejemplo, 2, 3 o 4 administraciones por semana) (también denominado aquí como un ciclo), seguidas de una semana sin administración de células que comprenden una molécula de CAR, y luego se da al sujeto una o más administraciones adicionales de células que comprenden una molécula de CAR (por ejemplo, más de una administración de células que comprenden una molécula de CAR por semana). En otra modalidad, el sujeto (por ejemplo, un sujeto humano) recibe más de un ciclo de células que comprenden una molécula de CAR, y el tiempo entre cada ciclo es menor de 10, 9, 8, 7, 6, 5, 4 o 3 días. En una modalidad, las células que comprenden una molécula de CAR se administran cada día de por medio para 3 administraciones por semana. En una modalidad, las células que comprenden una molécula de CAR se administran durante al menos dos, tres, cuatro, cinco, seis, siete, ocho o más semanas.

En una modalidad, la terapia descrita en el presente documento (por ejemplo, una terapia CAR CD20, una terapia CAR CD22, o una combinación del inhibidor de células B y células que expresan una molécula de CAR de CD19, por ejemplo, una molécula de CAR de CD19 descrita en el presente documento) se administran como un tratamiento de primera línea para la enfermedad, por ejemplo, el cáncer, por ejemplo, el cáncer que describe en el presente documento. En otra modalidad, la terapia descrita en el presente documento (por ejemplo, una terapia CAR CD20, una terapia CAR CD22, o una combinación del inhibidor de células B y células que expresan una molécula de CAR de CD19, por ejemplo, una molécula de CAR de CD19 descrita en el presente documento) se administran como un tratamiento de segunda, tercera o cuarta línea para la enfermedad, por ejemplo, el cáncer, por ejemplo, el cáncer que describe en el presente documento.

En una modalidad, se administra una población de células descritas en el presente documento. En algunas modalidades, la población de células es aislada o purificada.

En una modalidad, el método incluye la administración de una población de células, una pluralidad de que comprenden una molécula de CAR descrita en el presente documento. En algunas modalidades, la población de células que expresan CAR comprende una mezcla de células que expresan diferentes CAR. Por ejemplo, en una modalidad, la población de células que expresan CAR puede incluir una primera célula que expresa un CAR que tiene un dominio de unión anti-CD19 descrito en el presente documento, y una segunda célula que expresa un CAR que tiene un dominio de unión a antígeno de células B diferente. En algunas modalidades, la primera y la segunda poblaciones de células son células T. En algunas modalidades, la primera y la segunda poblaciones de células T son el mismo isotipo, por ejemplo, son ambas células T CD4+ o son ambas células T CD8+. En otras modalidades, la primera y la segunda poblaciones de células T son diferentes isotipos, por ejemplo, la primera población comprende células T CD4+ y la segunda población comprende células T CD8+. En algunas modalidades, la primera y segunda poblaciones de células T son los tipos de células descritos en WO2012/129514, el cual se incluye en su totalidad en el presente documento a manera de referencia. Como otro ejemplo, una población de células puede comprender un único tipo de célula que expresa tanto un CAR que tiene un dominio de unión anti-CD19 descrito en el presente documento como un CAR que tiene un dominio de unión a antígeno de células B diferente. Como otro ejemplo, una población de células puede comprender un único tipo de

célula que expresa un CAR que tiene dos o más (por ejemplo, 2, 3, 4, o 5) dominios de unión a antígeno de células B, por ejemplo, un CAR biespecífico, por ejemplo, tal como se describe en el presente documento. Como ejemplo adicional, la población de células que expresan CAR puede incluir una primera célula que expresa un CAR que incluye un dominio de unión anti-CD19, por ejemplo, tal como se describe en el presente documento, y una segunda célula que expresa un CAR que incluye un dominio de unión a antígeno a un blanco diferente de D19 (por ejemplo, CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, CD79a o mesotelina). En una modalidad, la población de células que expresan CAR incluye, por ejemplo, una primera célula que expresa un CAR que incluye un dominio primario de señalización intracelular, y una segunda célula que expresa un CAR que incluye un dominio secundario de señalización. En una modalidad, la población de células que expresan CAR incluye, por ejemplo, una primera célula que expresa un CAR que incluye un dominio secundario de señalización, y una segunda célula que expresa un CAR que incluye un dominio secundario de señalización diferente del primer dominio secundario de señalización.

Como un ejemplo, cuando el primer inhibidor de células B es una célula que expresa un CAR de CD19 y el segundo inhibidor de células B es una célula que expresa un CAR de CD10, el primer CAR y el segundo CAR pueden ser expresados por el mismo tipo de célula o por tipos diferentes de célula. Por ejemplo, en algunas modalidades, la célula que expresa un CAR de CD19 es una célula T CD4+ y la célula que expresa un CAR de CD10 es una célula T CD8+, o la célula que expresa un CAR de CD19 es una célula T CD8+ y la célula que expresa un CAR de CD10 es una célula T CD4+. En otras modalidades, la célula que expresa un CAR de CD19 es una célula T y la célula que expresa un CAR de CD10 es una célula NK, o la célula que expresa un CAR de CD19 es una célula NK y la célula que expresa un CAR de CD10 es una célula T. En otras modalidades, la célula que expresa un CAR de CD19 y la célula que expresa un CAR de CD10 son ambas células NK o son ambas células T, por ejemplo, son ambas células T CD4+ o son ambas células T CD8+. En aun otras modalidades, una sola célula expresa el CAR de CD19 y el CAR de CD10, y esta célula es, por ejemplo, una célula NK o una célula T, tal como una célula T CD4+ o una célula T CD8+. El primer CAR y el segundo CAR pueden comprender los mismos dominios de señalización intracelular o diferentes dominios de señalización intracelular. Por ejemplo, en algunas modalidades, el CAR de CD19 comprende un dominio de señalización de CD3 zeta y el CAR de CD10 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28, mientras que en algunas

modalidades, el CAR de CD19 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28 y el CAR de CD10 comprende un dominio de señalización de zeta CD3. En otras modalidades, cada uno del CAR de CD19 y el CAR de CD10 comprenden el mismo tipo de dominio primario de señalización, por ejemplo, un dominio de señalización de CD3 zeta, pero el CAR de CD19 y el CAR de CD10 comprenden diferentes dominios coestimuladores, por ejemplo, (1) el CAR de CD19 comprende un dominio coestimulador de 41BB y el CAR de CD10 comprende dominio coestimulador diferente, por ejemplo, un dominio coestimulador de CD27, (2) el CAR de CD19 comprende un dominio coestimulador de CD27 y el CAR de CD10 comprende un ejemplo de dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (3) el CAR de CD19 comprende un dominio coestimulador de 41BB y el CAR de CD10 comprende un dominio coestimulador de CD28, (4) el CAR de CD19 comprende un dominio coestimulador de CD28 y el CAR de CD10 comprende un dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (5) el CAR de CD19 comprende un dominio coestimulador de CD27 y el CAR de CD10 comprende un dominio coestimulador de CD28, o (6) el CAR de CD19 comprende un dominio coestimulador de CD28 y el CAR de CD10 comprende un dominio coestimulador de CD27. En otra modalidad, una célula comprende un CAR que comprende tanto un dominio de unión a antígeno de CD19 como un dominio de unión a antígeno de CD10, por ejemplo, un anticuerpo biespecífico.

Como otro ejemplo, cuando el primer inhibidor de células B es una célula que expresa un CAR de CD19 y el segundo inhibidor de células B es una célula que expresa un CAR de CD20, el primer CAR y el segundo CAR pueden ser expresados por el mismo tipo de célula o por tipos diferentes de célula. Por ejemplo, en algunas modalidades, la célula que expresa un CAR de CD19 es una célula T CD4+ y la célula que expresa un CAR de CD20 es una célula T CD8+, o la célula que expresa un CAR de CD19 es una célula T CD8+ y la célula que expresa un CAR de CD20 es una célula T CD4+. En otras modalidades, la célula que expresa un CAR de CD19 es una célula T y la célula que expresa un CAR de CD20 es una célula NK, o la célula que expresa un CAR de CD19 es una célula NK y la célula que expresa un CAR de CD20 es una célula T. En otras modalidades, la célula que expresa un CAR de CD19 y la célula que expresa un CAR de CD20 son ambas células NK o son ambas células T, por ejemplo, son ambas células T CD4+ o son ambas células T CD8+. En aun otras modalidades, una sola célula expresa el CAR de CD19 y el CAR de CD20, y esta célula es, por ejemplo, una célula NK o una célula T,

tal como una célula T CD4+ o una célula T CD8+. El primer CAR y el segundo CAR pueden comprender los mismos dominios de señalización intracelular o diferentes dominios de señalización intracelular. Por ejemplo, en algunas modalidades, el CAR de CD19 comprende un dominio de señalización de CD3 zeta y el CAR de CD20 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28, mientras que en algunas modalidades, el CAR de CD19 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28 y el CAR de CD20 comprende un dominio de señalización de zeta CD3. En otras modalidades, cada uno del CAR de CD19 y el CAR de CD20 comprenden el mismo tipo de dominio primario de señalización, por ejemplo, un dominio de señalización de CD3 zeta, pero el CAR de CD19 y el CAR de CD20 comprenden diferentes dominios coestimuladores, por ejemplo, (1) el CAR de CD19 comprende un dominio coestimulador de 41BB y el CAR de CD20 comprende dominio coestimulador diferente, por ejemplo, un dominio coestimulador de CD27, (2) el CAR de CD19 comprende un dominio coestimulador de CD27 y el CAR de CD20 comprende un ejemplo de dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (3) el CAR de CD19 comprende un dominio coestimulador de 41BB y el CAR de CD20 comprende un dominio coestimulador de CD28, (4) el CAR de CD19 comprende un dominio coestimulador de CD28 y el CAR de CD20 comprende un dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (5) el CAR de CD19 comprende un dominio coestimulador de CD27 y el CAR de CD20 comprende un dominio coestimulador de CD28, o (6) el CAR de CD19 comprende un dominio coestimulador de CD28 y el CAR de CD20 comprende un dominio coestimulador de CD27. En otra modalidad, una célula comprende un CAR que comprende tanto un dominio de unión a antígeno de CD19 como un dominio de unión a antígeno de CD20, por ejemplo, un anticuerpo biespecífico.

Como otro ejemplo, cuando el primer inhibidor de células B es una célula que expresa un CAR de CD19 y el segundo inhibidor de células B es una célula que expresa un CAR de CD22, el primer CAR y el segundo CAR pueden ser expresados por el mismo tipo de célula o por tipos diferentes de célula. Por ejemplo, en algunas modalidades, la célula que expresa un CAR de CD19 es una célula T CD4+ y la célula que expresa un CAR de CD22 es una célula T CD8+, o la célula que expresa un CAR de CD19 es una célula T CD8+ y la célula que expresa un CAR de CD22 es una célula T CD4+. En otras modalidades, la célula que expresa un CAR de CD19 es una célula T y la célula que expresa un CAR de CD22 es una célula NK, o la célula que

expresa un CAR de CD19 es una célula NK y la célula que expresa un CAR de CD22 es una célula T. En otras modalidades, la célula que expresa un CAR de CD19 y la célula que expresa un CAR de CD22 son ambas células NK o son ambas células T, por ejemplo, son ambas células T CD4+ o son ambas células T CD8+. En aun otras modalidades, una sola célula expresa el CAR de CD19 y el CAR de CD22, y esta célula es, por ejemplo, una célula NK o una célula T, tal como una célula T CD4+ o una célula T CD8+. El primer CAR y el segundo CAR pueden comprender los mismos dominios de señalización intracelular o diferentes dominios de señalización intracelular. Por ejemplo, en algunas modalidades, el CAR de CD19 comprende un dominio de señalización de CD3 zeta y el CAR de CD22 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28, mientras que en algunas modalidades, el CAR de CD19 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28 y el CAR de CD22 comprende un dominio de señalización de zeta CD3. En otras modalidades, cada uno del CAR de CD19 y el CAR de CD22 comprenden el mismo tipo de dominio primario de señalización, por ejemplo, un dominio de señalización de CD3 zeta, pero el CAR de CD19 y el CAR de CD22 comprenden diferentes dominios coestimuladores, por ejemplo, (1) el CAR de CD19 comprende un dominio coestimulador de 41BB y el CAR de CD22 comprende dominio coestimulador diferente, por ejemplo, un dominio coestimulador de CD27, (2) el CAR de CD19 comprende un dominio coestimulador de CD27 y el CAR de CD22 comprende un ejemplo de dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (3) el CAR de CD19 comprende un dominio coestimulador de 41BB y el CAR de CD22 comprende un dominio coestimulador de CD28, (4) el CAR de CD19 comprende un dominio coestimulador de CD28 y el CAR de CD22 comprende un dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (5) el CAR de CD19 comprende un dominio coestimulador de CD27 y el CAR de CD22 comprende un dominio coestimulador de CD28, o (6) el CAR de CD19 comprende un dominio coestimulador de CD28 y el CAR de CD22 comprende un dominio coestimulador de CD27. En otra modalidad, una célula comprende un CAR que comprende tanto un dominio de unión a antígeno de CD19 como un dominio de unión a antígeno de CD22, por ejemplo, un anticuerpo biespecífico.

Como otro ejemplo, cuando el primer inhibidor de células B es una célula que expresa un CAR de CD19 y el segundo inhibidor de células B es una célula que expresa un CAR de CD34, el primer CAR y el segundo CAR pueden ser expresados por el mismo tipo de célula o por tipos

diferentes de célula. Por ejemplo, en algunas modalidades, la célula que expresa un CAR de CD19 es una célula T CD4+ y la célula que expresa un CAR de CD34 es una célula T CD8+, o la célula que expresa un CAR de CD19 es una célula T CD8+ y la célula que expresa un CAR de CD34 es una célula T CD4+. En otras modalidades, la célula que expresa un CAR de CD19 es una célula T y la célula que expresa un CAR de CD34 es una célula NK, o la célula que expresa un CAR de CD19 es una célula NK y la célula que expresa un CAR de CD34 es una célula T. En otras modalidades, la célula que expresa un CAR de CD19 y la célula que expresa un CAR de CD34 son ambas células NK o son ambas células T, por ejemplo, son ambas células T CD4+ o son ambas células T CD8+. En aun otras modalidades, una sola célula expresa el CAR de CD19 y el CAR de CD34, y esta célula es, por ejemplo, una célula NK o una célula T, tal como una célula T CD4+ o una célula T CD8+. El primer CAR y el segundo CAR pueden comprender los mismos dominios de señalización intracelular o diferentes dominios de señalización intracelular. Por ejemplo, en algunas modalidades, el CAR de CD19 comprende un dominio de señalización de CD3 zeta y el CAR de CD34 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28, mientras que en algunas modalidades, el CAR de CD19 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28 y el CAR de CD34 comprende un dominio de señalización de zeta CD3. En otras modalidades, cada uno del CAR de CD19 y el CAR de CD34 comprenden el mismo tipo de dominio primario de señalización, por ejemplo, un dominio de señalización de CD3 zeta, pero el CAR de CD19 y el CAR de CD34 comprenden diferentes dominios coestimuladores, por ejemplo, (1) el CAR de CD19 comprende un dominio coestimulador de 41BB y el CAR de CD34 comprende dominio coestimulador diferente, por ejemplo, un dominio coestimulador de CD27, (2) el CAR de CD19 comprende un dominio coestimulador de CD27 y el CAR de CD34 comprende un ejemplo de dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (3) el CAR de CD19 comprende un dominio coestimulador de 41BB y el CAR de CD34 comprende un dominio coestimulador de CD28, (4) el CAR de CD19 comprende un dominio coestimulador de CD28 y el CAR de CD34 comprende un dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (5) el CAR de CD19 comprende un dominio coestimulador de CD27 y el CAR de CD34 comprende un dominio coestimulador de CD28, o (6) el CAR de CD19 comprende un dominio coestimulador de CD28 y el CAR de CD34 comprende un dominio coestimulador de CD27. En otra modalidad, una célula comprende un CAR que comprende tanto un dominio de unión a

antígeno de CD19 como un dominio de unión a antígeno de CD34, por ejemplo, un anticuerpo biespecífico.

Como otro ejemplo, cuando el primer inhibidor de células B es una célula que expresa un CAR de CD19 y el segundo inhibidor de células B es una célula que expresa un CAR de CD123, el primer CAR y el segundo CAR pueden ser expresados por el mismo tipo de célula o por tipos diferentes de célula. Por ejemplo, en algunas modalidades, la célula que expresa un CAR de CD19 es una célula T CD4+ y la célula que expresa un CAR de CD123 es una célula T CD8+, o la célula que expresa un CAR de CD19 es una célula T CD8+ y la célula que expresa un CAR de CD123 es una célula T CD4+. En otras modalidades, la célula que expresa un CAR de CD19 es una célula T y la célula que expresa un CAR de CD123 es una célula NK, o la célula que expresa un CAR de CD19 es una célula NK y la célula que expresa un CAR de CD123 es una célula T. En otras modalidades, la célula que expresa un CAR de CD19 y la célula que expresa un CAR de CD123 son ambas células NK o son ambas células T, por ejemplo, son ambas células T CD4+ o son ambas células T CD8+. En aun otras modalidades, una sola célula expresa el CAR de CD19 y el CAR de CD123, y esta célula es, por ejemplo, una célula NK o una célula T, tal como una célula T CD4+ o una célula T CD8+. El primer CAR y el segundo CAR pueden comprender los mismos dominios de señalización intracelular o diferentes dominios de señalización intracelular. Por ejemplo, en algunas modalidades, el CAR de CD19 comprende un dominio de señalización de CD3 zeta y el CAR de CD123 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28, mientras que en algunas modalidades, el CAR de CD19 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28 y el CAR de CD123 comprende un dominio de señalización de zeta CD3. En otras modalidades, cada uno del CAR de CD19 y el CAR de CD123 comprenden el mismo tipo de dominio primario de señalización, por ejemplo, un dominio de señalización de CD3 zeta, pero el CAR de CD19 y el CAR de CD123 comprenden diferentes dominios coestimuladores, por ejemplo, (1) el CAR de CD19 comprende un dominio coestimulador de 41BB y el CAR de CD123 comprende dominio coestimulador diferente, por ejemplo, un dominio coestimulador de CD27, (2) el CAR de CD19 comprende un dominio coestimulador de CD27 y el CAR de CD123 comprende un ejemplo de dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (3) el CAR de CD19 comprende un dominio coestimulador de 41BB y el CAR de CD123 comprende un dominio coestimulador de CD28, (4) el CAR de CD19 comprende un dominio coestimulador de CD28 y el CAR de CD123

comprende un dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (5) el CAR de CD19 comprende un dominio coestimulador de CD27 y el CAR de CD123 comprende un dominio coestimulador de CD28, o (6) el CAR de CD19 comprende un dominio coestimulador de CD28 y el CAR de CD123 comprende un dominio coestimulador de CD27. En otra modalidad, una célula comprende un CAR que comprende tanto un dominio de unión a antígeno de CD19 como un dominio de unión a antígeno de CD123, por ejemplo, un anticuerpo biespecífico.

Como otro ejemplo, cuando el primer inhibidor de células B es una célula que expresa un CAR de CD19 y el segundo inhibidor de células B es una célula que expresa un CAR de FLT-3, el primer CAR y el segundo CAR pueden ser expresados por el mismo tipo de célula o por tipos diferentes de célula. Por ejemplo, en algunas modalidades, la célula que expresa un CAR de CD19 es una célula T CD4+ y la célula que expresa un CAR de FLT-3 es una célula T CD8+, o la célula que expresa un CAR de CD19 es una célula T CD8+ y la célula que expresa un CAR de FLT-3 es una célula T CD4+. En otras modalidades, la célula que expresa un CAR de CD19 es una célula T y la célula que expresa un CAR de FLT-3 es una célula NK, o la célula que expresa un CAR de CD19 es una célula NK y la célula que expresa un CAR de FLT-3 es una célula T. En otras modalidades, la célula que expresa un CAR de CD19 y la célula que expresa un CAR de FLT-3 son ambas células NK o son ambas células T, por ejemplo, son ambas células T CD4+ o son ambas células T CD8+. En aun otras modalidades, una sola célula expresa el CAR de CD19 y el CAR de FLT-3, y esta célula es, por ejemplo, una célula NK o una célula T, tal como una célula T CD4+ o una célula T CD8+. El primer CAR y el segundo CAR pueden comprender los mismos dominios de señalización intracelular o diferentes dominios de señalización intracelular. Por ejemplo, en algunas modalidades, el CAR de CD19 comprende un dominio de señalización de CD3 zeta y el CAR de FLT-3 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28, mientras que en algunas modalidades, el CAR de CD19 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28 y el CAR de FLT-3 comprende un dominio de señalización de zeta CD3. En otras modalidades, cada uno del CAR de CD19 y el CAR de FLT-3 comprenden el mismo tipo de dominio primario de señalización, por ejemplo, un dominio de señalización de CD3 zeta, pero el CAR de CD19 y el CAR de FLT-3 comprenden diferentes dominios coestimuladores, por ejemplo, (1) el CAR de CD19 comprende un dominio coestimulador de 41BB y el CAR de FLT-3 comprende dominio coestimulador diferente, por

ejemplo, un dominio coestimulador de CD27, (2) el CAR de CD19 comprende un dominio coestimulador de CD27 y el CAR de FLT-3 comprende un ejemplo de dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (3) el CAR de CD19 comprende un dominio coestimulador de 41BB y el CAR de FLT-3 comprende un dominio coestimulador de CD28, (4) el CAR de CD19 comprende un dominio coestimulador de CD28 y el CAR de FLT-3 comprende un dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (5) el CAR de CD19 comprende un dominio coestimulador de CD27 y el CAR de FLT-3 comprende un dominio coestimulador de CD28, o (6) el CAR de CD19 comprende un dominio coestimulador de CD28 y el CAR de FLT-3 comprende un dominio coestimulador de CD27. En otra modalidad, una célula comprende un CAR que comprende tanto un dominio de unión a antígeno de CD19 como un dominio de unión a antígeno de FLT-3, por ejemplo, un anticuerpo biespecífico.

Como otro ejemplo, cuando el primer inhibidor de células B es una célula que expresa un CAR de CD19 y el segundo inhibidor de células B es una célula que expresa un CAR de ROR1, el primer CAR y el segundo CAR pueden ser expresados por el mismo tipo de célula o por tipos diferentes de célula. Por ejemplo, en algunas modalidades, la célula que expresa un CAR de CD19 es una célula T CD4+ y la célula que expresa un CAR de ROR1 es una célula T CD8+, o la célula que expresa un CAR de CD19 es una célula T CD8+ y la célula que expresa un CAR de ROR1 es una célula T CD4+. En otras modalidades, la célula que expresa un CAR de CD19 es una célula T y la célula que expresa un CAR de ROR1 es una célula NK, o la célula que expresa un CAR de CD19 es una célula NK y la célula que expresa un CAR de ROR1 es una célula T. En otras modalidades, la célula que expresa un CAR de CD19 y la célula que expresa un CAR de ROR1 son ambas células NK o son ambas células T, por ejemplo, son ambas células T CD4+ o son ambas células T CD8+. En aun otras modalidades, una sola célula expresa el CAR de CD19 y el CAR de ROR1, y esta célula es, por ejemplo, una célula NK o una célula T, tal como una célula T CD4+ o una célula T CD8+. El primer CAR y el segundo CAR pueden comprender los mismos dominios de señalización intracelular o diferentes dominios de señalización intracelular. Por ejemplo, en algunas modalidades, el CAR de CD19 comprende un dominio de señalización de CD3 zeta y el CAR de ROR1 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28, mientras que en algunas modalidades, el CAR de CD19 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28 y el CAR de ROR1 comprende un dominio de

señalización de zeta CD3. En otras modalidades, cada uno del CAR de CD19 y el CAR de ROR1 comprenden el mismo tipo de dominio primario de señalización, por ejemplo, un dominio de señalización de CD3 zeta, pero el CAR de CD19 y el CAR de ROR1 comprenden diferentes dominios coestimuladores, por ejemplo, (1) el CAR de CD19 comprende un dominio coestimulador de 41BB y el CAR de ROR1 comprende dominio coestimulador diferente, por ejemplo, un dominio coestimulador de CD27, (2) el CAR de CD19 comprende un dominio coestimulador de CD27 y el CAR de ROR1 comprende un ejemplo de dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (3) el CAR de CD19 comprende un dominio coestimulador de 41BB y el CAR de ROR1 comprende un dominio coestimulador de CD28, (4) el CAR de CD19 comprende un dominio coestimulador de CD28 y el CAR de ROR1 comprende un dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (5) el CAR de CD19 comprende un dominio coestimulador de CD27 y el CAR de ROR1 comprende un dominio coestimulador de CD28, o (6) el CAR de CD19 comprende un dominio coestimulador de CD28 y el CAR de ROR1 comprende un dominio coestimulador de CD27. En otra modalidad, una célula comprende un CAR que comprende tanto un dominio de unión a antígeno de CD19 como un dominio de unión a antígeno de ROR1, por ejemplo, un anticuerpo biespecífico.

De manera más general, cuando el primer inhibidor de células B comprende un CAR de CD19 y hay un segundo inhibidor de células B, por ejemplo, que comprende un segundo CAR, el primer CAR y el segundo inhibidor de células B pueden ser expresado por el mismo tipo de célula o por diferentes tipos de célula. Por ejemplo, en algunas modalidades, la célula que expresa un CAR de CD19 es una célula T CD4+ y la célula que expresa el segundo inhibidor de células B es una célula T CD8+, o la célula que expresa un CAR de CD19 es una célula T CD8+ y el segundo inhibidor de células B es una célula T CD4+. En otras modalidades, la célula que expresa un CAR de CD19 es una célula T y la célula que expresa el segundo inhibidor de células B es una célula NK, o la célula que expresa un CAR de CD19 es una célula NK y el segundo inhibidor de células B es una célula T. En otras modalidades, la célula que expresa un CAR de CD19 y la célula que expresa el segundo inhibidor de células B son ambas células NK o son ambas células T, por ejemplo, son ambas células T CD4+ o son ambas células T CD8+. En aun otras modalidades, una sola célula expresa el CAR de CD19 y el segundo inhibidor de células B, y esta célula es, por ejemplo, una célula NK o una célula T, tal como una célula T CD4+ o una célula T CD8+. El primer CAR y el segundo CAR pueden comprender los mismos dominios de

señalización intracelular o diferentes dominios de señalización intracelular. Por ejemplo, en algunas modalidades, el CAR de CD19 comprende un dominio de señalización de CD3 zeta y el segundo inhibidor de células B (o CAR) comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28, mientras que en algunas modalidades, el CAR de CD19 comprende un dominio coestimulador, por ejemplo, un dominio coestimulador de 41BB, CD27 o CD28 y el segundo inhibidor de células B comprende un dominio de señalización de zeta CD3. En otras modalidades, cada uno del CAR de CD19 y el segundo inhibidor de células B (o segundo CAR) comprenden el mismo tipo de dominio primario de señalización, por ejemplo, un dominio de señalización de CD3 zeta, pero el CAR de CD19 y el segundo inhibidor de células B (o segundo CAR) comprenden diferentes dominios coestimuladores, por ejemplo, (1) el CAR de CD19 comprende un dominio coestimulador de 41BB y el segundo inhibidor de células B (o segundo CAR) comprende dominio coestimulador diferente, por ejemplo, un dominio coestimulador de CD27, (2) el CAR de CD19 comprende un dominio coestimulador de CD27 y el segundo inhibidor de células B (o segundo CAR) comprende un ejemplo de dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (3) el CAR de CD19 comprende un dominio coestimulador de 41BB y el segundo inhibidor de células B (o segundo CAR) comprende un dominio coestimulador de CD28, (4) el CAR de CD19 comprende un dominio coestimulador de CD28 y el segundo inhibidor de células B (o segundo CAR) comprende un dominio coestimulador diferente, por ejemplo, un dominio coestimulador de 41BB, (5) el CAR de CD19 comprende un dominio coestimulador de CD27 y el segundo inhibidor de células B (o segundo CAR) comprende un dominio coestimulador de CD28, o (6) el CAR de CD19 comprende un dominio coestimulador de CD28 y el segundo inhibidor de células B (o segundo CAR) comprende un dominio coestimulador de CD27. En otra modalidad, una célula comprende un CAR que comprende tanto un dominio de unión a antígeno de CD19 como un dominio de unión a antígeno dirigido a uno segundo antígeno, por ejemplo, un anticuerpo biespecífico.

En una modalidad, el dominio coestimulador de 4-1BB comprende una secuencia de SEQ ID NO.: 16. En una modalidad, el dominio coestimulador de 4-1BB comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 20, 10 o 5 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de SEQ ID NO.: 16, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de SEQ ID NO.: 16. En una modalidad, el dominio

coestimulador de 4-1BB está codificado por una secuencia de ácido nucleico de SEQ ID NO.: 60, o una secuencia con 95-99 % de identidad frente a la misma.

En una modalidad, el dominio coestimulador de CD27 comprende una secuencia de SEQ ID NO.: 16. En una modalidad, el dominio coestimulador de CD27 comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 20, 10 o 5 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de SEQ ID NO.: 16, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de SEQ ID NO.: 16. En una modalidad, el dominio coestimulador de CD27 está codificado por una secuencia de ácido nucleico de SEQ ID NO.: 17, o una secuencia con 95-99 % de identidad frente a la misma.

En una modalidad, el dominio coestimulador de CD28 comprende una secuencia de SEQ ID NO.: 1317. En una modalidad, el dominio coestimulador de CD28 comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 20, 10 o 5 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de SEQ ID NO.: 1317, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de SEQ ID NO.: 1317. En una modalidad, el dominio coestimulador de CD28 está codificado por una secuencia de ácido nucleico de SEQ ID NO.: 1318, o una secuencia con 95-99 % de identidad frente a la misma.

En una modalidad, el dominio coestimulador de ICOS de tipo silvestre comprende una secuencia de SEQ ID NO.: 1319. En una modalidad, el dominio coestimulador de ICOS de tipo silvestre comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 20, 10 o 5 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de SEQ ID NO.: 1319, o una secuencia con 95-99% de identidad frente a una secuencia de aminoácidos de SEQ ID NO.: 1319. En una modalidad, el dominio coestimulador de ICOS de tipo silvestre está codificado por una secuencia de SEQ ID NO.: 1320, o una secuencia con 95-99% de identidad frente a la misma.

En una modalidad, el dominio coestimulador de ICOS mutante Y a F comprende una secuencia de SEQ ID NO.: 1321. En una modalidad, el dominio coestimulador de ICOS mutante Y a F comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 20, 10 o 5 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de SEQ ID NO.: 1321, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de SEQ ID NO.: 1321. En una

modalidad, el dominio coestimulador ICOS mutante Y a F está codificado por una secuencia de ácido nucleico con 95-99 % de identidad frente una secuencia de ácido nucleico de SEQ ID NO.: 1320 (donde SEQ ID NO.: 1320 codifica ICOS de tipo silvestre).

En algunas modalidades, el dominio primario de señalización comprende un dominio de señalización funcional de CD3 zeta. En algunas modalidades, el dominio de señalización funcional de CD3 zeta comprende SEQ ID NO.: 17 (CD3 zeta mutante) o SEQ ID NO.: 43 (CD3 zeta humana mutante).

En una modalidad, el método incluye la administración de una población de células, donde al menos una célula de la población expresa un CAR, por ejemplo, que tiene un dominio anti-CD19 descrito en el presente documento y un agente que incrementa la actividad de una célula que expresa CAR, por ejemplo, una segunda célula que expresa el agente que incrementa la actividad de una célula que expresa CAR. Por ejemplo, en una modalidad, el agente puede ser un agente que inhibe una molécula inhibidora inmunitaria. Ejemplos de moléculas inhibidoras inmunitarias incluyen PD1, PD-L1, CTLA4, TIM3, CEACAM (por ejemplo, CEACAM-1, CEACAM-3 y/o CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 y TGFR beta. En una modalidad, el agente que inhibe una molécula inhibidora inmunitaria comprende un primer polipéptido, por ejemplo, una molécula inhibidora, asociado a un segundo polipéptido que proporciona una señal positiva a la célula, por ejemplo, un dominio de señalización intracelular descrito en el presente documento. En una modalidad, el agente comprende un primer polipéptido, por ejemplo, de una molécula inhibidora tal como PD1, PD-L1, CTLA4, TIM3, CEACAM (por ejemplo, CEACAM-1, CEACAM-3 y/o CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 o TGFR beta, o un fragmento de cualquiera de estas (por ejemplo, al menos una porción de un dominio extracelular de cualquiera de estas), y un segundo polipéptido que es un dominio de señalización intracelular descrito en el presente documento (por ejemplo, que comprende un dominio coestimulador (por ejemplo, 41BB, CD27 o CD28, por ejemplo, como se describe en el presente documento) y/o un dominio primario de señalización (por ejemplo, un dominio de señalización de CD3 zeta descrito en el presente documento). En una modalidad, el agente comprende un primer polipéptido de PD1 o un fragmento de la misma (por ejemplo, al menos una porción del dominio extracelular de PD1), y un segundo polipéptido de un dominio de señalización intracelular descrito en el presente documento (por ejemplo, un dominio de señalización de CD28 descrito en el presente documento y/o un dominio de señalización de CD3 zeta descrito en el presente documento).

En una modalidad, el inhibidor de células B comprende un inhibidor de una o más de CD10, CD19, CD20, CD22, CD34, FLT-3 o ROR1. En una modalidad, el inhibidor de células B comprende una cantidad eficaz de una o más células que expresan una molécula de CAR que une a una o más de CD10, CD20, CD22, CD34, FLT-3, ROR1, CD79b, CD179b o CD79a. En una modalidad, el inhibidor de células B comprende un CAR de CD123. En una modalidad, el inhibidor de células B comprende una o más células que expresan una molécula de CAR que se une CD123. En una modalidad, la enfermedad es un cáncer negativo para CD19, por ejemplo, un cáncer recidivante negativo para CD19. En una modalidad, la célula que expresa un CAR se administra simultáneamente con, antes de, o después de uno o más inhibidores de células B.

En una modalidad, el método comprende además la administración de un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD19. En una modalidad, el inhibidor de CD19 comprende un CAR de CD19 y el inhibidor de células B comprende un CAR de CD123. En una modalidad, el CAR de CD19 o el CAR de CD123 comprende un dominio de señalización intracelular segmentado tal que la activación completa de la célula, por ejemplo, la población de células efectoras inmunes, se produce cuando tanto el CAR de CD19 como el CAR de CD123 se unen a una célula blanco, por ejemplo, una célula blanco CD19+CD123+ (por ejemplo, un blastocito de LLA B), en comparación con la activación cuando el CAR de CD19 y el CAR de CD123 se unen a una célula blanco que expresa uno de CD19 o CD123 (por ejemplo, una célula madre hematopoyética). En una modalidad, el CAR de CD123 comprende un dominio de señalización de 4-1BB y el CAR de CD19 comprende un dominio de señalización de CD3 zeta. En una modalidad, el CAR de CD123 comprende un dominio coestimulador, por ejemplo, un dominio de señalización de 4-1BB, y el CAR de CD19 comprende un dominio primario de señalización, por ejemplo, un dominio de señalización de CD3 zeta. En una modalidad, el CAR de CD123 comprende un dominio primario de señalización, por ejemplo, un dominio primario de señalización de CD3 zeta, y el CAR de CD19 comprende un dominio coestimulador, por ejemplo, un dominio de señalización de 4-1BB. En una modalidad, el inhibidor de células B comprende un CAR (por ejemplo, un CAR dirigido contra CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a), que comprende un dominio coestimulador, y el CAR de CD19 comprende un dominio primario de señalización. En una modalidad, el inhibidor de células B comprende un CAR (por ejemplo, un CAR dirigido contra CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a), que comprende un dominio primario de señalización, y el CAR de CD19 comprende un dominio coestimulador.

En una modalidad, el inhibidor de células B comprende una o más células que expresan una molécula de CAR que se une CD123, donde una célula que expresa un CAR de CD19 se administra simultáneamente con el inhibidor de células B. En una modalidad, el CAR de CD123 comprende un dominio de señalización de 4-1BB y el CAR de CD19 comprende un dominio de señalización de CD3 zeta.

En una modalidad, el método comprende además el trasplante de una célula, por ejemplo, una célula madre hematopoyética, o médula ósea, en el mamífero.

En otro aspecto, la invención se refiere a una célula que expresa una molécula de CAR descrita en el presente documento, por ejemplo, una molécula de CAR de CD19, para uso como un medicamento en combinación con un inhibidor de células B, por ejemplo, un inhibidor de células B descrito en el presente documento. En otro aspecto, la invención se refiere a un inhibidor de células B descrito en el presente documento para uso como un medicamento en combinación con una célula que expresa una molécula de CAR, por ejemplo, una molécula de CAR de CD19 descrita en el presente documento.

En otro aspecto, la invención se refiere a una célula que expresa una molécula de CAR descrita en el presente documento, por ejemplo, una molécula de CAR de CD19, para uso en combinación con un inhibidor de células B, por ejemplo, un inhibidor de células B descrito en el presente documento, en el tratamiento de una enfermedad que expresa CD19. En otro aspecto, la invención se refiere a un inhibidor de células B descrito en el presente documento para uso en combinación con una célula que expresa una molécula de CAR descrita en el presente documento, por ejemplo, una molécula de CAR de CD19, en el tratamiento de una enfermedad que expresa CD19. En otro aspecto, la invención se refiere a una célula que expresa una molécula de CAR descrita en el presente documento, por ejemplo, una molécula de CAR de CD19, para uso en combinación con un inhibidor de células B, por ejemplo, un inhibidor de células B descrito en el presente documento, en el tratamiento de un cáncer, por ejemplo, un cáncer descrito en el presente documento.

En una modalidad, el método incluye la administración de una población de células, donde al menos una célula de la población expresa una terapia en el presente documento (por ejemplo, un CAR CD20, un CAR CD22 o un CAR que tiene un dominio anti-CD19 descrito en el presente documento en combinación con un inhibidor de células B) y un agente que incrementa la actividad de una célula que expresa CAR, donde el agente es una citoquina, por

ejemplo, IL-7, IL-15, IL-21, o una combinación de las mismas. La citoquina se puede entregar en combinación con, por ejemplo, simultáneamente o poco después de, la administración de la o las células que expresan CAR. Alternativamente, la citoquina se puede entregar después de un período prolongado de tiempo después de la administración de la o las células que expresan CAR, por ejemplo, después de la evaluación de la respuesta del sujeto a la o las células que expresan CAR. También se proporcionan composiciones relacionadas para su uso y métodos para elaborar un medicamento.

En una modalidad, las células descritas en el presente documento (por ejemplo, células que expresan una molécula de CAR de CD20, células que expresan una molécula de CAR de CD22, o células que expresan una molécula de CAR de CD19, por ejemplo, una molécula de CAR de CD19 descrita en el presente documento, en combinación con un inhibidor de células B) son administradas en combinación con un agente que aumenta la eficacia de una célula que expresa una molécula de CAR o uno de los inhibidores, por ejemplo, un agente descrito en el presente documento.

En una modalidad, las células descritas en el presente documento (por ejemplo, células que expresan una molécula de CAR de CD20, células que expresan una molécula de CAR de CD22, o células que expresan una molécula de CAR de CD19, por ejemplo, una molécula de CAR de CD19 descrita en el presente documento, en combinación con un inhibidor de células B) son administradas en combinación un agente que reduce uno o más efectos secundarios asociados a la administración de una célula que expresa una molécula de CAR o uno de los inhibidores, por ejemplo, un agente descrito en el presente documento.

En una modalidad, las células que expresan una molécula de CAR de CD19, por ejemplo, una molécula de CAR de CD19 descrita en el presente documento, se administran en combinación con un inhibidor de células B y un agente que trata el linfoma de Hodgkin, por ejemplo, un agente descrito en el presente documento.

En algunos aspectos, la divulgación proporciona un método para tratar un paciente que no responde, responde parcialmente o es recidivante frente a un inhibidor de CD19, por ejemplo, una terapia con CAR de CD19, que comprende administrar al paciente un inhibidor de células B, por ejemplo, un inhibidor de células B tal como se describe en el presente, por ejemplo, un inhibidor de una o más de (por ejemplo, 2, 3, 4, 5, 6, 7, 8, 9, o todas) CD10, CD20, CD22, CD34, CD123 , FLT-3, ROR1, CD79b, CD179b o CD79a. En algunas modalidades, el inhibidor

de células B es una célula que expresa un CAR (por ejemplo, células T o células NK) que es un inhibidor de una o más de (por ejemplo, 2, 3, 4, 5, 6 o todas) CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1. En modalidades, el paciente tiene, o se identifica por tener, una célula cancerosa negativa para CD10 y una célula cancerosa es positiva para una o más de (por ejemplo, 2, 3, 4, 5, 6, 7, 8, 9 o todas) CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a. En algunas modalidades, el método comprende además administrar al paciente un inhibidor de células B para el cual la célula cancerosa es positiva, por ejemplo, un inhibidor de una o más de (por ejemplo, 2, 3, 4, 5, 6, 7, 8, 9 o todas) CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a, para la cual la célula cancerosa es positiva. En algunas modalidades, el método comprende además uno o dos pasos para determinar si el paciente comprende una célula cancerosa negativa para CD19, y un paso para determinar si el paciente comprende una célula cancerosa positiva para una o más de (por ejemplo, 2, 3, 4, 5, 6, 7, 8, 9 o todas) CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a. En modalidades, el sujeto tiene o se identifica por tener una población de células tumorales o cancerosas que dan resultado negativo para la expresión de CD19, que s emide mediant ela unión a un anticuerpo anti-CD19, por ejemplo, un anticuerpo con la misma especificidad como cualquiera de las moléculas de CAR en la **Tabla 2** o en la **Tabla 3.**

En otro aspecto, la invención presenta una composición que comprende una célula que expresa una molécula de receptor quimérico de antígeno (CAR) que une a CD19, en combinación con un inhibidor de células B, por ejemplo, un inhibidor de células B seleccionado de entre un inhibidor de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a, o una combinación de los mismos. La célula que expresa un CAR y el inhibidor de células B pueden estar presentes en una forma de dosis única o como formas de dos o más dosis.

En una modalidad, la composición es una composición farmacéuticamente aceptable.

En algunas modalidades, las composiciones descritas en el presente documento (por ejemplo, ácidos nucleicos, vectores o células) son para uso como un medicamento.

En algunas modalidades, las composiciones descritas en el presente documento son para uso en el tratamiento de una enfermedad asociada a la expresión de un antígeno de células B (por ejemplo, CD19), por ejemplo, una leucemia de células B o linfoma.

INHIBIDORES DE CD19

En algunas modalidades, el inhibidor de CD19 es una molécula pequeña, un anticuerpo, un fragmento de un anticuerpo o una terapia celular.

En algunas modalidades, el inhibidor de CD19 (por ejemplo, una terapia celular o un anticuerpo) se administra en combinación con, o está presente en una composición junto con un inhibidor de células B, por ejemplo, uno o más inhibidores de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a.

En una modalidad, la célula expresa una molécula de CAR que comprende un dominio de unión anti-CD19 (por ejemplo, un anticuerpo o fragmento de anticuerpo murino o humanizado que se une específicamente a CD19), un dominio transmembrana y un dominio de señalización intracelular (por ejemplo, un dominio de señalización intracelular que comprende un dominio coestimulador y/o un dominio primario de señalización). En una modalidad, el CAR comprende un anticuerpo o fragmento de anticuerpo que incluye un dominio de unión anti-CD19 descrito en el presente documento (por ejemplo, un anticuerpo o fragmento de anticuerpo murino o humanizado que se une específicamente a CD19 como se describe en el presente documento), un dominio transmembrana descrito en el presente documento y un dominio de señalización intracelular descrito en el presente documento (por ejemplo, un dominio de señalización intracelular que comprende un dominio coestimulador y/o un dominio primario de señalización descrito en el presente documento).

En una modalidad, la molécula de CAR comprende un dominio de unión anti-CD19 que comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena ligera (LC CDR1), la región 2 determinante de la complementariedad de cadena ligera (LC CDR2), la región 3 determinante de la complementariedad de cadena ligera (LC CDR3) de un dominio de unión anti-CD19 descrito en el presente documento, y/o una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión anti-CD19 descrito en el presente documento, por ejemplo, un dominio de unión anti-CD19 que comprende una o más, por ejemplo, las tres, LC CDR y una o más, por ejemplo, las tres, HC CDR. En una modalidad, el dominio de unión anti-CD19 comprende una o más (por ejemplo, las tres) de la

región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión anti-CD19 descrito en el presente documento, por ejemplo, el dominio de unión anti-CD19 tiene dos regiones variables de cadena pesada, cada una de las cuales comprende una HC CDR1, una HC CDR2 y una HC CDR3 descritas en el presente documento. En una modalidad, el dominio de unión anti-CD19 comprende una región variable de cadena ligera murina descrita en el presente documento (por ejemplo, en la **Tabla 3**) y/o una región variable de cadena pesada murina descrita en el presente documento (por ejemplo, en la **Tabla 3**). En una modalidad, el dominio de unión anti-CD19 es un scFv que comprende una cadena ligera murina y una cadena pesada murina de una secuencia de aminoácidos de la **Tabla 3**. En una modalidad, el dominio de unión anti-CD19 (por ejemplo, un scFv) comprende: una región variable de cadena ligera que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena ligera proporcionada en la **Tabla 3**, o una secuencia con 95-99 % de identidad frente una secuencia de aminoácidos de la **Tabla 3**; y/o una región variable de cadena pesada que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena pesada proporcionada en la **Tabla 3**, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de la **Tabla 3** En una modalidad, el dominio de unión anti-CD19 comprende una secuencia de SEQ ID NO.: 59, o una secuencia con 95-99 % de identidad frente a la misma. En una modalidad, el dominio de unión anti-CD19 es un scFv, y una región variable de cadena ligera que comprende una secuencia de aminoácidos descrita en el presente documento, por ejemplo, en la **Tabla 3**, se une a una región variable de cadena pesada que comprende una secuencia de aminoácidos descrita en este documento, por ejemplo, en la **Tabla 3**, a través de un enlazador, por ejemplo, un enlazador descrito en el presente documento. En una modalidad, el dominio de unión anti-CD19 incluye un enlazador $(Gly_4\text{-}Ser)n$, en el que n es 1, 2, 3, 4, 5 o 6, por ejemplo, 3 o 4 (SEQ ID NO.: 53). La región variable de cadena ligera y la región variable de cadena pesada de un scFv pueden estar, por ejemplo, en cualquiera de las siguientes orientaciones: región variable de cadena ligera-enlazador-región variable de cadena pesada o región variable de cadena pesada-enlazador-

región variable de cadena ligera.

En una modalidad, la molécula de CAR comprende un dominio de unión anti-CD19 humanizado que incluye una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena ligera (LC CDR1), la región 2 determinante de la complementariedad de cadena ligera (LC CDR2), la región 3 determinante de la complementariedad de cadena ligera (LC CDR3) de un dominio de unión anti-CD19 humanizado descrito en el presente documento, y/o una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión anti-CD19 humanizado descrito en el presente documento, por ejemplo, un dominio de unión anti-CD19 humanizado que comprende una o más, por ejemplo, las tres, LC CDR y una o más, por ejemplo, las tres, HC CDR. En una modalidad, el dominio de unión anti-CD19 humanizado comprende al menos HC CDR2. En una modalidad, el dominio de unión anti-CD19 humanizado comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión anti-CD19 humanizado descrito en el presente documento, por ejemplo, el dominio de unión anti-CD19 humanizado tiene dos regiones variables de cadena pesada, cada una de las cuales comprende una HC CDR1, una HC CDR2 y una HC CDR3 descritas en el presente documento. En una modalidad, el dominio de unión anti-CD19 humanizado comprende al menos HC CDR2. En una modalidad, la región variable de cadena ligera comprende una, dos, tres o las cuatro regiones marco de la secuencia de línea germinal VK3_L25. En una modalidad, la región variable de cadena ligera tiene una modificación (por ejemplo, una sustitución, por ejemplo, una sustitución de uno o más aminoácidos que se encuentran en la posición correspondiente de región variable de cadena ligera murina de SEQ ID NO.: 58, por ejemplo, una sustitución en una o más de las posiciones 71 y 87). En una modalidad, la región variable de cadena pesada comprende una, dos, tres o las cuatro regiones marco de la secuencia de línea germinal VH4_4-59. En una modalidad, la región variable de cadena pesada tiene una modificación (por ejemplo, una sustitución, por ejemplo, una sustitución de uno o más aminoácidos que se encuentran en la posición correspondiente de región variable de cadena pesada murina de SEQ ID NO.: 58, por ejemplo,

una sustitución en una o más de las posiciones 71, 73 y 78). En una modalidad, el dominio de unión anti-CD19 humanizado comprende una región variable de cadena ligera descrita en el presente documento (por ejemplo, en la Tabla 2) y/o una región variable de cadena pesada descrita en el presente documento (por ejemplo, en la **Tabla 2**). En una modalidad, el dominio de unión anti-CD19 humanizado es un scFv que comprende una cadena ligera y una cadena pesada de una secuencia de aminoácidos de la **Tabla 2**. En una modalidad, el dominio de unión anti-CD19 humanizado (por ejemplo, un scFv) comprende: una región variable de cadena ligera que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena ligera proporcionada en la **Tabla 2**, o una secuencia con 95-99 % de identidad frente una secuencia de aminoácidos de la **Tabla 2**; y/o una región variable de cadena pesada que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena pesada proporcionada en la **Tabla 2**, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de la **Tabla 2** En una modalidad, el dominio de unión anti-CD19 humanizado comprende una secuencia seleccionada de un grupo que consiste en SEQ ID NO.: 1, SEQ ID NO.: 2, SEQ ID NO.: 3, SEQ ID NO.: 4, SEQ ID NO.: 5, SEQ ID NO.: 6, SEQ ID NO.: 7, SEQ ID NO.: 8, SEQ ID NO.: 9, SEQ ID NO.: 10, SEQ ID NO.: 11 y SEQ ID NO.: 12, o una secuencia con 95-99 % de identidad frente a la misma. En una modalidad, el dominio de unión anti-CD19 humanizado es un scFv, y una región variable de cadena ligera que comprende una secuencia de aminoácidos descrita en el presente documento, por ejemplo, en la **Tabla 2**, se une a una región variable de cadena pesada que comprende una secuencia de aminoácidos descrita en este documento, por ejemplo, en la **Tabla 2**, a través de un enlazador, por ejemplo, un enlazador descrito en el presente documento. En una modalidad, el dominio de unión anti-CD19 humanizado incluye un enlazador $(Gly_4\text{-}Ser)n$, en el que n es 1, 2, 3, 4, 5 o 6, por ejemplo 3 o 4 (SEQ ID NO.: 53). La región variable de cadena ligera y la región variable de cadena pesada de un scFv pueden estar, por ejemplo, en cualquiera de las siguientes orientaciones: región variable de cadena ligera-enlazador-región variable de cadena pesada o región variable de cadena pesada-enlazador-región variable de cadena ligera.

En una modalidad, la molécula de CAR comprende un dominio de unión anti-CD19 que

incluye una o más (por ejemplo, 2, 3, 4, 5 o 6) LC CDR1, LC CDR2, LC CDR3, HC CDR1, HC CDR2, y HC CDR3 de un constructo de las **Tabla 4** y **Tabla 5**, por ejemplo, célula TCAR19 murina, célula TCAR19 humanizada, célula TCAR19 b humanizada o célula TCAR19 c humanizada.

En una modalidad, la molécula de CAR comprende una secuencia líder, por ejemplo, una secuencia líder descrita en el presente documento, por ejemplo, una secuencia líder de SEQ ID No.: 1, o con 95-99% de identidad frente a la misma, un dominio de unión anti-CD19 descrito en el presente documento, por ejemplo, un dominio de unión anti-CD19 que comprende una LC CDR1, una LC CDR2, una LC CDR3, una HC CDR1, una HC CDR2 y una HC CDR3 descrito en el presente documento, por ejemplo, un dominio de unión anti-CD19 murino descrito en la **Tabla 3**, un dominio de unión anti-CD19 humanizado descrito en la **Tabla 2** o una secuencia con 95-99 % de identidad frente al mismo, una región bisagra, por ejemplo una región bisagra descrita en el presente documento, por ejemplo, una región bisagra de SEQ ID NO. 14, o una secuencia con 95-99 % de identidad frente a la misma, un dominio transmembrana, por ejemplo, un dominio transmembrana descrito en el presente documento, por ejemplo, un dominio transmembrana que tiene una secuencia de SEQ ID NO.: 15 o una secuencia con 95-99 % de identidad frente a la misma, un dominio de señalización intracelular, por ejemplo, un dominio de señalización intracelular descrito en el presente documento (por ejemplo, un dominio de señalización intracelular que comprende un dominio coestimulador y/o un dominio primario de señalización). En una modalidad, el dominio de señalización intracelular comprende un dominio coestimulador, por ejemplo, un dominio coestimulador descrito en el presente documento, por ejemplo, un dominio coestimulador de 4-1BB que tiene una secuencia de SEQ ID NO.: 16 o SEQ ID NO.: 51, o que tiene 95-99 % de identidad frente a la misma, y/o un dominio primario de señalización, por ejemplo, un dominio primario de señalización descrito en el presente documento, por ejemplo, un dominio estimulador de CD3 zeta que tiene una secuencia de SEQ ID NO.: 17 o SEQ ID NO.: 43, o que tiene 95-99 % de identidad frente a la misma.

En una modalidad, la molécula de CAR comprende (por ejemplo, consiste en) una secuencia de aminoácidos SEQ ID NO.: 58, SEQ ID NO.: 31, SEQ ID NO.: 32, SEQ ID NO.: 33, SEQ ID NO.: 34, SEQ ID NO.: 35, SEQ ID NO.: 36, SEQ ID NO.: 37, SEQ ID NO.: 38, SEQ ID NO.: 39, SEQ ID NO.: 40, SEQ ID NO.: 41 o SEQ ID NO.: 42, o una secuencia de aminoácidos que tiene al menos una, dos, tres, cuatro, cinco, 10, 15, 20 o 30 modificaciones (por

ejemplo, sustituciones) pero no más de 60, 50 o 40 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de SEQ ID NO.: 58, SEQ ID NO.: 31, SEQ ID NO.: 32, SEQ ID NO.: 33, SEQ ID NO.: 34, SEQ ID NO.: 35, SEQ ID NO.: 36, SEQ ID NO.: 37, SEQ ID NO.: 38, SEQ ID NO.: 39, SEQ ID NO.: 40, SEQ ID NO.: 41 o SEQ ID NO.: 42 o una secuencia de aminoácidos que tiene 85%, 90%, 95%, 96%, 97%, 98% o 99% de identidad frente a una secuencia de aminoácidos de SEQ ID NO.: 58, SEQ ID NO.: 31, SEQ ID NO.: 32, SEQ ID NO.: 33, SEQ ID NO.: 34, SEQ ID NO.: 35, SEQ ID NO.: 36, SEQ ID NO.: 37, SEQ ID NO.: 38, SEQ ID NO.: 39, SEQ ID NO.: 40, SEQ ID NO.: 41 o SEQ ID NO.: 42.

La presente invención se refiere en general, en algunos aspectos, al uso de células, por ejemplo, células T o células asesinas naturales (NK), modificadas para expresar un CAR en combinación con uno o más inhibidores de células B para el tratamiento de una enfermedad asociada con la expresión de la proteína del grupo de diferenciación 19 (CD19). En algunas modalidades, el inhibidor de células B es un inhibidor de una o más de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a.

En algunas modalidades, el inhibidor de CD19 comprende una molécula de anticuerpo que tiene, por ejemplo, una molécula de anticuerpo que tiene una secuencia de unión a CD19 tal como se describe en el presente documento. Por ejemplo, la molécula de anticuerpo puede comprender CDR o VH y VL tal como se describe en cualquiera de las Tablas **2, 3, 4 y 5**, o una secuencia con homología a las mismas, por ejemplo, que tiene 95-99 % de identidad frente a las mismas. La molécula de anticuerpo puede comprender una región de unión a CD19 que tiene una secuencia descrita en esta sección, por ejemplo, en el contexto de un CAR.

En algunas modalidades, el inhibidor de células B se elige de entre un ácido nucleico inhibidor, un ligando soluble, un anticuerpo o fragmento de unión a antígeno del mismo, un CAR o una célula que expresa un CAR que se une a uno o más antígenos de células B, por ejemplo, una o más de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a.

DOMINIOS DE UNIÓN E INHIBIDORES DE CD20

En algunos aspectos, la presente descripción proporciona un inhibidor de CD20 o un dominio de unión, por ejemplo, un inhibidor de CD20 o un dominio de unión como se describe

en el presente documento. La descripción también proporciona un ácido nucleico que codifica el dominio de unión a CD20, por ejemplo, que codifica un CAR que comprende el dominio de unión a CD20. La composición también puede comprender un segundo agente, por ejemplo, una célula que expresan CAR anti-CD19 o un dominio de unión a CD19. Los agentes pueden ser, por ejemplo, codificados por un único ácido nucleico o por diferentes ácidos nucleicos.

En algunos aspectos, un inhibidor de CD20 o el dominio de unión se administra como monoterapia. En algunos aspectos, el inhibidor de CD20 o el dominio de unión se administra en combinación con un segundo agente, tal como una célula que expresa un CAR anti-CD19.

El inhibidor de CD20 puede ser, por ejemplo, una molécula pequeña, un anticuerpo o un fragmento de unión a antígeno del mismo, un CAR o una célula que expresa CAR. En una modalidad, el inhibidor de CD20 es un anticuerpo anti-CD20 o fragmento del mismo. En una modalidad, el anticuerpo es un anticuerpo monoespecífico y en otra modalidad el anticuerpo es un anticuerpo biespecífico. En una modalidad, el inhibidor de CD20 es anticuerpo monoclonal humano/de ratón quimérico, por ejemplo, rituximab. En una modalidad, el inhibidor de CD20 es un anticuerpo monoclonal humano tal como ofatumumab. En una modalidad, el inhibidor de CD20 es un anticuerpo humanizado tal como ocrelizumab, veltuzumab, obinutuzumab, ocaratuzumab o PRO131921 (Genentech). En una modalidad, el inhibidor de CD20 es una proteína de fusión que comprende una porción de un anticuerpo anti-CD20, tal como TRU-015 (Trubion Pharmaceuticals).

En una modalidad, el inhibidor de CD20 es una célula que expresa un CAR anti-CD20, por ejemplo, TCAR de CD20 o células NK que expresan CD20.

En algunas modalidades, el CAR de CD20 comprende una secuencia líder opcional (por ejemplo, una secuencia líder opcional descrita en el presente documento), un dominio de unión a antígeno extracelular, una bisagra (por ejemplo, una bisagra descrita en el presente documento), un dominio transmembrana (por ejemplo, un dominio transmembrana descrito en el presente documento) y un dominio estimulador intracelular (por ejemplo, un dominio estimulador intracelular descrito en el presente documento). En una modalidad, un ejemplo de constructo de CAR de CD20 comprende una secuencia líder opcional (por ejemplo, una secuencia líder opcional descrita en el presente documento), un dominio de unión a antígeno extracelular, una

bisagra, un dominio transmembrana, un dominio coestimulador intracelular (por ejemplo, un dominio coestimulador intracelular descrito en el presente documento) y un dominio estimulador intracelular.

En una modalidad, el dominio de unión a CD20 comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena ligera (LC CDR1), la región 2 determinante de la complementariedad de cadena ligera (LC CDR2), la región 3 determinante de la complementariedad de cadena ligera (LC CDR3) de un dominio de unión a CD20 descrito en el presente documento, y/o una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión a CD20 descrito en el presente documento, por ejemplo, un dominio de unión a CD20 que comprende una o más, por ejemplo, las tres, LC CDR y una o más, por ejemplo, las tres, HC CDR. Estas CDR pueden ser, por ejemplo, las de la **Tabla 12A, 12B** y/o **Tabla 13**. En una modalidad, el dominio de unión a CD20 humano comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión a CD20 humano descrito en el presente documento, por ejemplo, el dominio de unión a CD20 humano tiene dos regiones variables de cadena pesada, cada una de las cuales comprende una HC CDR1, una HC CDR2 y una HC CDR3 descritas en el presente documento. En una modalidad, el dominio de unión a CD20 comprende una región variable de cadena ligera descrita en el presente documento (por ejemplo, en la Tabla 15A o 15B) y/o una región variable de cadena pesada descrita en el presente documento (por ejemplo, en la Tabla 14A o 14B). En una modalidad, el dominio de unión a CD20 comprende una región variable de cadena pesada descrita en el presente documento (por ejemplo, en la **Tabla** 14A o 14B), por ejemplo, al menos dos regiones variables de cadena pesada descritas en el presente documento (por ejemplo, en la **Tabla** 14A o 14B). En una modalidad, el dominio de unión a CD20 es un scFv que comprende una cadena ligera y una cadena pesada de una secuencia de aminoácidos de las **Tabla** 14A o 14B o **Tabla** 15A o 15B. En una modalidad, el dominio de unión a CD20 (por ejemplo, un scFv) comprende: una región variable de cadena ligera que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10

modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena ligera proporcionada en la **Tabla** 15A o 15B, o una secuencia con 95-99 % de identidad frente una secuencia de aminoácidos de la **Tabla** 15A o 15B; y/o una región variable de cadena pesada que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena pesada proporcionada en la **Tabla** 14A o 14B, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de la **Tabla** 14A o 14B. El dominio de unión a CD20 puede ser parte, por ejemplo, de una molécula de anticuerpo o una molécula de CAR.

En una modalidad, la molécula de CAR comprende un dominio de unión anti-CD20 que incluye una o más (por ejemplo, 2, 3, 4, 5, o 6) LC CDR1, LC CDR2, LC CDR3, HC CDR1, HC CDR2, y HC CDR3 de un constructo de las **Tabla 12A, 12B** y/o **Tabla 13**, por ejemplo, CAR20-1, CAR20-2, CAR20-3, CAR20-4, CAR20-5, CAR20-6, CAR20-7, CAR20-8, CAR20-9, CAR20-10, CAR20-11, CAR20-12, CAR20-13, CAR20-14, CAR20-15 o CAR20-16.

En una modalidad, la molécula de CAR comprende un dominio de unión anti-CD22 que incluye una VL y/o una VH de un constructo de las **Tabla** 14A o 14B y **Tabla** 15A o 15B, por ejemplo, CAR20-1, CAR20-2, CAR20-3, CAR20-4, CAR20-5, CAR20-6, CAR20-7, CAR20-8, CAR20-9, CAR20-10, CAR20-11, CAR20-12, CAR20-13, CAR20-14, CAR20-15 o CAR20-16.

El scFv de CD20 puede estar precedido por una secuencia líder opcional tal como la proporcionada en la SEQ ID NO.: 13, y seguido por una secuencia de bisagra opcional tal como la proporcionada en la SEQ ID NO.: 14 o SEQ ID NO.: 45 o SEQ ID NO.: 47 o SEQ ID NO.: 49, una región transmembrana tal como la proporcionada en SEQ ID NO.: 15, un dominio de señalización intracelular que incluye SEQ ID NO.: 16 o SEQ ID NO.: 51 y una secuencia de CD3 zeta que incluye SEQ ID NO.: 17 o SEQ ID NO.: 43, por ejemplo, donde los dominios son contiguos y están en el mismo marco de lectura para formar una proteína de fusión única.

Modalidades adicionales incluyen una secuencia de nucleótidos que codifica un polipéptido de cualquiera de las **Tablas 11A-15B**. Modalidades adicionales incluyen una secuencia de nucleótidos que codifica un polipéptido de cualquiera de las **Tablas 11A-15B**, y cada uno de los dominios de SEQ ID NO.: 13, 14, 15, 16, 17 y, opcionalmente, 51.

En una modalidad, el dominio de unión a CD20 se distingue por características o propiedades funcionales particulares de un anticuerpo o fragmento de anticuerpo. Por ejemplo, en una modalidad, la porción de una composición de CAR de la invención que comprende un dominio de unión a antígeno une específicamente a CD20 humana o a un fragmento de la misma.

En una modalidad, el dominio de unión a CD20 es un fragmento, por ejemplo, un fragmento variable de cadena única (scFv). En una modalidad, el dominio de unión a CD20 es un Fv, un Fab, un (Fab')2 o un anticuerpo híbrido bi-funcional (por ejemplo, bi-específico) (por ejemplo, Lanzavecchia et al., Eur. J. Immunol. 17, 105 (1987)). En un aspecto, los anticuerpos y fragmentos de los mismos de la invención se unen a una proteína CD20 o a un fragmento de la misma con afinidad natural o aumentada. En algunos casos, un scFv humano se puede derivar de una biblioteca de expresión.

En una modalidad, el dominio de unión a CD20, por ejemplo, scFv, comprende al menos una mutación tal que el scFv mutado confiere una mayor estabilidad al constructo de TCAR20. En otra modalidad, el dominio de unión a CD20, por ejemplo, scFv, comprende al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 mutaciones como resultado de, por ejemplo, el proceso de humanización, tales que el scFv mutado confiere una mayor estabilidad al constructo de TCAR20.

En algunas modalidades, el inhibidor de CD20 comprende una molécula de anticuerpo que tiene, por ejemplo, una molécula de anticuerpo que tiene una secuencia de unión a CD20 tal como se describe en el presente documento. Por ejemplo, la molécula de anticuerpo puede comprender CDR o VH y VL tal como se describe en cualquiera de las Tablas **11A-15B**, o una secuencia con homología a las mismas, por ejemplo, que tiene 95-99 % de identidad frente a las mismas. La molécula de anticuerpo puede comprender una región de unión a CD20 que tiene una secuencia descrita en esta sección, por ejemplo, en el contexto de un CAR.

En un aspecto, la presente divulgación proporciona una población de células que expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD20. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de CD20.

En algunos aspectos, una molécula de anticuerpo o un dominio de unión descrito en este

documento se une a la misma (o sustancialmente la misma) o una superposición (o superposición sustancialmente) del epítope con una segunda molécula de anticuerpo a CD20, en el que la segunda molécula de anticuerpo es una molécula de anticuerpo descrita en este documento, por ejemplo, una molécula de anticuerpo seleccionada de las Tablas 11A-15B. En algunas formas de realización, una molécula de anticuerpo o un dominio de unión descrito en este documento compite por la unión, y/o se une a la misma (o sustancialmente la misma) o la superposición (o sustancialmente superposición) del epítope, con una segunda molécula de anticuerpo a CD20, en el que la segunda molécula de anticuerpo es una molécula de anticuerpo descrito en el presente documento, por ejemplo, una molécula de anticuerpo seleccionado de las Tablas 11A-15B, por ejemplo, como se determina por los métodos descritos en el ejemplo 25. en algunas realizaciones, un dominio biparatópico de unión a CD20 se une a un primer epítopo, por ejemplo, un epítopo unido por una molécula de anticuerpo seleccionado de las Tablas 11A-15B, y el dominio biparatópico de unión también se une a un segundo epítope, por ejemplo, un segundo epítopo unido por una molécula de anticuerpo seleccionado de las Tablas 11A-15B. En algunos aspectos, la presente descripción proporciona un método de tratamiento que comprende la administración de un primer dominio de unión a CD20 que se une a un primer epítope, por ejemplo, un epítope unido por una molécula de anticuerpo seleccionado de las Tablas 11A-15B y un segundo dominio de unión a CD20 que se une a un segundo epítope, por ejemplo, un segundo epítope unido por una molécula de anticuerpo seleccionada de las Tablas 11A-15B. En algunas realizaciones, los dominios de unión a CD20 son parte de las moléculas de CAR, por ejemplo, expresadas por una célula que expresa CAR.

DOMINIOS DE UNIÓN E INHIBIDORES DE CD22

En algunos aspectos, la presente descripción proporciona un inhibidor de CD22 o dominio de unión, por ejemplo, un inhibidor de CD22 o dominio de unión como se describe en el presente documento. La descripción también proporciona un ácido nucleico que codifica el dominio de unión a CD22, por ejemplo, que codifica un CAR que comprende el dominio de unión a CD22. La composición también puede comprender un segundo agente, por ejemplo, una célula que expresa un CAR anti-CD19 o un dominio de unión a CD19. Los agentes pueden ser, por ejemplo, codificados por un único ácido nucleico o diferentes ácidos nucleicos.

En algunos aspectos, un inhibidor de CD22 o dominio de unión se administra como

monoterapia. En algunos aspectos, el inhibidor de CD22 o dominio de unión se administra en combinación con un segundo agente, tal como una célula que expresan un CAR anti-CD19.

El inhibidor de CD22 puede ser, por ejemplo, una molécula pequeña, un anticuerpo o un fragmento de unión a antígeno del mismo, un CAR o una célula que expresa CAR. En una modalidad, el inhibidor de CD22 es un anticuerpo anti-CD22 o fragmento del mismo. En una modalidad, el anticuerpo es un anticuerpo monoespecífico y en otra modalidad el anticuerpo es un anticuerpo biespecífico. En una modalidad, el anticuerpo es un anticuerpo monoespecífico, opcionalmente conjugado con un segundo agente, tal como un agente quimioterapéutico. Por ejemplo, en una modalidad, el anticuerpo es un conjugado MMAE-anticuerpo monoclonal anti-CD22 (por ejemplo, DCDT2980S). En una modalidad, el anticuerpo es un scFv de un anticuerpo anti-CD22, por ejemplo, un scFv del anticuerpo RFB4. Este scFv se puede fusionar a la totalidad o a un fragmento de exotoxina A de Pseudomonas (por ejemplo, BL22). En una modalidad, el anticuerpo es un anticuerpo monoclonal anti-CD22 humanizado (por ejemplo, epratuzumab). En una modalidad, el anticuerpo o fragmento del mismo comprende la porción Fv de un anticuerpo anti-CD22, que está opcionalmente fusionada de manera covalente a la totalidad o a un fragmento (por ejemplo, un fragmento 38 KDa) de la exotoxina A de Pseudomonas (por ejemplo, moxetumomab pasudotox). En una modalidad, el anticuerpo anti-CD22 es un anticuerpo biespecífico anti-CD19/CD22, opcionalmente conjugado con una toxina. Por ejemplo, en una modalidad, el anticuerpo anti-CD22 comprende una porción de un anticuerpo biespecífico anti-CD19/CD22 (por ejemplo, dos ligandos scFv, reconociendo CD19 y CD22 humanas) opcionalmente enlazada a la totalidad o a una parte de la toxina de la difteria (DT), por ejemplo, los primeros 389 aminoácidos de la toxina de la difteria (DT), DT 390, por ejemplo, una toxina dirigida a un ligando tal como DT2219ARL). En otra modalidad, la porción biespecífica (por ejemplo, anti-CD19/anti-CD22) está enlazada a una toxina tal como la cadena A de la ricina desglicosilada (por ejemplo, Combotox).

En una modalidad, el inhibidor de CD22 es una célula que expresa un CAR anti-CD22, por ejemplo, un TCAR de CD22 o células NK que expresan CD22.

En un aspecto, la presente divulgación proporciona una población de células que expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD22. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que

expresa un CAR de CD22. Como otro ejemplo, la población de células TCAR puede incluir una única población que expresa más de uno, por ejemplo, 2, 3, 4, 5 o 6 o más, CAR, por ejemplo, un CAR de CD19 y un CAR de CD22.

En algunas modalidades, el CAR de CD22 comprende una secuencia líder opcional (por ejemplo, una secuencia líder opcional descrita en el presente documento), un dominio de unión a antígeno extracelular, una bisagra (por ejemplo, una bisagra descrita en el presente documento), un dominio transmembrana (por ejemplo, un dominio transmembrana descrito en el presente documento) y un dominio estimulador intracelular (por ejemplo, un dominio estimulador intracelular descrito en el presente documento). En una modalidad, un ejemplo de constructo de CAR de CD22 comprende una secuencia líder opcional (por ejemplo, una secuencia líder opcional descrita en el presente documento), un dominio de unión a antígeno extracelular, una bisagra, un dominio transmembrana, un dominio coestimulador intracelular (por ejemplo, un dominio coestimulador intracelular descrito en el presente documento) y un dominio estimulador intracelular.

En una modalidad, el dominio de unión a CD22 comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena ligera (LC CDR1), la región 2 determinante de la complementariedad de cadena ligera (LC CDR2), la región 3 determinante de la complementariedad de cadena ligera (LC CDR3) de un dominio de unión a CD22 descrito en el presente documento, y/o una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión a CD22 descrito en el presente documento, por ejemplo, un dominio de unión a CD22 que comprende una o más, por ejemplo, las tres, LC CDR y una o más, por ejemplo, las tres, HC CDR. Estas CDR pueden ser, por ejemplo, una o más CDR de la **Tabla 7A 7B, 7C, 8A** y/o la **Tabla 8B**. En una modalidad, el dominio de unión a CD22 comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión a CD22 descrito en el presente documento, por ejemplo, el dominio de unión a CD22 tiene dos regiones variables de cadena pesada, cada una de las cuales comprende una HC CDR1, una HC CDR2 y

una HC CDR3 descritas en el presente documento. En una modalidad, el dominio de unión a CD22 comprende una región variable de cadena ligera descrita en el presente documento (por ejemplo, en la **Tabla 10A o 10B**) y/o una región variable de cadena pesada descrita en el presente documento (por ejemplo, en la **Tabla 9A o 9B**). En una modalidad, el dominio de unión a CD22 comprende una región variable de cadena pesada descrita en el presente documento (por ejemplo, en la **Tabla 9A o 9B**), por ejemplo, al menos dos regiones variables de cadena pesada descritas en el presente documento (por ejemplo, en la **Tabla 9A o 9B**). En una modalidad, el dominio de unión a CD22 es un scFv que comprende una cadena ligera y una cadena pesada de una secuencia de aminoácidos de la **Tabla 9A o 9B** y **Tabla 10A o 10B**. En una modalidad, el dominio de unión a CD22 (por ejemplo, un scFv) comprende: una región variable de cadena ligera que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena ligera proporcionada en la **Tabla 10A o 10B**., o una secuencia con 95-99 % de identidad frente una secuencia de aminoácidos de la **Tabla 10A o 10B**.; y/o una región variable de cadena pesada que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena pesada proporcionada en la **Tabla 9A** o 9B o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de la **Tabla 9A o 9B.**

En una modalidad, la molécula de CAR comprende un dominio de unión anti-CD22 que incluye una o más (por ejemplo, 2, 3, 4, 5 o 6) LC CDR1, LC CDR2, LC CDR3, HC CDR1, HC CDR2 y HC CDR3 de un constructo de las **Tabla 7A 7B, 7C, 8A** y **Tabla 8B**, por ejemplo, m971, CAR22-1, CAR22-2, CAR22-3 , CAR22-4 , CAR22-5 , CAR22-6 , CAR22-7, CAR22-8 , CAR22-9 , CAR22-10, CAR22-11, CAR22-12, CAR22-13, CAR22-14, CAR22-15, CAR22-16, CAR22-17, CAR22-18, CAR22-19, CAR22-20, CAR22-21, CAR22-22, CAR22-23, CAR22-24, CAR22-25, CAR22-26, CAR22-27, CAR22-28, CAR22-29, CAR22-30, CAR22-31, CAR22-32, CAR22-33, CAR22-34, CAR22-35, CAR22-36, CAR22-37 o CAR22-38.

En una modalidad, la molécula de CAR comprende un dominio de unión anti-CD22 que incluye una VL y/o una VH de un constructo de las **Tabla 9A, 9B, 10A** y **Tabla 10B**, por ejemplo, m971, CAR22-1, CAR22-2, CAR22-3 , CAR22-4 , CAR22-5 , CAR22-6 , CAR22-7,

CAR22-8 , CAR22-9 , CAR22-10, CAR22-11, CAR22-12, CAR22-13, CAR22-14, CAR22-15, CAR22-16, CAR22-17, CAR22-18, CAR22-19, CAR22-20, CAR22-21, CAR22-22, CAR22-23, CAR22-24, CAR22-25, CAR22-26, CAR22-27, CAR22-28, CAR22-29, CAR22-30, CAR22-31, CAR22-32, CAR22-33, CAR22-34, CAR22-35, CAR22-36, CAR22-37 o CAR22-38, o una secuencia con 95-99 % de identidad frente a las mismas.

El scFv puede estar precedido por una secuencia líder opcional tal como la proporcionada en la SEQ ID NO.: 13, y seguido por una secuencia de bisagra opcional tal como la proporcionada en la SEQ ID NO.: 14 o SEQ ID NO.: 45 o SEQ ID NO.: 47 o SEQ ID NO.: 49, una región transmembrana tal como la proporcionada en SEQ ID NO.: 15, un dominio de señalización intracelular que incluye SEQ ID NO.: 16 o SEQ ID NO.: 51 y una secuencia de CD3 zeta que incluye SEQ ID NO.: 17 o SEQ ID NO.: 43, por ejemplo, donde los dominios son contiguos y están en el mismo marco de lectura para formar una proteína de fusión única.

Otras modalidades incluyen una secuencia de nucleótidos que codifica un polipéptido de cualquiera de las **Tablas 6A-10B.** Otras modalidades incluyen una secuencia de nucleótidos que codifica un polipéptido de cualquiera de las **Tablas 6A-10B**, y cada uno de los dominios de SEQ ID NO.: 13, 14, 15, 16, 17 y, opcionalmente, 51.

En una modalidad, el dominio de unión a CD22 se distingue por características o propiedades funcionales particulares de un anticuerpo o fragmento de anticuerpo. Por ejemplo, en una modalidad, la porción de una composición de CAR de la invención que comprende un dominio de unión a antígeno une específicamente a CD22 humana o a un fragmento de la misma.

En una modalidad, el dominio de unión a CD22 es un fragmento, por ejemplo, un fragmento variable de cadena única (scFv). En una modalidad, el dominio de unión a CD22 es un Fv, un Fab, un (Fab')2 o un anticuerpo híbrido bi-funcional (por ejemplo, bi-específico) (por ejemplo, Lanzavecchia et al., Eur. J. Immunol. 17, 105 (1987)). En un aspecto, los anticuerpos y fragmentos de los mismos de la invención se unen a una proteína CD22 o a un fragmento de la misma con afinidad natural o aumentada. En algunos casos, un scFv humano se puede derivar de una biblioteca de expresión.

En una modalidad, el dominio de unión a CD22, por ejemplo, scFv, comprende al menos una mutación tal que el scFv mutado confiere una mayor estabilidad al constructo de TCAR22.

En otra modalidad, el dominio de unión a CD22, por ejemplo, scFv, comprende al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 mutaciones como resultado de, por ejemplo, el proceso de humanización, tales que el scFv mutado confiere una mayor estabilidad al constructo de TCAR22.

En algunas modalidades, el inhibidor de CD22 comprende una molécula de anticuerpo que tiene, por ejemplo, una molécula de anticuerpo que tiene una secuencia de unión a CD22 tal como se describe en el presente documento. Por ejemplo, la molécula de anticuerpo puede comprender CDR o VH y VL tal como se describe en cualquiera de las Tablas **6A-10B**, o una secuencia con homología a las mismas, por ejemplo, que tiene 95-99 % de identidad frente a las mismas. La molécula de anticuerpo puede comprender una región de unión a CD22 que tiene una secuencia descrita en esta sección, por ejemplo, en el contexto de un CAR.

En una modalidad, la presente divulgación proporciona una población de células que expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD22. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de CD22.

En algunos aspectos, una molécula de anticuerpo o un dominio de unión descrito en este documento se une a la misma (o sustancialmente la misma) o una superposición (o superposición sustancialmente) del epítope con una segunda molécula de anticuerpo a CD22, en el que la segunda molécula de anticuerpo es una molécula de anticuerpo descrita en este documento, por ejemplo, una molécula de anticuerpo seleccionada de las Tablas 6A-10B. En algunas formas de realización, una molécula de anticuerpo o un dominio de unión descrito en este documento compite por la unión, y/o se une a la misma (o sustancialmente la misma) o la superposición (o sustancialmente superposición) del epítope, con una segunda molécula de anticuerpo a CD22, en el que la segunda molécula de anticuerpo es una molécula de anticuerpo descrito en el presente documento, por ejemplo, una molécula de anticuerpo seleccionado de las Tablas 6A-10B, por ejemplo, como se determina por los métodos descritos en el ejemplo 25. en algunas realizaciones, un dominio biparatópico de unión a CD22 se une a un primer epítopo, por ejemplo, un epítopo unido por una molécula de anticuerpo seleccionado de las Tablas 6A-10B, y el dominio biparatópico de unión también se une a un segundo epítope, por ejemplo, un segundo epítopo unido por una molécula de anticuerpo seleccionado de las Tablas 6A-10B. En algunos aspectos, la presente descripción proporciona un método de tratamiento que comprende la administración

de un primer dominio de unión a CD22 que se une a un primer epítope, por ejemplo, un epítope unido por una molécula de anticuerpo seleccionado de las Tablas 6A-10B y un segundo dominio de unión a CD22 que se une a un segundo epítope, por ejemplo, un segundo epítope unido por una molécula de anticuerpo seleccionada de las Tablas 6A-10B. En algunas realizaciones, los dominios de unión a CD22 son parte de las moléculas de CAR, por ejemplo, expresadas por una célula que expresa CAR.

En algunas modalidades, un dominio de unión a CD22 s eune a uno o más de los dominios similares a Ig 1, 2, 3, 4, 5, 6 o 7 de CD22. En algunas modalidades, el dominio de unión a CD22 se une a los dominios 1 y 2; a los dominios 3 y 4; o a los dominios 5, 6 y 7.

En algunos aspectos, la divulgación proporciona un método para tratar un cáncer CD19 negativo, por ejemplo, una leucemia, por ejemplo una LLA, por ejemplo una LLA-B, que comprende administrar un inhibidor de CD22, por ejemplo, un dominio de unión a CD22 o una célula que exprese un CAR-CD22 descrito en el presente documento. En algunas modalidades, el método incluye la etapa de determinar cuando el cáncer es CD-19 negativo. En algunas modalidades, el sujeto ha recibido un inhibidor de CD19, por ejemplo, una célula que expresa un CD19 CAR y esresistente, reincidente o refractario al inhibidor de CD19.

INHIBIDORES DE ROR1

El inhibidor de ROR1 puede ser, por ejemplo, una molécula pequeña, un anticuerpo o un fragmento del mismo. En una modalidad, el inhibidor de ROR1 es un anticuerpo anti-ROR1 o fragmento del mismo. En una modalidad, el anticuerpo anti-ROR1 o fragmento del mismo es un anticuerpo monoclonal, por ejemplo, cirmtuzumab.

En una modalidad, el inhibidor de ROR1 es una célula que expresa un CAR anti-ROR1, por ejemplo, TCAR de ROR1 o célula NK que expresa ROR1.

En algunas modalidades, el CAR de ROR1 comprende una secuencia líder opcional (por ejemplo, una secuencia líder opcional descrita en el presente documento), un dominio de unión a antígeno extracelular, una bisagra (por ejemplo, una bisagra descrita en el presente documento), un dominio transmembrana (por ejemplo, un dominio transmembrana descrito en el presente documento) y un dominio estimulador intracelular (por ejemplo, un dominio estimulador intracelular descrito en el presente documento). En una modalidad, un ejemplo de constructo de

CAR de ROR1 comprende una secuencia líder opcional (por ejemplo, una secuencia líder opcional descrita en el presente documento), un dominio de unión a antígeno extracelular, una bisagra, un dominio transmembrana, un dominio coestimulador intracelular (por ejemplo, un dominio coestimulador intracelular descrito en el presente documento) y un dominio estimulador intracelular.

En una modalidad, el dominio de unión comprende una parte ROR1 scFv, por ejemplo, una porción de scFv humano. El scFv puede estar precedido por una secuencia líder opcional tal como la proporcionada en la SEQ ID NO.: 13, y seguido por una secuencia de bisagra opcional tal como la proporcionada en la SEQ ID NO.: 14 o SEQ ID NO.: 45 o SEQ ID NO.: 47 o SEQ ID NO.: 49, una región transmembrana tal como la proporcionada en SEQ ID NO.: 15, un dominio de señalización intracelular que incluye SEQ ID NO.: 16 o SEQ ID NO.: 51 y una secuencia de CD3 zeta que incluye SEQ ID NO.: 17 o SEQ ID NO.: 43, por ejemplo, donde los dominios son contiguos y están en el mismo marco de lectura para formar una proteína de fusión única.

En algunas modalidades, la presente divulgación incluye un ácido nucleico recombinante que comprende una molécula de ácido nucleico que codifica un CAR de ROR1, donde la molécula de ácido nucleico comprende la secuencia de ácido nucleico que codifica un dominio de unión a ROR1, por ejemplo, tal como el descrito en el presente documento, por ejemplo, que es contiguo y está en el mismo marco de lectura que la secuencia de ácido nucleico que codifica un dominio de señalización intracelular. Un ejemplo de dominio de señalización intracelular que se puede usar en el CAR incluye, de manera enunciativa mas no limitativa, uno o más dominios de señalización intracelular, por ejemplo, CD3 zeta, CD28, 4-1BB y similares. En algunos casos, el CAR puede comprender cualquier combinación de CD3 zeta, CD28, 4-1BB y similares.

En una modalidad, el dominio de unión a ROR1 se distingue por características o propiedades funcionales particulares de un anticuerpo o fragmento de anticuerpo. Por ejemplo, en una modalidad, la porción de una composición de CAR de la invención que comprende un dominio de unión a antígeno une específicamente a ROR1 humana o a un fragmento de la misma. En ciertas modalidades, el scFv es contiguo y está en el mismo marco de lectura que una secuencia líder. En un aspecto, la secuencia líder es la secuencia del polipéptido proporcionada como SEQ ID NO.: 13.

En una modalidad, el dominio de unión a ROR1 es un fragmento, por ejemplo, un

fragmento variable de cadena única (scFv). En una modalidad, el dominio de unión a ROR1 es un Fv, un Fab, un (Fab')2 o un anticuerpo híbrido bi-funcional (por ejemplo, bi-específico) (por ejemplo, Lanzavecchia et al., Eur. J. Immunol. 17, 105 (1987)). En un aspecto, los anticuerpos y fragmentos de los mismos de la invención se unen a una proteína ROR1 o a un fragmento de la misma con afinidad natural o aumentada. En algunos casos, un scFv humano se puede derivar de una biblioteca de expresión.

En una modalidad, el dominio de unión a ROR1, por ejemplo, scFv, comprende al menos una mutación tal que el scFv mutado confiere una mayor estabilidad al constructo de TCAR de ROR1. En otra modalidad, el dominio de unión a ROR1, por ejemplo, scFv, comprende al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 mutaciones como resultado del proceso de humanización tales que el scFv mutado confiere una mayor estabilidad al constructo de TCAR de ROR1.

En una modalidad, la presente divulgación proporciona una población de células que expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de ROR1. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de ROR1.

INHIBIDORES DE CD123

El inhibidor de CD123 puede ser, por ejemplo, una molécula pequeña, anticuerpo, o fragmento del mismo (por ejemplo, un anticuerpo monoespecífico o biespecífico o un fragmento del mismo); una proteína recombinante, por ejemplo, una proteína de fusión, que se une a CD123; un ácido nucleico inhibidor; o una célula que expresa un CAR de CD123, por ejemplo, una célula TCAR de CD123.

En una modalidad, el inhibidor de CD123 es una proteína recombinante, por ejemplo, que comprende el ligando natural (o un fragmento) del receptor de CD123, por ejemplo, SL-401 (también llamado DT388IL3; University of Texas Southwestern Medical Center).

En otra modalidad, el inhibidor de CD123 es un anticuerpo anti-CD123 o un fragmento del mismo, por ejemplo, un anticuerpo monoclonal (por ejemplo, un anticuerpo monoespecífico o biespecífico o un fragmento del mismo), tal como CSL360 (CSL Limited), CSL362 (CSL Limited) o MGD006 (MacroGenics).

En una modalidad, el inhibidor de CD123 es una célula que expresa un CAR anti-CD123, por ejemplo, un TCAR de CD123 o células NK que expresan CD123.

En algunas modalidades, el CAR de CD123 comprende una secuencia líder opcional (por ejemplo, una secuencia líder opcional descrita en el presente documento), un dominio de unión a antígeno extracelular, una bisagra (por ejemplo, una bisagra descrita en el presente documento), un dominio transmembrana (por ejemplo, un dominio transmembrana descrito en el presente documento) y un dominio estimulador intracelular (por ejemplo, un dominio estimulador intracelular descrito en el presente documento). En una modalidad, un ejemplo de constructo de CAR de CD123 comprende una secuencia líder opcional (por ejemplo, una secuencia líder opcional descrita en el presente documento), un dominio de unión a antígeno extracelular, una bisagra, un dominio transmembrana, un dominio coestimulador intracelular (por ejemplo, un dominio coestimulador intracelular descrito en el presente documento) y un dominio estimulador intracelular.

En una modalidad, el dominio de unión a CD123 comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena ligera (LC CDR1), la región 2 determinante de la complementariedad de cadena ligera (LC CDR2), la región 3 determinante de la complementariedad de cadena ligera (LC CDR3) de un dominio de unión a CD20 descrito en el presente documento, y/o una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión a CD123 descrito en el presente documento, por ejemplo, un dominio de unión a CD123 que comprende una o más, por ejemplo, las tres, LC CDR y una o más, por ejemplo, las tres, HC CDR. Estas CDR pueden ser, por ejemplo, cualquiera de las **Tablas 17, 18, 26** o **27**. En una modalidad, el dominio de unión a CD123 comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión a CD123 descrito en el presente documento, por ejemplo, el dominio de unión a CD123 tiene dos regiones variables de cadena pesada, cada una de las cuales comprende una HC CDR1, una HC CDR2 y una HC CDR3 descritas en el presente documento. En una modalidad, el dominio de unión a CD123

comprende una región variable de cadena ligera descrita en el presente documento y/o una región variable de cadena pesada descrita en el presente documento. En una modalidad, el dominio de unión a CD123 comprende una región variable de cadena pesada descrita en el presente documento, por ejemplo, al menos dos regiones variables de cadena pesada descritas en el presente documento. En una modalidad, el dominio de unión a CD123 es un scFv que comprende una cadena ligera y una cadena pesada de una secuencia de aminoácidos de las **Tabla 16** o **Tabla 25**. En una modalidad, el dominio de unión a CD123 (por ejemplo, un scFv) comprende: una región variable de cadena ligera que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena ligera de las **Tabla 16** o **Tabla 25**, o una secuencia con 95-99 % de identidad frente región variable de cadena ligera de las **Tablas 16** o **Tabla 25**; y/o una región variable de cadena pesada que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena pesada de las **Taba 16** o **Tabla 25**, o una secuencia con 95-99 % de identidad frente a una región variable de cadena pesada de las **Tablas 16** o **Tabla 25.**

En una modalidad, la molécula de CAR comprende un dominio de unión anti-CD123 que incluye una o más (por ejemplo, 2, 3, 4, 5 o 6) LC CDR1, LC CDR2, LC CDR3, HC CDR1, HC CDR2 y HC CDR3 de un constructo de las **Tabla 17 y Tabla 18**, por ejemplo, CAR123-1, CAR123-2, CAR123-3 o CAR123-4. En una modalidad, la molécula de CAR comprende un dominio de unión anti-CD123 que incluye una o más (por ejemplo, 2, 3, 4, 5 o 6) LC CDR1, LC CDR2, LC CDR3, HC CDR1, HC CDR2 y HC CDR3 de un constructo de las **Tabla 26** y **Tabla 27**, por ejemplo, hzCAR123.

El scFv de CD123 puede estar precedido por una secuencia líder opcional tal como la proporcionada en la SEQ ID NO.: 13, y seguido por una secuencia de bisagra opcional tal como la proporcionada en la SEQ ID NO.: 14 o SEQ ID NO.: 45 o SEQ ID NO.: 47 o SEQ ID NO.: 49, una región transmembrana tal como la proporcionada en SEQ ID NO.: 15, un dominio de señalización intracelular que incluye SEQ ID NO.: 16 o SEQ ID NO.: 51 y una secuencia de CD3 zeta que incluye SEQ ID NO.: 17 o SEQ ID NO.: 43, por ejemplo, donde los dominios son contiguos y están en el mismo marco de lectura para formar una proteína de fusión única.

Otras modalidades incluyen una secuencia de nucleótidos que codifica un polipéptido de cualquiera de las **Tablas 16-27.** Otras modalidades incluyen una secuencia de nucleótidos que codifica un polipéptido de cualquiera de las **Tablas 16-27**, y cada uno de los dominios de SEQ ID NO.: 13, 14, 15, 16, 17 y, opcionalmente, 51.

En una modalidad, el dominio de unión a CD123 se distingue por características o propiedades funcionales particulares de un anticuerpo o fragmento de anticuerpo. Por ejemplo, en una modalidad, la porción de una composición de CAR de la invención que comprende un dominio de unión a antígeno une específicamente a CD123 humana o a un fragmento de la misma.

En una modalidad, el dominio de unión a CD123 es un fragmento, por ejemplo, un fragmento variable de cadena única (scFv). En una modalidad, el dominio de unión a CD123 es un Fv, un Fab, un (Fab')2 o un anticuerpo híbrido bi-funcional (por ejemplo, bi-específico) (por ejemplo, Lanzavecchia et al., Eur. J. Immunol. 17, 105 (1987)). En un aspecto, los anticuerpos y fragmentos de los mismos de la invención se unen a una proteína CD123 o a un fragmento de la misma con afinidad natural o aumentada. En algunos casos, un scFv humano se puede derivar de una biblioteca de expresión.

En una modalidad, el dominio de unión a CD123, por ejemplo, scFv, comprende al menos una mutación tal que el scFv mutado confiere una mayor estabilidad al constructo de TCAR123. En otra modalidad, el dominio de unión a CD123, por ejemplo, scFv, comprende al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 mutaciones como resultado de, por ejemplo, el proceso de humanización, tales que el scFv mutado confiere una mayor estabilidad al constructo de TCAR123.

En algunas modalidades, el inhibidor de CD123 comprende una molécula de anticuerpo, por ejemplo, una molécula de anticuerpo que tiene una secuencia de unión a CD22 tal como se describe en el presente documento. Por ejemplo, la molécula de anticuerpo puede comprender CDR o VH y VL tal como se describe en cualquiera de las Tablas **16-27**, o una secuencia con homología a las mismas, por ejemplo, que tiene 95-99 % de identidad frente a las mismas. La molécula de anticuerpo puede comprender una región de unión a CD123 que tiene una secuencia descrita en esta sección, por ejemplo, en el contexto de un CAR.

En una modalidad, la presente divulgación proporciona una población de células que

expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD123. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de CD123.

INHIBIDORES DE CD10

El inhibidor de CD10 puede ser, por ejemplo, una molécula pequeña, anticuerpo, o fragmento del mismo (por ejemplo, un anticuerpo monoespecífico o biespecífico o un fragmento del mismo); una proteína recombinante, por ejemplo, una proteína de fusión, que se une a CD10; un ácido nucleico inhibidor; o una célula que expresa un CAR de CD10, por ejemplo, una célula TCAR de CD10.

En una modalidad, el inhibidor de CD10 comprende una pequeña molécula, tal como sacubitril (Novartis), valsartán/sacubritril (Novartis), omapatrilat (Bristol-Myers Squibb), RB-101, UK-414,495 (Pfizer), o una sal farmacéuticamente aceptable o derivada de la misma.

En una modalidad, el inhibidor de CD10 es una célula que expresa un CAR anti-CD34, por ejemplo, un TCAR de CD34 o células NK que expresan CD10.

En una modalidad, la presente divulgación proporciona una población de células que expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD10. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de CD10.

INHIBIDORES DE CD34

El inhibidor de CD24 puede ser, por ejemplo, una molécula pequeña, anticuerpo, o fragmento del mismo (por ejemplo, un anticuerpo monoespecífico o biespecífico o un fragmento del mismo); una proteína recombinante, por ejemplo, una proteína de fusión, que se une a CD24; un ácido nucleico inhibidor; o una célula que expresa un CAR de CD24, por ejemplo, una célula TCAR de CD34.

En una modalidad, el inhibidor de CD34 comprende un anticuerpo monoclonal o un

fragmento del mismo que se dirige a CD34 o un inmunoliposoma que comprende un anticuerpo monoclonal anti-CD34 o un fragmento del mismo.

En una modalidad, el inhibidor de CD34 es una célula que expresa un CAR anti-CD34, por ejemplo, un TCAR de CD34 o células NK que expresan CD34.

En una modalidad, la presente divulgación proporciona una población de células que expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD34. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de CD34.

INHIBIDORES DE FLT-3

El inhibidor de FLT-3 puede ser, por ejemplo, una molécula pequeña, anticuerpo, o fragmento del mismo (por ejemplo, un anticuerpo monoespecífico o biespecífico o un fragmento del mismo); una proteína recombinante, por ejemplo, una proteína de fusión, que se une a FLT; un ácido nucleico inhibidor; o una célula que expresa un CAR de FLT-3, por ejemplo, una célula TCAR de FLT-3

En algunas modalidades, el inhibidor de FLT-3 comprende una molécula pequeña, tal como quizartinib (Ambit Biosciences), midostaurina (Universidad Técnica de Dresde), sorafenib (Bayer y Onyx Pharmaceuticals), sunitinib (Pfizer), lestaurtinib (Cephalon), o una sal farmacéuticamente aceptable o derivada de los mismos.

En una modalidad, el inhibidor de FLT-3 es una célula que expresa un CAR anti-FLT-3, por ejemplo, TCAR de FLT-3 o células NL que expresan CAR de FLT-3.

En una modalidad, la presente divulgación proporciona una población de células que expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de FLT-3. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de FLT-3.

INHIBIDORES DE CD79b

En ciertas modalidades, la célula que expresa un CAR de CD19 se administra con un inhibidor de CD79b. El inhibidor de CD79b puede ser, por ejemplo, una molécula pequeña, anticuerpo, o fragmento del mismo (por ejemplo, un anticuerpo monoespecífico o biespecífico o un fragmento del mismo); una proteína recombinante, por ejemplo, una proteína de fusión, que se une a CD79b; un ácido nucleico inhibidor; o una célula que expresa un CAR de CD79b, por ejemplo, una célula NK o una célula T que expresa un CAR de CD79b. En una modalidad, el inhibidor de CD79b es una célula que expresa un CAR anti-CD79b, por ejemplo, un TCAR de CD79b o células NK que expresan CD79b. Ejemplos de inhibidores de CD79b se describen más detalladamente a continuación.

En una modalidad, la presente divulgación proporciona una población de células que expresan CAR, por ejemplo, células TCAR o células NK que expresan CAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD79b. Por ejemplo, en una modalidad, la población de células que expresan CAR incluye una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de CD79b.

INHIBIDORES DE CD179b

En ciertas modalidades, la célula que expresa un CAR de CD19 se administra con un inhibidor de CD179b. El inhibidor de CD179b puede ser, por ejemplo, una molécula pequeña, anticuerpo, o fragmento del mismo (por ejemplo, un anticuerpo monoespecífico o biespecífico o un fragmento del mismo); una proteína recombinante, por ejemplo, una proteína de fusión, que se une a CD179b; un ácido nucleico inhibidor; o una célula que expresa un CAR de CD179b, por ejemplo, una célula NK o una célula T que expresa un CAR de CD179b. En una modalidad, el inhibidor de CD179b es una célula que expresa un CAR anti-CD179b, por ejemplo, un TCAR de CD179b o células NK que expresan CD179b. Ejemplos de inhibidores de CD179b se describen más detalladamente a continuación.

En una modalidad, la presente divulgación proporciona una población de células que expresan CAR, por ejemplo, células TCAR o células NK que expresan CAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD179b. Por ejemplo, en una

modalidad, la población de células que expresan CAR puede incluir una primera célula que expresa un CAR de CD20 y una segunda célula que expresa un CAR de CD179b.

INHIBIDORES DE C79a

En ciertas modalidades, la célula que expresa un CAR de CD19 se administra con un inhibidor de CD79a. El inhibidor de CD79a puede ser, por ejemplo, una molécula pequeña, anticuerpo, o fragmento del mismo (por ejemplo, un anticuerpo monoespecífico o biespecífico o un fragmento del mismo); una proteína recombinante, por ejemplo, una proteína de fusión, que se une a CD79a; un ácido nucleico inhibidor; o una célula que expresa un CAR de CD79a, por ejemplo, una célula NK o una célula T que expresa un CAR de CD79a. En una modalidad, el inhibidor de CD79a es una célula que expresa un CAR anti-CD79a, por ejemplo, un TCAR de CD79a o células NK que expresan CD79a. Ejemplos de inhibidores de CD79a se describen más detalladamente a continuación.

En una modalidad, la presente divulgación proporciona una población de células que expresan CAR, por ejemplo, células TCAR o células NK que expresan CAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD79a. Por ejemplo, en una modalidad, la población de células que expresan CAR incluye una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de CD79a.

MOLÉCULAS DE CAR

Los dominios de unión descritos en el presente documento (por ejemplo, dominios de unión frente a uno o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a) pueden comprender adicionalmente una o más secuencias adicionales de aminoácidos.

En una modalidad, la molécula de CAR comprende un dominio transmembrana de una proteína seleccionada del grupo que consiste en la cadena alfa, beta o zeta del receptor de células T, CD28, CD3 épsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 y CD154. En una modalidad, el dominio transmembrana comprende una secuencia de SEQ ID NO.: 15. En una modalidad, el dominio transmembrana comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 20, 10 o 5 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de SEQ ID NO.: 15, o una secuencia con 95-99 % de identidad

frente a una secuencia de aminoácidos de SEQ ID NO.: 15.

En una modalidad, el dominio de unión está conectado al dominio transmembrana mediante una región bisagra, por ejemplo, una región bisagra descrita en el presente documento. En una modalidad, la región bisagra codificada comprende una SEQ ID NO.: 14 o SEQ ID NO.: 45, o una secuencia con 95-99 % de identidad frente a la misma.

En una modalidad, la molécula de CAR comprende además una secuencia que codifica un dominio coestimulador, por ejemplo, un dominio coestimulador descrito en el presente documento. En una modalidad, el dominio coestimulador comprende un dominio de señalización funcional de una proteína seleccionada del grupo que consiste en OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278) y 4-1BB (CD137). En una modalidad, el dominio coestimulador comprende una secuencia de SEQ ID NO.: 16. En una modalidad, el dominio coestimulador comprende una secuencia de SEQ ID NO.: 51. En una modalidad, el dominio coestimulador comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 20, 10 o 5 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de SEQ ID NO.: 16 o SEQ ID NO.: 51, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de SEQ ID NO.: 16 o SEQ ID NO.: 51. En una modalidad, el dominio coestimulador comprende un dominio de señalización funcional de una proteína seleccionada del grupo que consiste en una molécula CMH clase I, proteínas receptoras de TNF, proteínas similares a inmunoglobulina, receptores de citoquina, integrinas, moléculas de activación de señalización de linfocitos (proteínas SLAM), receptores activadores de células NK, BTLA, receptor de ligandos Toll, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alfa, CD8beta, IL2Rbeta, IL2Rgamma, IL7Ralfa, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (táctil), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, y un ligando

que se une específicamente a CD83. En algunas modalidades, el dominio coestimulador comprende 4-1BB, CD27, CD28 o ICOS.

En una modalidad, la molécula de CAR comprende además una secuencia que codifica un dominio de señalización intracelular, por ejemplo, un dominio de señalización intracelular descrito en el presente documento. En una modalidad, el dominio de señalización intracelular comprende un dominio de señalización funcional de 4-1BB y/o un dominio de señalización funcional de CD3 zeta. En una modalidad, el dominio de señalización intracelular comprende la secuencia de SEQ ID NO.: 16 y/o la secuencia de SEQ ID NO.: 17. En una modalidad, el dominio de señalización intracelular comprende la secuencia de SEQ ID NO.: 16 y/o la secuencia de SEQ ID NO.: 43. En una modalidad, el dominio de señalización intracelular comprende un dominio de señalización funcional de CD27 y/o un dominio de señalización funcional de CD3 zeta. En una modalidad, el dominio de señalización intracelular comprende la secuencia de SEQ ID NO.: 51 y/o la secuencia de SEQ ID NO.: 17. En una modalidad, el dominio de señalización intracelular comprende la secuencia de SEQ ID NO.: 51 y/o la secuencia de SEQ ID NO.: 43. En una modalidad, el dominio de señalización intracelular comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones) pero no más de 20, 10 o 5 modificaciones de una secuencia de aminoácidos de SEQ ID NO.: 16 o SEQ ID NO.: 51 y/o una secuencia de aminoácidos de SEQ ID NO.: 17 o SEQ ID NO.: 43, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de SEQ ID NO.: 16 o SEQ ID NO.: 51 y/o una secuencia de aminoácidos de SEQ ID NO.: 17 o SEQ ID NO.: 43. En una modalidad, el dominio de señalización intracelular comprende la secuencia de SEQ ID NO.: 16 o SEQ ID NO.: 51 y la secuencia de SEQ ID NO.: 17 o SEQ ID NO.: 43, donde las secuencias que comprenden el dominio de señalización intracelular se expresan en el mismo marco y como una única cadena de polipéptido.

En una modalidad, la molécula de CAR comprende además una secuencia líder, por ejemplo, una secuencia líder descrita en el presente documento. En una modalidad, la secuencia líder comprende una secuencia de aminoácidos de SEQ ID NO.: 13, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de SEQ ID NO.: 13.

En un aspecto, el CAR (por ejemplo, un CAR CD19, un CAR ROR1, un CAR CD20, un CAR CD22, un CAR CD23, un CAR CD10, un CAR CD34, un CAR FLT-3, un CAR CD79b, un

CAR CD179b o un CAR CD79a) comprende una secuencia líder opcional (por ejemplo, una secuencia líder opcional descrita en el presente documento), un dominio extracelular de unión a antígeno, una bisagra (por ejemplo una bisagra descrita en el presente documento), un dominio transmembrana (por ejemplo, un dominio transmembrana descrito en el presente documento) y un dominio estimulador intracelular (por ejemplo, un dominio estimulador intracelulr descrito en el presente documento). En un aspecto, un constructo ejemplar de CAR comprende una secuencia líder opcional (por ejemplo, una secuencia líder descrita en el presente documento), un dominio extracelular de unión a antigeno, una bisagra, un domino transmembrana, un dominio coestimulador intracelular (por ejemplo, un dominio coestimulador intracelular descrito en el presente documento) y un dominio intracelular estimulatorio.

ANTICUERPOS BIESPECÍFICOS

Una molécula de anticuerpo biespecífica (que puede, por ejemplo, ser administrada sola o como parte de un CAR) puede comprender dos regiones VH y dos regiones VL. En algunas modalidades, el anticuerpo hacia arriba o la porción del mismo (por ejemplo, scFv) se acomoda con su VH (VH_1) hacia arriba de su VL (VL_1) y el anticuerpo hacia abajo o la porción del mismo (por ejemplo, scFv) se acomoda con su VL (VL_2) hacia arriba de su VH (VH_2), tal que la molécula de anticuerpo biespecífica en general tiene la estructura VH_1-VL_1-VL_2-VH_2. En otras modalidades, el anticuerpo hacia arriba o la porción del mismo (por ejemplo, scFv) se acomoda con su VL (VL_1) hacia arriba de su VH (VH_1) y el anticuerpo hacia abajo o la porción del mismo (por ejemplo, scFv) se acomoda con su VH (VH_2) hacia arriba de su VL (VL_2), tal que la molécula de anticuerpo biespecífica en general tiene la estructura VL_1-VH_1-VH_2-VL_2.

INHIBIDORES BIESPECÍFICOS DE CD22/C19

En una modalidad, el inhibidor de células B comprende una molécula de anticuerpo de CAR19/CAR22 biespecífica. Por ejemplo, en algunas modalidades, el inhibidor de células B comprende una o más secuencias de aminoácidos de la **Tabla 28** o una secuencia que tiene una identidad de 95-99 % frente a las mismas. Se proporcionan además ácidos nucleicos de acuerdo con la **Tabla 28** o una secuencia que tiene una identidad de 95-99 % a los mismos. En una modalidad, el inhibidor de células B comprende una molécula de anticuerpo específica para

CD19 de las **Tablas 2** o **3** (o una secuencia que tiene 95-99 % de identidad frente a la misma) y una molécula de anticuerpo específica para CD22 de la **Tabla 6A o 6B** (o una secuencia que tiene 95-99 % de identidad frente a la misma). En una modalidad, el inhibidor de células B comprende una molécula de anticuerpo específica para CD19 que tiene una o más CDR de las **Tabla 4** o **Tabla 5** (o una secuencia que tiene 1, 2, 3, 4, 5, o 6 alteraciones, por ejemplo, sustituciones de las mismas) y una molécula de anticuerpo específica para CD22 que tiene CDR de las **Tabla 7A 7B, 7C** o **Tabla 8A, o 8B** (o una secuencia que tiene 1, 2, 3, 4, 5, o 6 alteraciones, por ejemplo, sustituciones de las mismas)

INHIBIDORES DE MTOR

En una modalidad, las células que expresan una molécula de CAR, por ejemplo, una molécula de CAR de CD19, una molécula de CAR de CD20, una molécula de CAR de CD22, por ejemplo, una molécula de CAR descrita en el presente documento, opcionalmente se administran en combinación con un inhibidor de células B y son co-administrados con una dosis potenciadora inmune baja de un inhibidor de mTOR. Al margen de las limitaciones que impone la teoría, se cree que el tratamiento con una dosis potenciadora inmune baja (por ejemplo, una dosis que no es suficiente para suprimir completamente el sistema inmunitario pero suficiente para mejorar la función inmunitaria) produce también una disminución de las células T PD-1 positivas o un aumento de las células PD-1 negativas. Las células T PD-1 positivas, pero no las células T PD-1 negativas, se pueden agotar mediante el apareamiento con células que expresan un ligando PD-1, por ejemplo, PD-L1 o PD-L2.

En una modalidad, este enfoque se puede usar para optimizar el desempeño de las células CAR descritas en el presente documento en el sujeto. Al margen de las limitaciones que impone la teoría, se cree que, en una modalidad, mejora el desempeño de células efectoras inmunes endógenas no modificadas, por ejemplo, células T. Al margen de las limitaciones que impone la teoría, se cree que, en una modalidad, mejora el desempeño de una célula que expresa CAR. En otras modalidades, las células, por ejemplo, las células T, que han sido modificadas o serán modificadas para expresar CAR, pueden ser tratadas ex vivo por contacto con una cantidad de un inhibidor de mTOR que aumenta el número de células efectoras inmunes negativas PD1, por ejemplo, células T, o aumenta la relación de células efectoras inmunes PD1 negativas, por ejemplo, células T/células efectoras inmunes PD1 positivas, por ejemplo, células T.

En una modalidad, la administración de una dosis potenciadora inmune baja de un inhibidor de mTOR, por ejemplo, un inhibidor alostérico, por ejemplo, RAD001, o un inhibidor catalítico, se inicia antes de la administración de una célula que expresa un CAR descrita en el presente documento, por ejemplo, células T. En una modalidad, las células CAR se administran después de un tiempo suficiente, o una dosis suficiente, de un inhibidor de mTOR, tal que el nivel de células efectoras inmunes PD1 negativas, por ejemplo, células T, o la relación de células efectoras inmunes PD1 negativas, por ejemplo, células T/células efectoras inmunes PD1 positivas, por ejemplo, células T, se ha aumentado, al menos transitoriamente.

En una modalidad, la célula, por ejemplo, una célula T, que será modificada para expresar CAR, se cultiva durante un tiempo suficiente, o después de recibir una dosis potenciadora inmune baja suficiente de un inhibidor de mTOR, tal que el nivel de células efectoras inmunes PD1 negativas, por ejemplo, células T, o la relación de células efectoras inmunes PD1 negativas, por ejemplo, células T/células efectoras inmunes PD1 positivas, por ejemplo, células T, en el sujeto o recolectadas del sujeto, se ha aumentado, al menos transitoriamente.

Características o modalidades adicionales de las composiciones o métodos descritos en el presente documento incluyen una o más de los siguientes:

En algunas modalidades, el inhibidor de células B comprende un inhibidor de una o más de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1. En algunas modalidades, el inhibidor de células B comprende una cantidad eficaz de una o más células que expresan una molécula de CAR que une a una o más de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1.

En algunas modalidades, la una o más células que expresan una molécula de CAR que une a CD19 se administran simultáneamente con, antes de, o después de los uno o más inhibidores de células B.

En algunas modalidades, el sujeto tiene o se identifica por tener una diferencia, por ejemplo, una diferencia estadísticamente significativa, entre un nivel determinado en comparación con un nivel de referencia de uno o más marcadores enumerados en la **Tabla 29** en una muestra biológica.

En algunas modalidades, el sujeto tiene o se identifica por tener una diferencia entre una característica determinada en comparación con una característica de referencia, en una

característica de CD19, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de terminación prematuro, o ambos, en una muestra biológica.

En algunas modalidades, el sujeto tiene o se identifica por tener una diferencia, por ejemplo, una diferencia estadísticamente significativa, entre un nivel determinado en comparación con un nivel de referencia de células Treg en una muestra biológica.

En una realización, el método comprende administrar al sujeto una dosis terapéuticamente eficaz de un receptor quimérico de antígeno (CAR) terapia, por ejemplo, una terapia CAR tal como se describe en el presente documento, por ejemplo, una terapia que comprende una célula que expresa un CAR- CD19 y opcionalmente uno o más inhibidores de las células B, y si el sujeto se identifica por tener una diferencia, por ejemplo, una diferencia estadísticamente significativa, entre un nivel determinado en comparación con un nivel de referencia, o una característica determinada en comparación con una característica de referencia, en una o más de (i) un nivel o actividad de uno o más marcadores enumerados en la Tabla 29; (ii) una característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de parada prematuro o ambos, o (iii) un nivel de las células Treg en una muestra biológica. En una realización, el método comprende determinar si el sujeto tiene una diferencia de, por ejemplo, una diferencia estadísticamente significativa, entre un nivel determinado en comparación con un nivel de referencia, o una característica determinada en comparación con una característica de referencia, en una o más de (i) un nivel de uno o más marcadores enumerados en la Tabla 29; (ii) una característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de parada prematuro o ambos, o (iii) un nivel o actividad de las células Treg en una muestra biológica, y administrar al sujeto una dosis terapéuticamente eficaz de una terapia de receptor quimérico de antígeno (CAR), por ejemplo, una terapia CAR tal como se describe en el presente documento, por ejemplo, una terapia que comprende una célula que expresa un CAR-CD19 y opcionalmente uno o más inhibidores de células B. En una realización, el método comprende determinar si el sujeto tiene una diferencia de, por ejemplo, una diferencia estadísticamente significativa, entre un nivel determinado en comparación con un nivel de referencia, o una característica determinada en comparación con una característica de referencia, en una o más de (i) un nivel de uno o más marcadores enumerados en la Tabla 29; (ii) una característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de parada prematuro o ambos, o (iii) un nivel

o actividad de las células Treg en una muestra biológica, y administrar al sujeto una dosis terapéuticamente eficaz de una terapia de receptor quimérico de antígeno (CAR), por ejemplo, una terapia CAR tal como se describe en el presente documento, por ejemplo, una terapia que comprende una célula que expresa un CAR-CD19 y opcionalmente uno o más inhibidores de células B. En una realización, el método comprende administrar a un sujeto una dosis terapéuticamente eficaz de un receptor quimérico de antígeno (CAR), por ejemplo, una terapia CAR tal como se describe en el presente documento, por ejemplo, una terapia que comprende una célula que expresa un CAR-CD19, la determinación de si el sujeto tiene una diferencia de, por ejemplo, una diferencia estadísticamente significativa, entre un nivel determinado en comparación con un nivel de referencia, o una característica determinada en comparación con una característica de referencia, en una o más de (i) un nivel de uno o más marcadores enumerados en la Tabla 29 ; (ii) una característica de CD19, por ejemplo, una mutación, por ejemplo, una mutación que causa un desplazamiento del marco o un codón de parada prematuro o ambos, o (iii) un nivel o actividad de las células Treg en una muestra biológica, y si la diferencia está presente, administrar a un sujeto una dosis terapéuticamente eficaz de uno o más inhibidores de células B.

En algunas modalidades, el sujeto tiene o se identifica por tener un aumento, por ejemplo, un aumento estadísticamente significativo, entre un nivel determinado en comparación con un nivel de referencia de células Treg en una muestra biológica.

En algunas modalidades, el sujeto ha recaído o se identifica por haber recaído después del tratamiento con la una o más células que expresan una molécula de CAR que une a CD19, por ejemplo, un CAR de CD19.

En algunas modalidades, el inhibidor de células B comprende una cantidad eficaz de una o más células que expresan: una molécula de CAR que une a CD10, por ejemplo, un CAR de CD10 tal como se describe en el presente documento; una molécula de CAR que une a CD20, por ejemplo, un CAR de CD20 tal como se describe en el presente documento; una molécula de CAR que une a CD22, por ejemplo, un CAR de CD22 tal como se describe en el presente documento; una molécula de CAR que une a CD34, por ejemplo, un CAR de CD34 tal como se describe en el presente documento; una molécula de CAR que une a CD123, por ejemplo, un

CAR de CD123 tal como se describe en el presente documento; una molécula de CAR que une a FLT-3, por ejemplo, un CAR de FLT-3 tal como se describe en el presente documento; o una molécula de CAR que une a ROR1, por ejemplo, un CAR de ROR1 tal como se describe en el presente documento.

En algunas modalidades, el inhibidor de CD19 comprende un anticuerpo o fragmento de anticuerpo que incluye un dominio de unión a CD19, un dominio transmembrana y un dominio de señalización intracelular que comprende un dominio estimulador, y donde dicho dominio de unión a CD19 comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena ligera (LC CDR1), la región 2 determinante de la complementariedad de cadena ligera (LC CDR2), la región 3 determinante de la complementariedad de cadena ligera (LC CDR3) de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera de CD19 enumeradas en las **Tablas 2 o 3**; y una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada de CD19 enumeradas en las **Tablas 2** o **3**.

En algunas modalidades, un CAR de CD19 comprende una región variable de cadena ligera enumerada en las **Tablas 2** o **3** y cualquier región variable de cadena pesada enumerada en las **Tablas 2** o **3**.

En algunas modalidades, el inhibidor de CD10 comprende un dominio de unión anti-CD19 que comprende una secuencia seleccionada de un grupo que consiste en SEQ ID NO.: 1, SEQ ID NO.: 2, SEQ ID NO.: 3, SEQ ID NO.: 4, SEQ ID NO.: 5, SEQ ID NO.: 6, SEQ ID NO.: 7, SEQ ID NO.: 8, SEQ ID NO.: 9, SEQ ID NO.: 10, SEQ ID NO.: 11 y SEQ ID NO.: 12, o una secuencia con 95-99 % de identidad frente a la misma. En algunas modalidades, el CAR de CD19 comprende un polipéptido de SEQ ID NO: 58.

En algunas modalidades, el inhibidor de células B comprende un CAR de CD20 que comprende un anticuerpo o fragmento de anticuerpo que incluye un dominio de unión a CD20, un dominio transmembrana y un dominio de señalización intracelular que comprende un dominio estimulador, y donde dicho dominio de unión a CD20 comprende una o más de la región 1 determinante de la complementariedad de cadena ligera (LC CDR1), la región 2

determinante de la complementariedad de cadena ligera (LC CDR2), la región 3 determinante de la complementariedad de cadena ligera (LC CDR3) de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera de CD20 enumeradas en la **Tabla 13**; y una o más de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada de CD20 enumeradas en la **Tabla 12A o 12B** .

En algunas modalidades, el inhibidor de células B comprende un CAR de CD22 que comprende un anticuerpo o fragmento de anticuerpo que incluye un dominio de unión a CD22, un dominio transmembrana y un dominio de señalización intracelular que comprende un dominio estimulador, y donde dicho dominio de unión a CD22 comprende una o más de la región 1 determinante de la complementariedad de cadena ligera (LC CDR1), la región 2 determinante de la complementariedad de cadena ligera (LC CDR2), la región 3 determinante de la complementariedad de cadena ligera (LC CDR3) de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera de CD22 enumeradas en las **Tablas 8A, 8B, 10A o 10B**; y una o más de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada de CD22 enumeradas en las **Tablas 7A 7B, 7C 9A o 9B**.

En algunas modalidades, el CAR de CD22 comprende cualquier región variable de cadena ligera enumerada en la **Tabla 10A o 10B**. En algunas modalidades, el CAR de CD22 comprende cualquier región variable de cadena pesada enumerada en la **Tabla 9A o 9B.** En algunas modalidades, un CAR de CD22 comprende cualquier región variable de cadena ligera enumerada en la **Tabla 10A o 10B** y cualquier región variable de cadena pesada enumerada en la **Tabla 9A o 9B.**

En algunas modalidades, el inhibidor de células B comprende un CAR que comprende un anticuerpo o fragmento de anticuerpo que incluye un dominio de unión a antígeno, un dominio transmembrana y un dominio de señalización intracelular que comprende un dominio estimulador, y donde dicho dominio de unión a antígeno comprende una o más (por ejemplo,

todas) de la región 1 determinante de la complementariedad de cadena ligera (LC CDR1), la región 2 determinante de la complementariedad de cadena ligera (LC CDR2), la región 3 determinante de la complementariedad de cadena ligera (LC CDR3), y una o más (por ejemplo, todas) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3).

En algunas modalidades, el inhibidor de células B comprende un CAR que comprende un scFv. En algunas modalidades, el inhibidor de células B comprende un CAR que comprende un dominio transmembrana que comprende un dominio transmembrana de una proteína seleccionada del grupo que consiste en la cadena alfa, beta o zeta del receptor de células T, CD28, CD3 épsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 y CD154. En algunas modalidades, el dominio de unión a antígeno está conectado al dominio transmembrana mediante una región bisagra. En algunas modalidades, la región bisagra codificada comprende una SEQ ID NO.: 14, o una secuencia con 95-99% de identidad frente a la misma. En algunas modalidades, el dominio coestimulador es un dominio de señalización funcional obtenido de una proteína seleccionada del grupo que consiste en OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278) y 4-1BB (CD137). En algunas modalidades, el dominio coestimulador es un dominio de señalización funcional obtenido de una proteína seleccionada del grupo que consiste en una molécula CMH clase I, proteínas receptoras de TNF, proteínas similares a inmunoglobulina, receptores de citoquina, integrinas, moléculas de activación de señalización de linfocitos (proteínas SLAM), receptores activadores de células NK, BTLA, receptor de ligandos Toll, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alfa, CD8beta, IL2Rbeta, IL2Rgamma, IL7Ralfa, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (táctil), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, y un ligando que se une específicamente a

CD83. En algunas modalidades, el dominio coestimulador comprende una secuencia de SEQ ID NO.: 16 o SEQ ID NO.: 51. En algunas modalidades, el dominio de señalización intracelular comprende un dominio de señalización funcional de 4-1BB y/o un dominio de señalización funcional de CD3 zeta.

En algunas modalidades, el dominio de señalización intracelular comprende la secuencia de SEQ ID NO.: 16 y/o la secuencia de SEQ ID NO.: 17 o SEQ ID NO.: 43. En algunas modalidades, el CAR comprende además una secuencia líder. En algunas modalidades, la secuencia líder comprende SEQ ID NO.: 13.

En algunas modalidades, las células que expresan la molécula de CAR comprenden células T o células NK.

En algunas modalidades, la enfermedad asociada con la expresión de CD19 se selecciona de una enfermedad proliferativa tal como un cáncer o tumor maligno, o una condición pre-cancerosa tal como una mielodisplasia, un síndrome mielodisplasico o una preleucemia, o es una indicación no oncológica asociada con la expresión de CD19. En algunas modalidades, la enfermedad es una o más de un cáncer hematológico, leucemia aguda, leucemia linfoide aguda de células B (LLA B), leucemia linfoide aguda de células T (LLA T), linfoma linfocítico de células pequeñas (LLCP), leucemia linfoide aguda (LLA), leucemia crónica, leucemia mielógena crónica (LMC) o leucemia linfocítica crónica (LLC).

En algunas modalidades, el método comprende además la administración de un agente que aumenta la eficacia de una célula que expresa una molécula de CAR. En algunas modalidades, el método comprende además la administración de un agente que reduce uno o más efectos secundarios asociados con la administración de una célula que expresa una molécula de CAR. En algunas modalidades, las células que expresan una molécula de CAR se administran en combinación con un agente que trata la enfermedad asociada con CD19.

En algunas modalidades, de acuerdo con un método descrito en el presente documento, por ejemplo, un método para proporcionar inmunidad anti-tumoral a un mamífero, o un método de tratamiento de un mamífero, un mamífero es no respondedor, respondedor parcial o respondedor total a una terapia contra el cáncer administrada previamente, por ejemplo, una terapia con CAR de CD19 o una terapia contra el cáncer diferente a una célula que expresa un CAR de CD19. En algunas modalidades, el mamífero es no recidivante, recidivante parcial o

recidivante total a una terapia contra el cáncer administrada previamente, por ejemplo, una terapia con CAR de CD10 o una terapia contra el cáncer diferente de una célula que expresa un CAR de CD19. En algunas modalidades, el mamífero comprende una célula cancerosa negativa para CD19 o una célula cancerosa positiva para CD19, opcionalmente, el mamífero comprende además una célula positiva para CD11, positiva para CD123, positiva para FLT-3, positiva para ROR-1, positiva para CD79b, positiva para CD179b, positiva para CD79a, positiva para CD10, positiva para CD34 y/o positiva para CD20. En algunas modalidades, el mamífero tiene un cáncer LLA recidivante. En algunas modalidades, se administró al mamífero previamente una célula que expresa un CAR de CD10, y este es refractario al tratamiento con CAR de CD19.

En algunas modalidades, el agente es un inhibidor de mTOR y se administra al sujeto una dosis potenciadora inmune baja de un inhibidor de mTOR, por ejemplo, RAD001 o rapamicina. En algunas modalidades, el inhibidor de mTOR es un RAD001. En algunas modalidades, la dosis comprende un inhibidor de mTOR alostérico y un inhibidor de mTOR catalítico. En algunas modalidades, el inhibidor de mTOR se administra durante una cantidad de tiempo suficiente para disminuir la proporción de células T PD-1 positivas, aumentar la proporción de células T PD-1 negativas o aumentar la relación de células T PD-1 negativas/células T PD-1 positivas en la sangre periférica del sujeto o en una preparación de células T aisladas del sujeto.

En algunas modalidades, la célula efectora inmune, por ejemplo, una célula T, que será modificada para expresar CAR, se cultiva durante un tiempo suficiente, o después de recibir una dosis potenciadora inmune baja suficiente de un inhibidor de mTOR, tal que el nivel de células efectoras inmunes PD1 negativas, por ejemplo, células T, o la relación de células efectoras inmunes PD1 negativas, por ejemplo, células T/células efectoras inmunes PD1 positivas, por ejemplo, células T, en el sujeto o recolectadas del sujeto, se ha aumentado, al menos transitoriamente. En algunas modalidades, la dosis de un inhibidor de mTOR se asocia con una inhibición de mTOR de al menos 5 % pero no más de 90 %, por ejemplo, medida por la inhibición de p70 S6 K. En algunas modalidades, la dosis de un inhibidor de mTOR se asocia con una inhibición de mTOR de al menos 10 % pero no más de 40 %, por ejemplo, medida por la inhibición de p70 S6 K.

En alguna modalidad, el método comprende adicionalmente administrar un inhibidor de un punto de comprobación. En algunas modalidades, el sujeto recibe un tratamiento previo con

un agente, por ejemplo, un inhibidor de mTOR, y/o un inhibidor de punto de control, antes de iniciar una terapia con TCAR. En algunas modalidades, el sujeto recibe tratamiento simultáneamente con un agente, por ejemplo, un inhibidor de mTOR, y/o un inhibidor de punto de control. En algunas modalidades, el sujeto recibe tratamiento con un agente, por ejemplo, un inhibidor de mTOR, y/o un inhibidor de punto de control, después de la terapia con TCAR.

En algunas modalidades, el nivel determinado o la característica determinada se adquiere antes de, al mismo tiempo, o durante el curso de una terapia con CAR.

En algunas modalidades, el método comprende someter a ensayo una firma genética que indica si el sujeto es propenso a recaer o ha recaído. En algunas modalidades, el método comprende someter a ensayo una firma genética en un sujeto antes del tratamiento con una célula que expresa CAR, por ejemplo, tratamiento con TCAR (por ejemplo, un tratamiento con TCAR19, por ejemplo, terapia con CTL019) que predice la recaída frente al tratamiento con CAR. En algunas modalidades, el nivel de uno o más marcadores es el nivel de al menos 2, 3, 4, 5, 6, 7, 8, 9 o 10 marcadores enumerados en la **Tabla 29**. En algunas modalidades, el nivel del marcador comprende un nivel de ARNm o un nivel de una proteína soluble.

En algunas modalidades, la característica de CD19 es una mutación en el exón 2, por ejemplo, una mutación que causa un desplazamiento del marco o un codón prematuro de terminación o ambos. En algunas modalidades, el nivel de células T_{REG} se determina mediante la tinción de una muestra para un marcador expresado por células T_{REG}. En algunas modalidades, el nivel de células T_{REG} es el nivel de células Treg en una ubicación relevante en el cuerpo del sujeto, por ejemplo, en un microambiente canceroso.

En algunas modalidades, el método comprende además la disminución de la firma T_{REG} en el sujeto antes de la aféresis. En algunas modalidades, el método comprende además la disminución de la firma T_{REG} en el sujeto, por ejemplo, mediante la administración de ciclofosfamida, un anticuerpo anti-GITR, o ambos, al sujeto. En algunas modalidades, el método comprende tratar previamente a un sujeto con ciclofosfamida, un anticuerpo anti-GITR, o ambos, antes de recolectar las células para la fabricación de productos de células que expresan CAR. En algunas modalidades, el método comprende además la obtención de una muestra del sujeto, donde la muestra comprende una fracción celular (por ejemplo, que comprende sangre), una fracción de tejido, una muestra de aféresis, una muestra de médula ósea.

En algunas modalidades, la célula expresa una molécula inhibidora que comprende un primer polipéptido que comprende al menos una porción de una molécula inhibidora, asociado a un segundo polipéptido que comprende una señal positiva de un dominio de señalización intracelular. En algunas modalidades, la molécula inhibidora comprende un primer polipéptido que comprende al menos una porción de PD1 y un segundo polipéptido que comprende un dominio coestimulador y un dominio primario de señalización.

En algunas modalidades, el método comprende someter a ensayo una firma genética que indica si un sujeto tratado con la célula es propenso a recaer o ha recaído. En algunas modalidades, el método comprende someter a ensayo la firma genética en la célula antes de la infusión en el sujeto. En algunas modalidades, el método comprende además reducir la firma de T_{REG} de una población de células que comprende la célula transducida. En algunas modalidades, la reducción de la firma de T_{REG} comprende realizar reducción de CD25 en poblaciones de células.

En algunas modalidades, el sujeto en un mamífero, por ejemplo, un humano.

A menos que se defina lo contrario, todos los términos técnicos y científicos usados en el presente documento tienen el mismo significado que el comúnmente entendido por una persona del oficio normalmente versada en la materia a la que atañe el invento. Aunque métodos y materiales similares o equivalentes a los descritos en el presente documento se pueden usar en la práctica o en las pruebas de la presente invención, métodos y materiales adecuados se describen a continuación. Todas las publicaciones, solicitudes de patente, patentes y otras referencias mencionadas en el presente documento (por ejemplo números de referencia de secuencia de bases de datos) se incluyen aquí en su totalidad como referencia. Por ejemplo, todas las secuencias de GenBank, Unigene y Entrez referidas en el presente documento, por ejemplo, en cualquier tabla del presente documento, se incorporan como referencia. A menos que se especifique lo contrario, los números de acceso especificados en el presente documento, incluyendo los de cualquier tabla del presente documento, se refieren a las entradas actuales de las bases de datos a la fecha de 8 de abril de 2015. Cuando un gen o proteína se refiere a un apluralidad de números de acceso de secuencia, todas las variantes de la secuencia quedan comprendidas.

Además, los materiales, métodos y ejemplos son únicamente ilustrativos y no pretenden ser limitantes.

Los encabezamientos, subtítulos o elementos listados con números o con letras, por ejemplo, (a), (b), (I), etc., se presentan únicamente para facilitar la lectura. El uso de encabezamientos o elementos listados con números o con letras en este documento no requiere seguir los pasos o elementos en orden alfabético ni sugiere que los pasos o elementos sean continuos entre sí.

Otras características, objetos y ventajas de la invención serán evidentes a partir de la descripción y los dibujos, y de las reivindicaciones.

BREVE DESCRIPCIÓN DE LOS DIBUJOS

Las Figuras 1A y 1B son diagramas esquemáticos de CAR representativas.

Las Figuras 2A y 2B son imágenes de análisis inmunohistoquímico de un linfoma de Hodgkin que muestra presencia de células que expresan CD19 en el tumor. La Figura 2A es una ampliación a 1x y la Figura 2B es una ampliación a 20x.

La Figura 3 es un diagrama esquemático del montaje experimental de un estudio para evaluar la eficacia terapéutica del tratamiento con TCAR19 en pacientes con linfoma de Hodgkin.

Las Figuras 4A, 4B, 4C y 4D muestran el análisis de citometría de flujo para la expresión de PD1 y CAR19 en células T. La Figura 4A y 4B son perfiles de citometría de flujo representativos que demuestran la distribución de la expresión de PD-1 y CAR19 en células T CD4+ de sujetos con respuesta total (CR) o sin respuesta (NR) a la terapia con TCAR. La Figura 4C es un gráfico que muestra el porcentaje de células PD1 en la población de células T CD4+ de grupos de sujetos con diferentes respuestas a la terapia con TCAR. La Figura 4D es un gráfico que muestra el porcentaje de células PD1 en la población de células T CD8+ de grupos de sujetos con diferentes respuestas a la terapia con TCAR.

Las Figuras 5A y 5B muestran la distribución de la expresión de PD1 en células que expresan CD4 y CAR19 (Fig. 5A) o células que expresan CD8 y CAR19 (Fig. 5B) de grupos de sujetos con diferentes respuestas a la terapia con TCAR.

La Figura 6 muestra el análisis de citometría de flujo de la expresión de PD1, CAR 19, LAG3 y TIM3 en células T de sujetos con respuesta total (CR) o sin respuesta (NR) a la terapia con TCAR.

Las Figuras 7A y 7B muestran la distribución de la expresión PD1 y LAG3 (Fi. 7A) o de la expresión de PD1 y TIM3 (Fig. 7B) de grupos de sujetos con diferentes respuestas a la terapia con TCAR.

La Figura 8 muestra el inmunofenotipo IgA de células plasmáticas de un paciente con mieloma que recibió TCAR19, demostrando la respuesta a la terapia con TCAR19.

Las Figuras 9A y 9B muestran la expresión del receptor de IL-7 (CD127) en líneas celulares cancerosas y células TCAR. La expresión de CD127 se midió por análisis de citometría de lujo en tres líneas celulares cancerosas: RL (linfoma de células del manto), JEKO (también conocidas como Jeko-1, linfoma de células del manto) y Nalm-6 (LLA B) (Fig. 9A). La expresión de CD127 se midió por análisis de citometría de flujo de células (TCAR) positivas para CD3 que habían sido infundidas y circulaban en ratones NSG (Fig. 9B).

Las Figuras 10A, 10B y 10C muestran la respuesta anti-tumoral después del tratamiento con TCAR19 y después del tratamiento con IL-7. Los ratones GSN injertados con una línea celular de linfoma de manto que expresan luciferasa (RL-luc) en el día 0 fueron tratados con diferentes dosis de células TCAR19 en el Día 6, y se monitoreó la carga tumoral. Los ratones se dividieron en 4 grupos y recibieron células TCAR19, 0,5 x 10^6 células TCAR19 (TCAR19 0.5E6), 1 x 10^6 células TCAR19 (TCAR19 1E6) o 2 x 10^6 células TCAR19 (TCAR19 2E6). La carga tumoral después del tratamiento con TCAR se midió por detección de bioluminiscencia (BLI media) (Fig. 10A). Los ratones que recibieron 0,5 x 10^6 células TCAR19 (TCAR19 0.5E6) o 1 x 10^6 células TCAR19 (TCAR19 1E6) se aleatorizaron para recibir IL-7 humana recombinante (rhIL-7) o no. La carga tumoral, representada aquí por bioluminiscencia media (BLI), se controló para los tres ratones (# 3827, # 3829 y # 3815, que recibieron la dosis inicial de TCAR19 indicada) de la Figura 10A que fueron tratados con IL-7 a partir del día 85 (Fig. 10B). Se administró IL-7 a través de inyección IP 3 veces por semana. La carga tumoral, representada aquí por medio de bioluminiscencia (BLI) antes del día 85 (PRE) y después del día 115 (POST) se comparó entre los ratones que no recibieron IL-7 (CTRL) y ratones que recibieron tratamiento con IL-7 (IL-7) (Fig. 10C).

Las Figuras 11A y 11B muestran la dinámica de células T después del tratamiento con IL-7. El nivel de células T humanas detectado en la sangre se controló para cada uno de los ratones que recibieron IL-7 o los ratones de control (Fig. 11A). El nivel de células TCAR19 (células CD3+) detectado en la sangre se midió antes (PRE) y 14 días después (día 14) del inicio del tratamiento con IL-7 (Fig. 11B).

La Figura 12 representa las estructuras de dos ejemplos de configuraciones RCAR. Los miembros de unión a antígeno comprenden un dominio de unión a antígeno, un dominio transmembrana y un dominio interruptor. Los miembros de unión intracelular comprenden un dominio interruptor, un dominio coestimulador de señalización y un dominio primario de señalización. Las dos configuraciones demuestran que el primer y el segundo dominios interruptores descritos en este documento pueden estar en diferentes orientaciones con respecto al miembro de unión a antígeno y el miembro de unión intracelular. Otras configuraciones RCAR se describen más adelante.

La Figura 13 representa dos constructos para CAR biespecíficos con dominios de unión anti-C22 y anti-CD19. 4G4S" representa la secuenci enlazadora GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 1311).

La Figura 14 es un gráfico que representa la actividad de constructos de CAR de CD19/CD22 biespecíficos en un ensayo de NFAT.

Las Figuras 15A, 15B y 15C son gráficos que muestran el grado de activación de células TCAR (medido por luminiscencia relativa) en presencia de diversas líneas celulares blanco tumorales. La Figura 15A muestra la activación de células TCAR en presencia de la línea celular blanco que expresa CD20, Daudi. La Figura 15B muestra la activación de células TCAR en presencia de la línea celular blanco que expresa CD20, Raji. La Figura 15B muestra la activación de células TCAR en presencia de un control negativo que no expresa cD20, K562.

La Figura 16 es un esquema de ejemplo que ilustra una visión general del análisis de firmas de genes. Brevemente, para cada conjunto de genes, se aplicó un modelo estadístico de 2 grupos con el fin de determinar si el meta-gen era estadísticamente diferente entre CR, PR y NR. Los CR son más como células T_{EFF} en reposo, mientras que los NR son más como células T_{EFF} activadas. Los genes regulados positivamente en células T_{EFF} activadas versus en reposo también se regularon activamente en NR.

La Figura 17 representa ejemplos de resultados (p = 0,000215) que ilustran que los genes T_{REG} tienen niveles de expresión altos en muestras de pacientes pediátricos que presentaban una respuesta total y se volvieron recidivantes (R) en comparación con pacientes que presentaban una respuesta total (CR) y no tuvieron recaídas. El eje x son las muestras por grupo de respuesta, donde CR = paciente con respuesta total sin recaída y R = paciente con recaída. El eje y son los puntajes de expresión de meta-genes normalizados.

Las Figuras 18A, 18B y 18C son gráficos que muestran la activación de células T de CAR en presencia de líneas celulares blanco tumorales. En la Figura 18A, se mezclaron células JNL que expresan CAR con líneas celulares blanco que expresan CD22 Daudi usando las relaciones E:T indicadas. En la Figura 18B, se mezclaron células JNL que expresan CAR con líneas celulares blanco que expresan CD22 Raji usando las relaciones E:T indicadas. En la Figura 18C, se mezclaron células JNL que expresan CAR con líneas celulares K562 de control negativo usando las relaciones E:T indicadas.

La Figura 19 es un gráfico que muestra expresión del receptor quimérico de antígeno por células T primarias en la superficie celular. Se usaron proteína-L-biotina/SA-PE (Fig. 19-1 y Fig. 19-2) y rhCD22-Fc/anti-Fc488 (Fig. 19-3 y 19-4) para determinar los niveles de expresión superficial de CAR. Las células sin CAR se usaron como control negativo.

Las Figuras 20A, 20B, 20C, 20D, 20E y 20F son gráficos que muestran un ensayo de destrucción de blancos con células tumorales T primarias. Las células T primarias activadas y transducidas con CAR de CD22 se mezclaron con líneas celulares blanco que expresan luciferasa de manera estable en las relaciones indicadas, y se midió la destrucción celular. El porcentaje de destrucción se normalizó a hCD22-8 (transducción 28,8 %). Líneas celulares que expresan CD22 Raji (Fig. 20A), SEM (Fig. 20B), K562-hCD22 (Fig. 20C), Daudi (Fig. 20D) y Nalm6 (Fig. 20E) se usaron para someter a prueba los clones de CAR de CD22 de función en comparación con el CAR de CD22 control positivo m971 (m971-HL), el CAR control negativo M971-LH y las células T no transducidas como control negativo. La línea celular K562 no expresa CD22 y fue usada como control negativo (Fig. 20F).

Las Figuras 21A, 21B, 21C, 21D, 21E y 21F son gráficos que muestran la inducción de una respuesta de citoquinas proinflamatorias significativa por clones de CAR de CD22. Se usaron ensayos de destrucción de células T primarias para determinar la capacidad del clon de CAR de CD22 para producir citoquinas proinflamatorias IFN-g, IL-2 y TNFa. Se co-cultivaron

células efectoras durante 20 horas con cada una de las diferentes líneas celulares blanco, normalizadas a transducción 28,8 %. Se tomaron sobrenadantes de diferentes cultivos con diferentes relaciones E:T de 2,5:1 y 10:1 de células blanco que expresan CD22 Raji (Fig. 21A), células blanco que expresan CD22 Nalm6 (Fig. 21B), células blanco que expresan CD22 Daudi (Fig. 21C), células blanco que expresan CD22 SEM (Fig. 21D), células blanco que expresan CD22 K562-hCD22 (Fig. 21E), y células que no expresan CD22 K562 (control negativo) (Fig. 21F).

La Figura 22 es un gráfico que representa la expresión de varios antígenos de células B en LLA recidivante, según se detecta mediante citometría de flujo. Las muestras de 16 r/r pacientes fueron seleccionadas mediante citometría de flujo multiparamétrica para los siguientes marcadores: CD19 (16 puntos), CD22 (16 puntos), CD123 (16 puntos), FLT-3 (9 puntos), ROR-1 (3 puntos), CD79b (15 puntos), CD179b (8 puntos), CD79a (16 puntos), CD10 (16 puntos), CD34 (16 puntos) y CD20 (16 puntos). CD22 y CD123 se expresaron altamente (> 60 %) y de manera homogénea en los blastos de r/r pacientes con LLA (la barra indica el % de expresión medio, respectivamente, 99,50 %, 98,80 %, 95,70 %, 72,00 %, 47,00 %, 15,00 %, 13,45 %, 4,200 %, 98,00 %, 87,65 % y 7,00 %). Para cada paciente, el porcentaje de células que expresan el marcador indicado se muestra como un punto de datos único.

La Figura 23 es un conjunto de gráficos que muestran la expresión de CD22 y CD123 en 6 pacientes con recaída de leucemia negativa para CD19, tanto antes del tratamiento con TCAR19 (inicial) como después (recaída negativa para CD19). En todos los análisis, la población de interés fue separada con base en características de dispersión frontal versus dispersión lateral, seguido por separación de singletes, y las células vivas fueron separadas usando Live Dead Aqua (Invitrogen). La separación se incluyó para control de calidad. La estrategia de separación incluyó: separación por tiempo → SSC bajas → singletes → vivas → CD45dim → CD10+.

La Figura 24 es un conjunto de gráficos que muestran la expresión de CD22 en blastos de pacientes recidivantes con enfermedad negativa para CD19 después de recibir tratamiento con TCAR19 (ensayos clínicos UPCC04409/CHP959, UPN del paciente indicado en la casilla cuadrada). La fila superior muestra la expresión de CD19 y CD22 en blastos antes del tratamiento con TCAR19, mientras que la fila inferior muestra el fenotipo de la enfermedad en

la recaída. La expresión CD22 se mantuvo también en la recaída cuando la expresión de CD19 se perdió.

La Figura 25 es un conjunto de gráficos que muestran la expresión de CD123 en blastos de pacientes recidivantes con enfermedad negativa para CD19 después de recibir tratamiento con TCAR19 (ensayos clínicos UPCC04409/CHP959, UPN del paciente indicado en la casilla cuadrada). La fila superior muestra la expresión de CD19 y CD123 en blastos antes del tratamiento con TCAR19, mientras que la fila inferior muestra el fenotipo de la enfermedad en la recaída. La expresión CD123 se mantuvo en la recaída en la mayoría de los pacientes, mientras que la expresión de CD19 se perdió.

La Figura 26 es un gráfico que muestra la expresión media de CD19, CD22 y CD123 antes y después del tratamiento con TCAR19 en pacientes con recaída de una enfermedad negativa para CD19. La expresión de CD19 se perdió en la recaída (94,25 % versus 0 %, p = 0,0009), mientras que CD22 (99,20 % versus 97,30 %, p = ns) y CD123 (63,00 % versus 48,75 %, p = ns) se siguieron expresando. Para cada paciente, el porcentaje de células que expresan el marcador indicado se muestra como un punto de datos único.

Las Figuras 27A y 27B son una serie de gráficos que muestran la expresión de CD22 en muestras de 16 r/r pacientes y 4 pacientes con recaída de enfermedad negativa para CD19 después de recibir tratamiento con terapia de TCAR19. Las muestras se examinaron mediante citometría de flujo multiparamétrica para detectar el marcador de células B, CD22. CD22 se expresó altamente (> 60 %) y de manera homogénea en los blastos de 11/15 r/r pacientes con LLA (Fig. 27A). CD22 fue positiva en 4/4 pacientes con recaída de leucemia negativa para CD19, tanto antes del tratamiento con TCAR19 (inicial) como después (recaída negativa para CD19) (2 puntos) (Fig. 27B). Estrategia de separación: SSC bajas→ singletes → en vivo → CD45dim

Las Figuras 28A, 28B y 28C es una serie de gráficos que muestran el efecto de TCAR de CD22 en la expresión de CD19 y CD22. Se muestra el esquema de los dos constructos de CAR22 que se generaron usando diferentes orientaciones de cadena (H a L y L a H) (Fig. 28A). El scFv anti-CD22 (M971) fue sometido a optimización de codones y se clonó en el vector CAR19 murino que contiene los dominios bisagra de CD8, coestimulador de 41-BB y de señalización de zeta CD3 (Fig. 28A). La expresión del control de isotipo, CD19 y CD22 en la línea celular NALM6 de LLA se muestra como intensidad de fluorescencia media (MFI) (Fig.

28B) y capacidad de unión a anticuerpos (ABC) (FIG. 28C). En NALM-6, la expresión de CD10 fue más alta que la expresión de CD22. Sin embargo, en la mayoría las muestras de LLA primaria, las expresiones de CD19 y CD22 fueron similares (véase la Fig. 27A).

Las Figuras 29A, 29B y 29C es una serie de gráficos que muestran las expansiones de células T de donantes normales para generar TCAR22 y TCAR19 (junto con células UTD). Las duplicaciones de población (PD) versus los días de cultivo: al final de la expansión (día 11), las células TCAR22 y células T de control alcanzaron alrededor de 4,5 PD, sin diferencia significativa en comparación con las células TCAR19 o UDT (Fig. 29A). El volumen de células T (FL) versus los días de cultivo: en el día 6 no había volumen máximo (alrededor de 450 fl), mientras que en los siguientes días el volumen se redujo a 300 fl cuando las células se cosechan y se congelan. No se observaron diferencias significativas versus células TCAR19 o UTD (Fig. 29B). La expresión de CAR en células T CD4+ y CD8+ en el día 11 de expansión se muestra en la figura. 29C. La separación para la expresión de CAR se basa en UDT. Estrategia de separación: Linfocitos FSS vs SSC → singletes → vivas → CD3+.

La Figura 30 es una serie de gráficos que muestran un ensayo de degranulación de CD107a con producción de citoquinas intra-citoplasmáticas. Células HtoL y LtoH de TCAR19, TCAR22 fueron co-cultivadas con diferentes blancos (medio solo, PMA/ionomicina, MOLM-14 y NALM-6). Las células HtoL de TCAR19 y TCAR22 muestran altos niveles de degranulación de CD107a, producción de TNFa, IFNg e IL-2 cuando se co-cultivaron con la línea celular de LLA (NALM-6), pero no cuando se co-cultivaron con controles negativos. Las células LtoH de UTD y TCAR22 no mostraron ni degranulación ni producción de citoquinas. Estrategia de separación: Linfocitos FSS vs SSC → singletes → vivas → CD3+.

La Figura 31 es un gráfico que muestra un ensayo de destrucción de células con base en la luciferasa. Las células Htol de TCAR22 y TCAR19, pero no las células UTD, fueron capaces de lisar las células NALM-6 cuando se co-cultivaron durante 24 horas. Se observó una correlación directa entre la actividad de citotoxicidad y las relaciones E:T, con un mejor efecto anti-leucemia en la relación E:T 2:1 (78 % y 75 % de destrucción para TCAR 19 y TCAR 22).

Las Figuras 32A y 32B son una serie de gráficos que muestran un ensayo de proliferación con base en CFSE. El co-cultivo durante 5 días de TCAR22 y TCAR19 con la línea celular NALM-6 de LLA generó la proliferación significativa de células T (94 % y 92,9 % respectivamente). También se muestran los controles (TCM = solo medio, PI =

PMA/ionomicina, MOLM-14) (Fig. 32A). En histogramas que muestran la dinámica de dilución CFSE en TCAR19 y TCAR22, la mayoría de las células T se sometieron a múltiples ciclos de proliferación (Fig. 32B). Estrategia de separación: Linfocitos FSS vs SSC → singletes → vivas → CD3+.

La Figura 33 es una serie de gráficos que muestran la producción de citoquinas. Se incubaron células TCAR22, TCAR19 y UTD durante 24 horas con diferentes blancos irradiados (solo medio, PMA/ionomicina, MOLM-14 y NALM-6). Cuando se co-cultivaron con líneas celulares NALM-6 de LLA, solo HtoL de TCAR22 y TCAR19 fueron capaces de liberar múltiples citoquinas (IFNg, IL-2, GM-CSF, TNFa y MIP1b se muestran en el presente documento). Los resultados se muestran como la intensidad de fluorescencia media (MFI).

Las Figuras 34A y 34B son una serie de gráficos que muestran la degranulación de células T con blastos de LLA primaria. Las células TCAR22, TCAR19 y UTD se co-incubaron durante 4 horas con blastos derivados de un paciente con LLA (CHP-959-101) al inicio del estudio y después del tratamiento con TCAR19 cuando el paciente presentó recaída con una enfermedad negativa para CD19. Tanto las células TCAR19 como las células TCAR22 fueron capaces de degranulación al inicio (cuando los blastos son CD19+ y CD22+), pero en la recaída solamente TCAR22 degranuló (cuando la enfermedad es negativa para CD19) (Fig. 34A). Gráficos de puntos que muestran la degranulación de CD107a en células efectoras TCAR19 y TCAR22 positivas para CD8 y negativas para CD22 después de incubación con muestra CHP101 en recaída demuestran que solo TCAR22 mostró degranulación tanto en cédulas T CD8 como en células T CD4 (Fig. 34B). Estrategia de separación: Linfocitos FSS vs SSC → singletes → vivas → CD3+.

Las Figuras 35A, 35B, 35C y 35D son una serie de gráficos que muestran la eficacia in vivo de TCAR22 contra NALM-6. A. Esquema del experimento: 1 millón de células NALM-6 luciferasa+/ratón fueron inyectadas por vía intravenosa en ratones NSG. Tras 6 días, el injerto tumoral fue evaluado mediante bioluminiscencia. Luego se aleatorizaron ratones para recibir células T o diferentes dosis de TCAR22 (entre 1,25 y 5 millones total de células/ratón, con expresión de CAR 75 %). Luego se monitorearon los ratones para identificar la carga tumoral, la expansión de células T PB, y la supervivencia (Fig. 35A). La carga tumoral por bioluminiscencia (BLI) detectó una respuesta anti-leucemia relacionada con la dosis. Los ratones que recibieron $5e^6$ de células TCAR22 mostraron un mejor control tumoral (Fig. 35B). Los

ratones tratados con TCAR22 mostraron una mejor supervivencia general (OS) estadísticamente significativa en comparación con los ratones tratados con células UTD. Para OS, hubo una correlación significativa entre la dosis más alta de TCAR22 y mejor OS (Fig. 35C). La expansión in vivo de células T se controló semanalmente mediante sangrados retro-orbitales. Una semana después de la infusión con células T, los ratones que recibieron la dosis mayor de TCAR22 mostraron mejor expansión de TCAR (mediana de 12 células T/µl) (Fig. 35D).

Las Figuras 36A y 36B son una serie de gráficos que muestran una comparación in vivo entre TCAR22 y TCAR19 contra NALM-6. Esquema del experimento: 1 millón de células NALM-6 luciferasa+/ratón fueron inyectadas por vía intravenosa en ratones NSG. Tras 6 días, el injerto tumoral fue evaluado mediante bioluminiscencia. Luego se aleatorizaron ratones para recibir células T, TCAR19 o TCAR22 no transducidas (5 millones de células en total, con expresión de CAR 75 %). Luego se monitorearon los ratones para identificar la carga tumoral, la expansión de células T PB, y la supervivencia (Fig. 36A). La carga tumoral por bioluminiscencia (BLI) demostró respuesta anti-leucemia tanto en ratones tratados con TCAR22 como en ratones tratados con TCAR 19, mientras que los ratones UTD avanzaron rápidamente (Fig. 36B). los ratones tratados con TCAR19 mostraron una mejor supervivencia general (OS) en comparación con aquellos tratados con TCAR22, posiblemente debido a la expresión de blanco diferente en NALM-6 (CD19>>CD22) (FIG. 36C).

Las Figuras 37A y 37B son una serie de gráficos que muestran una comparación in vivo entre TCAR22 y TCAR19 en un modelo de LLA primaria. Los blastos de un paciente con LLA primaria (JH331) fueron transferidos in vivo y transducidos con luciferasa para seguir la carga tumoral. Esquema del experimento: 1 millón de células JH331 luciferasa+/ratón fueron inyectadas por vía intravenosa en ratones NSG. Tras 14 días, el injerto tumoral fue evaluado mediante bioluminiscencia. Luego se aleatorizaron ratones para recibir células T, TCAR19 o TCAR22 no transducidas (5 millones de células en total, con expresión de CAR 75 %). Luego se monitorearon los ratones para identificar la carga tumoral, la expansión de células T PB, y la supervivencia (Fig. 37A). La carga tumoral por bioluminiscencia (BLI) detectó respuesta anti-leucemia tanto en ratones tratados con TCAR22 como en ratones tratados con TCAR 19, mientras que los ratones UTD avanzaron rápidamente (Fig. 37B).

Las Figuras 38A, 38B y 38C son una serie de imágenes que muestran micro-organización celular de tejidos para expresión de CD22 en 28 tejidos humanos normales

mediante tinción inmunohistoquímica. Los órganos linfoides resultaron positivos para la expresión CD22 (amígdalas, ganglios linfáticos, bazo y timo) (Fig. 38A). Los órganos no linfoides no mostraron expresión de CD22 (Fig. 38B). Se observaron células B residentes positiva para CD22 en múltiples tejidos (Fig. 38C). * = tinción no específica.

La Figura 39 es un gráfico que muestra datos de expresión en ARN de CD22 GeneAtlas U133A. La expresión de CD22 se observó a alto nivel en las células B, las amígdalas y los ganglios linfáticos. Las líneas celulares de leucemia/linfoma y linfoblásticas B también fueron muy positivas.

La Figura 40 es una serie de gráficos que muestran un ensayo de liberación de cromo-51 para toxicidad de TCAR22. Tanto las células TCAR22 como las TCAR19, pero no las UTD, activaron la lisis de la línea celular NALM-6 de LLA. No se observó ningún efecto citotóxico de TCAR22 en tejidos normales (CD34 +, progenitores neuronales humanos o neuronas y queratinocitos) o de control (línea celular K562).

La Figura 41 muestra una representación gráfica de la expresión de CAR en células JNL transducidas con constructos de CAR anti-CD123 evaluadas por FACS y reportadas como el porcentaje de células que muestra señal por encima del nivel de señal en células no transducidas (negativas para CAR) usando proteína L como reactivo de detección.

Las Figuras 42A, 42B y 42C muestran representaciones gráficas de la actividad de CAR de CD123 en células JNL. Se evaluaron constructos de CAR anti-CD123 para detectar actividad usando una línea celular Jurkat que contiene el reportero de luciferasa activado por el promotor NFAT (denominado células JNL). La actividad de CAR se midió como la activación de este reportero activado por NFAT.

Las figuras 43A y 43B muestran actividad y expresión de CD123. La Figura 43A muestra una representación gráfica de la expresión de CAR de CD123 en células T primarias. Se determinó el porcentaje de células transducidas (que expresan el CAR anti-CD123 en la superficie celular) y su intensidad de fluorescencia relativa de expresión mediante análisis de citometría de flujo en LSRFortessa BD o BD-FACSCanto usando proteína L como reactivo de detección. La separación de gráficos de histograma de intensidad de fluorescencia relativa desde dicho FACS para señal por encima de las células sin manchar muestra el porcentaje de células T transducidas. La transducción resultó en un rango de células positivas TCAR entre 12 y 42 %. La Figura 43B muestra una representación gráfica de la destrucción celular mediada por TCAR

de CD123. La destrucción de células T se dirigió hacia células de leucemia mielógena aguda MOLM13 que expresan CD123 que expresan luciferasa de manera estable. Las células T no transducidas fueron usadas para determinar los niveles de destrucción basal no específica. Las actividades citolíticas de TCAR-CD123 se midieron en un rango de relaciones de células efectoras:células blanco de 4:1 y diluciones descendentes duplicadas de células T donde los efectores se definieron como células T que expresan el receptor quimérico anti-CD123. Los ensayos se iniciaron mediante la mezcla de un número apropiado de células T con un número constante de células blanco. Después de 20 horas, se midió la señal de luciferasa usando Bright-Glo Luciferase Assay™ en el instrumento EnVision.

Las Figuras 44A y 44B muestran la eficacia de transducción de células T con CAR de CD123. La Figura 44A muestra la eficacia de transducción de células T con 1172 y 1176. La Figura 44B muestra la eficacia de transducción de células T con CAR 2-4 de CD123.

La Figura 45 muestra la citometría de flujo de CAR 2-4 de CD123 y 1172 y 1176 para determinar la relación CD4:CD8.

La Figura 46 muestra la degranulación de CAR 2-4 de CD123 y 351172 y 1176 tras la exposición a células tumorales CD123+.

La Figura 47 muestra una representación gráfica de un ensayo de luciferasa para evaluar la citotoxicidad de células TCAR (clones NVS 2-4, 1172 y 1176) hacia células blanco tumorales (MOLM14).

La Figura 48 muestra una comparación de la carga tumoral en ratones NSG inyectados con células MOLM14 que expresan luciferasa en el día 6 (antes de la inyección con TCAR) y en el día 13 (6 días después de la inyección con clones NVS 2-4, 1172 o 1176) o en el día 20.

Las Figuras 49A, 49B, 49C, 49D, 49E y 49F, muestra que CD123 se expresa altamente en recaídas de leucemia linfoblástica aguda de células B negativa para CD19 que ocurren después de tratamiento con TCAR19. La figura 49A muestra la expresión de CD123 en comparación con CD19 en 42 muestras de LLA recidivante/refractaria. La figura 49B muestra la co-expresión de CD123 y CD19 en blastos de LLA B. Separación en blastos (SSC bajas, singlete, vivas, CD45dim). La Figura 49C muestra la estrategia de separación para las células madre de leucemia (LSC). CD123 se expresa altamente en este subgrupo. La Figura 49D muestra la co-expresión de CD123 y CD19, y resultados del análisis FISH. Las Figuras 49E y

49F muestran la comparación de la expresión de CD19 y CD123 al inicio o después de la recaída.

Las Figuras 50A, 50B, 50C, 50D, 50E y 50F, muestra los resultados de diversos ensayos in vitro usando células T que expresan un CAR de CD19 (CAR19) o un CAR de CD123 (CAR123). La Figura 50A muestra la expresión de CD19 y CD123; la figura 50B muestra un ensayo de degranulación de CD107a; la Figura 50C muestra la capacidad de destrucción de células blanco; las Figuras 50D y 50E muestran la capacidad de proliferación; la Figura 50F muestra la producción de citoquinas para las citoquinas indicadas.

LasFiguras 51A, 51B y 51C, muestra que las células TCAR que expresan CAR de CD19 (CAR19) o CAR de CD123 (CAR123) tuvieron un efecto antitumoral en un modelo de ratón in vivo. La figura 51A muestra la carga tumoral representada mediante imágenes bioluminiscentes; la figura 51B muestra la curva de supervivencia general de los ratones que recibieron terapia con TCAR; y la Figura 51C muestra la expansión de las células TCAR123 en la sangre periférica.

Las Figuras 352A, 52B, 52C, 52D, 52E y 52F, muestra que TCAR123 está activa en un modelo de ratón in vivo de recaída por pérdida de antígeno. La Figura 52A muestra el esquema experimental; la Figura 52B muestra progresión de la enfermedad representada mediante imágenes bioluminiscentes en la enfermedad inicial y la enfermedad reincidente con respecto a la expresión de CD19 (gráfico superior) y en respuesta al tratamiento con terapia con TCAR19 (gráfico inferior); la Figura 52C muestra imágenes bioluminiscentes de ratones a los que se administraron células T no transducidas o células TCAR19; la Figura 52D muestra el esquema experimental para tratamiento con TCAR19 o TCAR123; la Figura 52E muestra la progresión de la enfermedad; y la figura 52F muestra la supervivencia general de los ratones tratados.

Las Figuras 53A, 53B y 53C, muestra interacciones TCAR-LLA en médula ósea del cráneo de ratones xenoinjertos. La Figura 53A muestra el esquema experimental; la Figura 53B muestra imágenes de plano XY multifotón representativas de células TCAR19 y células TCAR123 que interactúan con el tumor de LLA modificadas para expresar ya sea CD19 y CD123 o solo CD123 (las células móviles se indican con círculos y rayas, las células no móviles se indican con flechas); y la Figura 53C es una representación gráfica de las imágenes de microscopía.

Las Figuras 54A, 54B y 54C, muestra la prevención de recaídas negativas para CD19 usando TCAR19 y TCAR123. La Figura 54A muestra el esquema experimental; la Figura 54B muestra la progresión de la enfermedad (carga tumoral representada mediante BLI) de los

ratones tratados con células T transducidas (gráfico superior), TCAR19 (gráfico medio), o la combinación de TCAR19 y TCAR123 (gráfico inferior); y la Figura 54C muestra la supervivencia general de este experimento.

Las Figuras 55A y 55B, muestra células T que expresan tanto CAR19 como CAR123 (Figura 37A) y los resultados de un ensayo de degranulación (Figura 55B).

Las Figuras 56A y 56B, muestra la caracterización de blastos de LLA. La Figura 56A muestra la expresión de diversos marcadores CD19, CD123, CD10, CD34 y CD20; y la Figura 56B muestra la estrategia de separación para clasificar las células CD19-CD123+.

Las Figuras 57A, 57B, 57C y 57D, muestra la actividad contra la leucemia de TCAR123. La Figura 57A muestra la expresión de CD19 y CD123 en las células NALM6; la Figura 57B muestra la carga tumoral (representada mediante BLI) en respuesta a la terapia con TCAR19 o TCAR123; la Figura 57C muestra la supervivencia global de los ratones a los que se administró TCAR19 o TCAR123; y la Figura 57D muestra la supervivencia general de los ratones a los que se administraron dosis variables de TCAR123.

Las Figuras 58A y 58B, muestra la caracterización del modelo in vivo de recaída por pérdida de antígeno. La Figura 58A muestra la expresión de CD123 en enfermedad recidivante negativa para CD19; y la Figura 58B muestra el ensayo de degranulación de células TCAR19 o TCAR123 cuando se cultivan con células iniciales o recidivantes in vitro.

La Figura 59 muestra que la proliferación de células T transducidas que expresan CAR aumenta gracias a dosis bajas de RAD001 en un sistema de cultivo celular. Las células TCAR fueron co-cultivadas con células NALM 6 (Nalm-6) en presencia de diferentes concentraciones de RAD001 (nM). El número de células T positivas para CD3 positivas para CAR (negro) y el número total de células T (gris) se evaluó después de 4 días de co-cultivo.

La Figura 60 representa mediciones de crecimiento tumoral de células NALM6-luc con dosificación diaria de RAD001 de 0,3; 1; 3 y 10 mg/kg (mpk) o dosificación de vehículo. Los círculos denotan el vehículo; los cuadrados denotan la dosis de 10 mg/kg de RAD001; los triángulos denotan la dosis de 3 mg/kg de RAD001; los triángulos invertidos indican la dosis de 1 mg/kg de RAD001; y los diamantes denotan la dosis de 0,3 mg/kg de RAD001.

Las Figuras 61A y 61B muestran las curvas farmacocinéticas que muestran la cantidad de RAD001 en la sangre de los ratones NSG con tumores NALM6. La Figura 61A muestra el día 0 PK después de la primera dosis de RAD001. La Figura 61B muestra el día 14 PK después de la dosis final de RAD001. Los diamantes denotan la dosis de 10 mg/kg de RAD001; los

cuadrados denotan la dosis de 1 mg/kg de RAD001; los triángulos indican la dosis de 3 mg/kg de RAD001; y las x denotan la dosis de 10 mg/kg de RAD001.

Las Figuras 62A y 62B muestran la proliferación in vivo de células TCAR de CD19 humanizadas con y sin dosis de RAD001. Las dosis bajas de RAD001 (0,003 mg/kg) administradas diariamente producen un aumento en la proliferación de células TCAR, por encima del nivel normal de proliferación de huCAR19. La Figura 62A muestra células TCAR CD4+; la Figura 62B muestra células TCAR CD8+. Los círculos denotan PBS; los cuadrados denotan huCTL019; los triángulos denotan huCTL019 con 3 mg/kg de RAD001; los triángulos invertidos denotan huCTL019 con 0,3 mg/kg de RAD001; los diamantes denotan huCTL019 con 0,03 mg/kg de RAD001; y los círculos denotan huCTL019 con 0.003 mg/kg de RAD001.

La Figura 63 muestra análisis multiplex FIHC AQUA, los cuales muestran una diferencia significativa entre las poblaciones de célula CD3+/PD-1+ en sitios primarios y secundarios de muestras de pacientes humanos con DLBCL.

La Figura 64 muestra análisis AQUA, el cual muestra diferentes niveles de CD19 (panel inferior) y PD-L1 (panel superior) en sitios primarios y secundarios de muestras de pacientes con DLBCL. Un total de 40 muestras de pacientes humanos con DLBCL, 25 sitios primarios y 15 sitios secundarios, se sometieron a análisis multiplex FIHC y luego a análisis AQUA para identificar los niveles de expresión de proteínas PD-L1 y CD19.

LA FIG. 65 muestra un esquema de dos poblaciones de células que expresan CAR. En la población de la izquierda (agrupada), cada célula expresa un tipo de CAR. En la población de la derecha (CAR bicistrónico), cada célula expresa dos tipos de CAR.

LA FIG. 66 muestra diagramas de los CAR bicistrónicos. El CAR superior tiene un CAR CD19 y un CAR CD22, separados por un sitio de escisión de la proteasa P2A. El CAR inferior tiene un CAR CD19 y un CAR CD123, separadas por un sitio de escisión de la proteasa P2A.

LA FIG. 67 muestra la coexpresión de CARs CD19 y CD22 de un vector bicistrónico.

LA FIG. 68, panel superior, muestra la coexpresión de CARs CD19 y CD123 de un vector bicistrónico. LA FIG. 68, panel inferior, muestra el efecto anti-leucémico de estas células.

LA FIG. 69 muestra la carga tumoral en ratones con xenoinjertos CD19-negativas B-LLA después del tratamiento con un control UTD, CART19, o CART22.

LA FIG. 70 muestra la expresión de PD-L1, PD1, LAG3, y TIM3 (de izquierda a derecha en cada juego de cuatro barras) en muestras de ganglios linfáticos y la médula ósea de los pacientes cinco CR, un paciente no clasificados, y seis pacientes con EP.

LA FIG. 71 es un gráfico que muestra la activación (en RLU) de varios constructos CAR CD22 en presencia y ausencia de un competidor M971.

LA FIG. 72 es un gráfico que muestra la activación (en RLU) de los constructos adicionales CAR CD22.

LA FIG. 73 muestra tres gráficos de barras que indican la actividad CAR CD22 en un ensayo de IFN-gamma.

LA FIG. 74 muestra la actividad de unión de los CARs CD22-64 y CD22-65.

LA FIG. 75 es un diagrama de la cartografía de los epítopos unidos por varios scFv CD22.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

A menos que se defina lo contrario, todos los términos técnicos y científicos usados en el presente documento tienen el mismo significado que comúnmente entendería una persona medianamente versada en la materia la cual pertenece la presente invención.

A menos que se defina lo contrario, todos los términos técnicos y científicos utilizados aquí tienen el mismo significado que el comúnmente entendido por un experto ordinario en la técnica a la que pertenece la invención.

El término "un" y "una" se refiere a uno o a más de uno (es decir, a al menos uno) del objeto gramatical del artículo. A modo de ejemplo, "un elemento" significa un elemento o más de un elemento.

El término "aproximadamente" cuando se hace referencia a un valor medible tal como una cantidad, una duración temporal, y similares, se entiende para abarcar variaciones de ± 20% o en algunos casos ± 10%, o en algunos casos ± 5%, o en algunos casos ± 1%, o en algunos casos ± 0,1% del valor especificado, ya que tales variaciones son apropiadas para llevar a cabo los métodos descritos.

El término “aféresis” como se usa en el presente documento se refiere al proceso extracorporal conocido en la técnica mediante el cual la sangre de un donante o paciente es removida del donante o paciente y pasada a través de un aparato que extrae constituyentes articulares seleccionados y regresa el remanente a la circulación del donante o paciente, mediante retransfusión por ejemplo. Así una “muetsra de aféresis” se refiere a una muetsra obtenida

mediante una aféresis.

El término "bioequivalente" se refiere a una cantidad de un agente que no sea el compuesto de referencia (por ejemplo, RAD001), requerida para producir un efecto equivalente al efecto producido por la dosis de referencia o la cantidad de referencia del compuesto de referencia (por ejemplo, RAD001). En una modalidad el efecto es el nivel de inhibición de mTOR, por ejemplo, tal como se mida por la inhibición de la quinasa p70 S6, por ejemplo, según se evaluó en un in vivo o in vitro de ensayo, por ejemplo, como se mida por un ensayo descrito en el presente documento, por ejemplo, el ensayo Boulay o medición de los niveles S6 fosforilados por Western blot. En una modalidad, el efecto es la alteración de la proporción de células inmunes efectoras PD-1 positivas /PD-1 negativas, mediante la clasificación de células. En una modalidad una cantidad bioequivalente o dosis de un inhibidor de mTOR es la cantidad o dosis que alcanza el mismo nivel de inhibición de la quinasa P70 S6 como lo hace la dosis de referencia o la cantidad de referencia de un compuesto de referencia. En una modalidad, una cantidad bioequivalente o dosis de un inhibidor de mTOR es la cantidad o dosis que alcanza el mismo nivel de alteración en la proporción de células inmunes efectoras PD-1 positivas /PD-1 negativas, como hace la dosis de referencia o la cantidad de referencia de un compuesto de referencia.

El término “inhibición” o “inhibidor” incluye una reducción en un cierto parámetro, por ejemplo, la actividad, de una molédula dada, por ejemplo CD20, CD10, CD19, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a. Por ejemplo, inhibición de la actividad, por ejemplo la actividad de CD20, CD10, CD19, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a, de al menos 5%, 10%, 20%, 30%, 40%, o más que s eincluye en este término. Así, la inhibición no necesita de ser del 100%. Las actividades d elos inhibidores pueden ser determinadas como se describe en el presente documento o mediante ensayos conocidos en la técnica. Un “inhibidor de una célula B” e suna molécula, por ejemplo, una molécula pequeña, anticuerpo, CAR o célula que comprende un CAR, que causa la reducción en un cierto parámetro, por ejemplo, la actividad, por ejemplo, el crecimiento o la proliferación, de una célula B, o que causa la reducción en un cierto parámetro, por ejemplo, una actividad de una molécula asociada con una célula B. Ejemplos no limitantes denoléculas asociadas con una celula B incluyen proteínas expresadas en la superficie de las células B, por ejemplo CD20, CD10, CD19, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a.

El término "Receptor Quimérico de Antígeno" o, alternativamente, un "CAR" se refiere a un conjunto de polipéptidos, típicamente dos, en las realizaciones más simples, los cuales,

cuando se encuentran en una célula inmune efectora, proporcionan especificidad a la célula por un blanco celular, típicamente, una célula cancerosa, y con generación de una señal intracelular. En algunas realizaciones, uun CAR comprende al menos un dominio extracelular de unión al antígeno, un dominio transmembrana y un dominio de señalización citoplásmico (también denominado aquí como "un dominio de señalización intracelular") que comprende un dominio funcional de señalización derivado de una molécula de estimulación y/o una molécula coestimuladora tal como se define a continuación. En algunos aspectos, el conjunto de polipéptidos está en la misma cadena del polipéptido, por ejemplo, comprenden una proteína quimérica de fusión. En algunas realizaciones, el conjunto de polipéptidos no es contiguo entre sí, por ejemplo, los polipéptidos están en diferentes cadenas polipeptídicas. En algunas realizaciones, el conjunto de polipéptidos incluye un interruptor de dimerización que, en la presencia de una molécula de dimerización, puede acoplar los polipéptidos con otros, por ejemplo, se puede acoplar un dominio de unión a antígeno con un dominio de señalización intracelular. En un aspecto, la molécula estimuladora del CAR es la cadena zeta asociada con el complejo receptor de las células T (por ejemplo, CD3 zeta). En un aspecto, el dominio de señalización citoplásmico comprende un dominio principal de señalización (por ejemplo, un dominio de señalización primario de CD3-zeta). En un aspecto, el dominio de señalización citoplásmico comprende además uno o más dominios funcionales de señalización derivados de al menos una molécula coestimuladora tal como se define a continuación. En un aspecto, la molécula coestimuladora se selecciona de entre las moléculas co-estimuladoras descritas en este documento, por ejemplo, 41BB (es decir, CD137), CD27 y/o CD28. En un aspecto, el CAR comprende una proteína quimérica de fusión que comprende un dominio extracelular de unión a antígeno, un dominio transmembrana y un dominio de señalización intracelular que comprende un dominio de señalización funcional derivado de una molécula estimuladora. En un aspecto, el CAR comprende una proteína quimérica de fusión que comprende un dominio extracelular de unión a antígeno, un dominio transmembrana y un dominio de señalización intracelular que comprende un dominio de señalización funcional derivado de una molécula coestimuladora y un dominio de señalización funcional derivado de una molécula estimuladora. En un aspecto, el CAR comprende una proteína quimérica de fusión que comprende un dominio extracelular de unión a antígeno, un dominio transmembrana y un dominio de señalización intracelular que comprende dos dominios de señalización funcionales derivados de una o más molécula(s) coestimuladoras y un dominio de señalización funcional derivado de una molécula estimuladora. En un aspecto, el CAR comprende una proteína quimérica de fusión

que comprende un dominio extracelular de unión a antígeno, un dominio transmembrana y un dominio de señalización intracelular que comprende al menos dos dominios de señalización funcionales derivados de una o más molécula(s) coestimuladoras y un dominio de señalización funcional derivado de una molécula estimuladora. En un aspecto, el CAR comprende una secuencia líder opcional en el extremo amino-terminal (N-ter) de la proteína de fusión CAR. En un aspecto, el CAR comprende, además, una secuencia líder en el extremo N-terminal del dominio extracelular de unión al antígeno, en el que la secuencia líder se escinde opcionalmente desde el dominio de unión a antígeno (por ejemplo, un scFv) durante el procesamiento celular y la localización del CAR en la membrana celular.

La frase "enfermedad asociada con la expresión de CD20" como se utiliza aquí incluye, pero no se limita a, una enfermedad asociada con la expresión de CD20 (por ejemplo, CD20 de tipo silvestre o mutante) o una condición asociada con las células que expresan, o en cualquier momento expresaron CD20 (por ejemplo, CD20 de tipo silvestre o mutante) incluyendo, por ejemplo, una enfermedad proliferativa, tal como un cáncer o tumor maligno o una afección precancerosa tal como una mielodisplasia, un síndrome mielodisplásico o una preleucemia; o una indicación relación con el cáncer asociado con las células que expresan CD20 (por ejemplo, CD20 de tipo silvestre o mutante). Para evitar dudas, una enfermedad asociada con la expresión de CD20 puede incluir una condición asociada con las células que no expresan actualmente CD20, por ejemplo, porque la expresión CD20 se ha inhibido, por ejemplo, debido al tratamiento con una molécula diana de CD20, por ejemplo, un CAR CD20, pero que a la vez expresa CD20. En un aspecto, un cáncer asociado con la expresión de CD20 es un cáncer hematológico. En un aspecto, un cáncer hematológico incluye pero no se limita a AML, síndrome mielodisplásico, ALL, leucemia de células pilosas, leucemia prolinfocítica, leucemia mieloide crónica, linfoma de Hodgkin, neoplasia blástica plasmocitoide de células dendríticas, y similares. Además de la enfermedad asociada con la expresión de la expresión de CD20 incluyen, pero no se limitan a cánceres, tumores malignos, condiciones precancerosas o enfermedades proliferativas asociadas por ejemplo, con la expresión atípica y/ o no clásica de CD20. Las indicaciones no relacionadas con cáncer asociadas con la expresión de CD20 también pueden ser incluidas.

En algunas modalidades, las células que expresan CD20, o que en algún momento expresaron ARNm de CD20. En una modalidad, las células que expresan CD20 producen una protéina CD20 (por ejemplo, CD20 de tipo silvestre o mutante), y la protéina CD20 puede estar

presente a niveles normales o reducidos. En una modalidad, las células que expresan CD20 producen niveles detectables de protéina CD20 en un momento, y subsecuentemente producen una cantidad sustancialmente no detectable de proteína CD20.

La frase "enfermedad asociada con la expresión de CD22" como se utiliza aquí incluye, pero no se limita a, una enfermedad asociada con la expresión de CD22 (por ejemplo, CD22 de tipo silvestre o mutante) o una condición asociada con las células que expresan, o en cualquier momento expresaron CD22 (por ejemplo, CD22 de tipo silvestre o mutante) incluyendo, por ejemplo, una enfermedad proliferativa, tal como un cáncer o tumor maligno o una afección precancerosa tal como una mielodisplasia, un síndrome mielodisplásico o una preleucemia; o una indicación relación con el cáncer asociado con las células que expresan CD22 (por ejemplo, CD22 de tipo silvestre o mutante). Para evitar dudas, una enfermedad asociada con la expresión de CD22 puede incluir una condición asociada con las células que no expresan actualmente CD22, por ejemplo, porque la expresión CD22 se ha inhibido, por ejemplo, debido al tratamiento con una molécula diana de CD22, por ejemplo, un CAR CD22, pero que a la vez expresa CD22. En un aspecto, un cáncer asociado con la expresión de CD22 es un cáncer hematológico. En un aspecto, un cáncer hematológico incluye pero no se limita a AML, síndrome mielodisplásico, ALL, leucemia de células pilosas, leucemia prolinfocítica, leucemia mieloide crónica, linfoma de Hodgkin, neoplasia blástica plasmocitoide de células dendríticas, y similares. Además de la enfermedad asociada con la expresión de la expresión de CD22 incluyen, pero no se limitan a cánceres, tumores malignos, condiciones precancerosas o enfermedades proliferativas asociadas por ejemplo, con la expresión atípica y/ o no clásica de CD22. Las indicaciones no relacionadas con cáncer asociadas con la expresión de CD22 también pueden ser incluidas.

En algunas modalidades, las células que expresan CD22, o que en algún momento expresaron ARNm de CD22. En una modalidad, las células que expresan CD22 producen una protéina CD22 (por ejemplo, CD22 de tipo silvestre o mutante), y la protéina CD22 puede estar presente a niveles normales o reducidos. En una modalidad, las células que expresan CD22 producen niveles detectables de protéina CD22 en un momento, y subsecuentemente producen una cantidad sustancialmente no detectable de proteína CD22.

Tal como se usa en el presente documento, a menos que se especifique lo contrario, los términos "prevenir", "previniendo" y "prevención" se refieren a una acción que se produce antes

de que el sujeto comienza a sufrir de la condición, o la recaída de la enfermedad. La prevención no tiene por qué resultar en una prevención completa de la condición; la prevención parcial o la reducción de la afección o un síntoma de la enfermedad, o reducción del riesgo de desarrollar la condición, es abarcada por este término.

Administrada/o "en combinación", como se usa en el presente documento, significa que dos (o más) tratamientos diferentes se administran al sujeto durante el curso de la aflicción del sujeto que padece el trastorno, por ejemplo, se administran dos o más tratamientos después de que el sujeto ha sido diagnosticado con el trastorno y antes de que el trastorno se haya curado o eliminado o de que el tratamiento haya cesado por otras razones. En algunas modalidades, la administración de un tratamiento todavía está ocurriendo cuando comienza la administración del segundo tratamiento, de manera tal que hay una superposición en términos de administración de los tratamientos. En el presente documento esto se denomina a veces "simultánea" o "administración simultánea". En otras modalidades, la administración de un tratamiento termina antes de que comience la administración del otro tratamiento. En algunas modalidades de cualquiera de los casos, el tratamiento es más eficaz gracias a la administración combinada. Por ejemplo, el segundo tratamiento es más eficaz, por ejemplo, se observa un efecto equivalente con una cantidad menor del segundo tratamiento, o los síntomas del segundo tratamiento se reducen en mayor medida que lo que se observa cuando el segundo tratamiento se administra sin el primer tratamiento, o se observa la misma situación con el primer tratamiento. En algunas modalidades, la administración es tal que la reducción en un síntoma, u otro parámetro relacionado con el trastorno, es mayor que lo que se observa cuando un tratamiento se administra sin el otro. El efecto de los dos tratamientos puede ser parcialmente aditivo, totalmente aditivo o más que aditivo. La administración puede ser tal que un efecto del primer tratamiento administrado sigue siendo detectable cuando se administra el segundo tratamiento. En una modalidad, la célula que expresa un CAR se administra a una dosis y/o esquema de dosificación descritos en el presente documento, y el inhibidor de células B, o agente que aumenta la actividad de la célula que expresa un CAR de CD19, se administra a una dosis y/o esquema de dosificación descritos en el presente documento.

"Derivado de" tal como ese término se utiliza en el presente documento, indica una relación entre una primera y una segunda molécula. Se refiere en general a la similitud estructural entre la primera molécula y una segunda molécula y no sugiere o incluye un proceso

o limitación fuente en una primera molécula que se deriva de una segunda molécula. Por ejemplo, en el caso de un dominio de señalización intracelular que se deriva de una molécula de CD3zeta, el dominio de señalización intracelular retiene suficiente estructura CD3zeta tal que disponga de la función requerida, es decir, la capacidad para generar una señal en las condiciones apropiadas. No tiene ninguna connotación o incluye una limitación a un determinado proceso de producción del dominio de señalización intracelular, por ejemplo, no quiere decir que, para proporcionar el dominio de señalización intracelular, se debe comenzar con una secuencia CD3zeta y eliminar la secuencia no deseada, o imponer mutaciones, para llegar al dominio de señalización intracelular.

El término "dominio de señalización" se refiere a la porción funcional de una proteína que actúa mediante la transmisión de información dentro de la célula para regular la actividad celular a través de vías de señalización definidas mediante la generación de segundos mensajeros o funcionar como efectores para responder a tales mensajeros.

Tal como se utiliza aquí, el término "CD19" se refiere al Cluster de diferenciación 19de proteína, que es un determinante antigénico detectable en las células precursoras de leucemia. Las secuencias de aminoácidos y de ácido nucleico humanas y murinas se pueden encontrar en bases de datos públicas, tales como GenBank, UniProt y Swiss-Prot. Por ejemplo, la secuencia de aminoácidos de CD19 humano se puede encontrar como UniProt/Swiss-Prot Nº de Acceso P15391 y la codificación de la secuencia de nucleótidos de CD19 humana se puede encontrar en el Nº de Acceso NM_001178098. Como se usa en el presente documento, "CD19" incluye proteínas que comprenden mutaciones, por ejemplo, mutaciones puntuales, fragmentos, inserciones, deleciones y variantes de corte y empalme de longitud completa de CD19 de tipo silvestre. El CD19 se expresa en la mayoría de los cánceres de linaje B, incluyendo, por ejemplo, leucemia linfoblástica aguda, leucemia de linfocitos crónica y linfoma no Hodgkin. A continuación se proporcionan otras células con expresión de CD19 en la definición de "enfermedad asociada con la expresión de CD19". También es un marcador temprano de progenitores de células B. Véase, por ejemplo, Nicholson et al. Mol. Immun. 34 (16-17): 1157-1165 (1997). En un aspecto, la parte de unión a antígeno del CAR reconoce y se une a un antígeno en el dominio extracelular de la proteína CD19. En un aspecto, la proteína CD19 se expresa en una célula de cáncer.

El término "anticuerpo", como se usa en el presente documento, se refiere a una proteína

o secuencia de polipéptido derivado de una molécula de inmunoglobulina que se une específicamente con un antígeno. Los anticuerpos pueden ser inmunoglobulinas policlonales o monoclonales, múltiples o una sola cadena, o intactas, y pueden ser derivadas de fuentes naturales o de fuentes recombinantes. Los anticuerpos pueden ser tetrámeros de moléculas de inmunoglobulina.

El término "fragmento de anticuerpo" se refiere a al menos a una porción de un anticuerpo, que conserva la capacidad de interactuar específicamente con (por ejemplo, mediante la unión, impedimento estérico, la estabilización/ desestabilización, distribución espacial) un epítope de un antígeno. Ejemplos de fragmentos de anticuerpos incluyen, pero no se limitan a, Fab, Fab', $F(ab')_2$, fragmentos Fv, fragmentos de anticuerpos scFv, Fv(sdFv) ligado a disulfuro, un fragmento Fd que consiste en los dominios VH y CH1, anticuerpos lineales, anticuerpos de dominio único, tales como sdAb (ya sea VL o VH), dominios VHH de camélidos, anticuerpos multi-específicos formados a partir de fragmentos de anticuerpo tal como un fragmento bivalente que comprende dos fragmentos Fab unidos por un puente disulfuro en la región bisagra, y una CDR aislada u otros fragmentos de unión a epítope de un anticuerpo. Un fragmento de unión a antígeno también se puede incorporar en los anticuerpos de dominio único, maxicuerpos, minicuerpos, nanocuerpos, intracuerpos, diacuerpos, triacuerpos, tetracuerpos, v-NAR y bis-scFv (véase, por ejemplo, Hollinger y Hudson, Nature Biotechnology 23: 1126-1136 , 2005). Los fragmentos de unión a antígeno también pueden ser injertados en estructuras basadas en polipéptidos tales como fibronectina de tipo III (Fn3) (véase la Patente de EE.UU. No.: 6.703.199, que describe minicuerpos de polipéptido de fibronectina).

El término "scFv" se refiere a una proteína de fusión que comprende al menos un fragmento de anticuerpo que comprende una región variable de una cadena ligera y que comprende al menos un fragmento de anticuerpo que comprende una región variable de una cadena pesada, en el que las regiones variables de cadena ligera y pesada están ligadas de forma contigua, por ejemplo, a través de un enlazador sintético, por ejemplo, un enlazador de polipéptido corto flexible y capaz de ser expresado como un polipéptido de cadena única, y en el que el scFv conserva la especificidad del anticuerpo intacto del que se deriva. Salvo que se especifique, como se usa en el presente documento un scFv puede tener las regiones variables VL y VH en cualquier orden, por ejemplo, con respecto a los extremos N-terminales y C-terminales del polipéptido, el scFv puede comprender VL-enlazador-VH o puede comprender

VH-enlazador-VL.

El término "región determinante de complementariedad" o "CDR", como se usa en el presente documento, se refiere a las secuencias de aminoácidos dentro de las regiones variables de anticuerpos que confieren la especificidad al antígeno y la afinidad de unión. Por ejemplo, en general, hay tres CDR en cada región variable de la cadena pesada (por ejemplo, HCDR1, HCDR2 y HCDR3) y tres CDR en cada región variable de la cadena ligera (LCDR1, LCDR2 y LCDR3). Los límites precisos de la secuencia de aminoácidos de una CDR dada pueden determinarse utilizando cualquiera de una serie de esquemas bien conocidos, incluyendo los descritos por Kabat et al. (1991), “Sequences of Proteins of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (“Kabat” numbering scheme), Al-Lazikani et al., (1997) JMB 273,927-948 (“Chothia” numbering scheme), o una combinación de los mismos. Bajo el esquema de numeración de Kabat, en algunas realizaciones, los residuos de aminoácidos de la CDR en el dominio variable de cadena pesada (VH) se numeran 31-35 (HCDR1), 50-65 (HCDR2) y 95-102 (HCDR3); y los residuos de aminoácidos de la CDR del dominio variable de la cadena ligera (VL) se numeran 24-34 (LCDR1), 50-56 (LCDR2) y 89-97 (LCDR3). Bajo el esquema de numeración de Chothia, en algunas realizaciones, los aminoácidos de la CDR de la VH se numeran 26-32 (HCDR1), 52-56 (HCDR2) y 95-102 (HCDR3); y los residuos de aminoácidos de la CDR de la VL se numeran 26-32 (LCDR1), 50-52 (LCDR2), y 91-96 (LCDR3). En un esquema de numeración de Kabat y Chothia combinados, en algunas realizaciones, las CDR corresponden a los residuos de aminoácidos que son parte de una CDR de Kabat, Chothia una CDR, o ambos. Por ejemplo, en algunas realizaciones, las CDR corresponden a los residuos de aminoácidos 26 a 35 (HCDR1), 50-65 (HCDR2) y 95-102 (HCDR3) en una VH, por ejemplo, una VH de mamífero, por ejemplo, una VH humana; y los residuos de aminoácidos 24 a 34 (LCDR1), 50-56 (LCDR2), y 89-97 (LCDR3) en una VL, por ejemplo, una VL de mamífero, por ejemplo, una VL humana.

Tal como se utiliza aquí, el término "dominio de unión" o "molécula de anticuerpo" se refiere a una proteína, por ejemplo, una cadena de inmunoglobulina o fragmento de la misma, que comprende la secuencia de dominio variable de al menos una inmunoglobulina. El término "dominio de unión" o "molécula de anticuerpo" abarca los anticuerpos y fragmentos de anticuerpos. En una realización, una molécula de anticuerpo es una molécula de anticuerpo multiespecífica, por ejemplo, que comprende una pluralidad de secuencias de dominio variable

de inmunoglobulina, en el que una secuencia de dominio variable de primera inmunoglobulina de la pluralidad tiene especificidad de unión para un primer epítope y una secuencia de dominio variable de la segunda inmunoglobulina de la pluralidad tiene especificidad de unión para un segundo epítope. En una realización, una molécula de anticuerpo multiespecífica es una molécula de anticuerpo biespecífica. Un anticuerpo biespecífico tiene especificidad por no más de dos antígenos. Una molécula de anticuerpo biespecífica se caracteriza por una secuencia de dominio variable de una primera inmunoglobulina que tiene especificidad de unión para un primer epítope y una secuencia de dominio variable de una segunda inmunoglobulina que tiene especificidad de unión para un segundo epítope.

La porción del CAR de la invención que comprende un anticuerpo o fragmento de anticuerpo del mismo puede existir en una variedad de formas en las que el dominio de unión a antígeno se expresa como parte de una cadena polipeptídica contigua incluyendo, por ejemplo, un fragmento de anticuerpo de dominio único (sdAb), un anticuerpo de cadena sencilla (scFv), un anticuerpo humanizado, o un anticuerpo biespecífico (Harlow et al., 1999, In: Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, NY; Harlow et al., 1989, In: Antibodies: A Laboratory Manual, Cold Spring Harbor, New York; Houston et al., 1988, Proc. Natl. Acad. Sci. USA 85:5879-5883; Bird et al., 1988, Science 242:423-426). En un aspecto, el dominio de unión a antígeno de una composición de CAR de la invención comprende un fragmento de anticuerpo. En un aspecto adicional, el CAR comprende un fragmento de anticuerpo que comprende un scFv.

El término " cadena pesada de anticuerpo ", se refiere a la mayor de los dos tipos de cadenas de polipéptidos presentes en las moléculas de anticuerpo en sus conformaciones naturales, y que normalmente determina la clase a la que pertenece el anticuerpo.

El término "cadena ligera de anticuerpo," se refiere a la más pequeña de los dos tipos de cadenas de polipéptidos presentes en las moléculas de anticuerpo en sus conformaciones naturales. Cadenas ligeras kappa (K) y lambda (λ) se refiere a los dos isotipos principales de cadena ligera de un anticuerpo.

El término "anticuerpo recombinante" se refiere a un anticuerpo que se genera usando tecnología de ADN recombinante, tal como, por ejemplo, un anticuerpo expresado por un sistema de expresión de bacteriófago o de levadura. El término también debe interpretarse en el sentido de un anticuerpo que se ha generado por la síntesis de una molécula de ADN que

codifica el anticuerpo y que la molécula de ADN expresa una proteína de anticuerpo, o una secuencia de aminoácidos que especifica el anticuerpo, en donde la secuencia de ADN o de aminoácidos han sido obtenidas utilizando la tecnología de ADN o de secuencia de aminoácidos recombinante que está disponible y es bien conocida en la técnica.

El término "antígeno" o "Ag" se refiere a una molécula que provoca una respuesta inmune. Esta respuesta inmune puede implicar o bien la producción de anticuerpos, o la activación de células específicas inmunológicamente competentes, o ambos. El experto en la técnica entenderá que cualquier macromolécula, incluyendo prácticamente todas las proteínas o péptidos, puede servir como un antígeno. Además, los antígenos se pueden derivar de ADN recombinante o genómico. Un experto en la técnica entenderá que cualquier ADN, que comprende una secuencia de nucleótidos o una secuencia parcial de nucleótidos que codifica una proteína que provoca por lo tanto una respuesta inmune codifica un "antígeno" tal como ese término se utiliza en el presente documento. Además, un experto en la técnica entenderá que un antígeno no tiene que ser codificado exclusivamente por una secuencia de nucleótidos de la longitud completa de un gen. Es fácilmente evidente que la presente invención incluye, pero no se limita al uso de secuencias parciales de nucleótidos de más de un gen y que estas secuencias de nucleótidos están dispuestas en varias combinaciones para codificar polipéptidos que provocan la respuesta inmune deseada. Además, un experto en la técnica entenderá que un antígeno no tiene que ser codificado por un "gen" en absoluto. Es fácilmente evidente que un antígeno se pueden generar sintetizado o se puede derivar de una muestra biológica, o puede ser además una macromolécula diferente de un polipéptido. Una muestra biológica de este tipo puede incluir, pero no está limitado a una muestra de tejido, una muestra de tumor, una célula o un fluido con otros componentes biológicos.

Los términos "compiten" o "competencia cruzada" se utilizan indistintamente en este documento para referirse a la capacidad de una molécula de anticuerpo para interferir con la unión de una molécula de anticuerpo, por ejemplo, un anticuerpo anti-CD20 o molécula de anticuerpo CD22 que se proporcionan en este documento, a un objetivo, por ejemplo, CD20 o CD22 humano. La interferencia con la unión puede ser directa o indirecta (por ejemplo, a través de una modulación alostérica de la molécula de anticuerpo o el objetivo). La medida en que una molécula de anticuerpo es capaz de interferir con la unión de otra molécula de anticuerpo a la diana, y por tanto, si se puede decir para competir, se puede determinar usando un ensayo de

unión de competencia, por ejemplo, como se describe en el presente documento. En algunas formas de realización, un ensayo de unión competitiva es un ensayo de competición cuantitativo. En algunas realizaciones, se dice que una primera molécula de anticuerpo para competir por la unión a la diana con una segunda molécula de anticuerpo cuando la unión de la primera molécula de anticuerpo a la diana se reduce en 10% o más, por ejemplo, 20% o más, 30% o más, 40% o más, 50% o más, 55% o más, 60% o más, 65% o más, 70% o más, 75% o más, 80% o más, 85% o más, 90% o más, 95% o más, 98% o más, 99% o más en un ensayo de unión competitiva (por ejemplo, un ensayo de competición descrito en el presente documento).

Tal como se utiliza aquí, el término "epítope" se refiere a los restos de un antígeno (por ejemplo, CD20 o CD22 humano) que interactúan específicamente con una molécula de anticuerpo. A dichos restos, se hace referencia aquí como determinantes epitópicos, por lo general comprenden, o son parte de los elementos, tales como cadenas laterales de aminoácidos o cadenas laterales de azúcares. Un determinante epitópico se puede definir, por ejemplo, por métodos conocidos en la técnica o descrita en este documento, por ejemplo, por cristalografía o por intercambio de hidrógeno-deuterio. Al menos uno o algunos de los restos en la molécula de anticuerpo, que interactúan específicamente con un determinante epitópico, se encuentran normalmente en una CDR(s). Normalmente un epítopo tiene unas específicas características estructurales tridimensionales. Normalmente un epítopo tiene características de carga específicas. Algunos epítopos son epítopos lineales mientras que otros son epítopos conformacionales.

El término "efecto anti-cáncer" se refiere a un efecto biológico que se puede manifestar por diversos medios, incluyendo pero no limitado a, por ejemplo, una disminución en el volumen del tumor, una disminución en el número de células cancerosas, una disminución en el número de metástasis, un aumento de la esperanza de vida, disminución en la proliferación de células de cáncer, disminución de la supervivencia de células de cáncer, o la mejora de varios síntomas fisiológicos asociados con la afección cancerosa. Un "efecto anti-cáncer" también se manifiesta por la capacidad de los péptidos, polinucleótidos, células y anticuerpos descritos en el presente documento en la prevención de la aparición de cáncer en el primer lugar. El término "efecto anti-tumor" se refiere a un efecto biológico que se puede manifestar por diversos medios, incluyendo pero no limitado a, por ejemplo, una disminución en el volumen del tumor, una disminución en el número de células tumorales, una disminución de la proliferación de células

tumorales , o una disminución en la supervivencia de células tumorales.

El término "autólogo" se refiere a cualquier material derivado de la misma persona a la que sea más tarde reintroducido en el individuo.

El término "alogénico" se refiere a cualquier material derivado de un animal diferente de la misma especie al individuo al que se introduce el material. Dos o más individuos se dice que son alogénicos entre sí cuando los genes en uno o más loci no son idénticos. En algunos aspectos, el material alogénico de individuos de la misma especie puede ser suficientemente diferente genéticamente para interactuar antigénicamente

El término "xenogénico" se refiere a un injerto procedente de un animal de una especie diferente.

El término "cáncer" se refiere a una enfermedad caracterizada por el crecimiento incontrolado de células aberrantes. Las células cancerosas se pueden propagar de forma local o a través del torrente sanguíneo y sistema linfático a otras partes del cuerpo. Los ejemplos de diversos tipos de cáncer se describen en el presente documento e incluyen, pero no se limitan a, cáncer de mama, cáncer de próstata, cáncer de ovario, cáncer cervical, cáncer de piel, cáncer pancreático, cáncer colorrectal, cáncer renal, cáncer de hígado, cáncer de cerebro, linfoma, leucemia, pulmón cáncer y similares. Los términos "tumor" y "cáncer" se usan indistintamente en el presente documento, por ejemplo, tanto en términos abarcan sólidos y líquidos, por ejemplo, difusa o circulante, los tumores. Tal como se utiliza aquí, el término "cáncer" o "tumor" incluye un tumor premaligno, así como cánceres malignos y tumores.

Los términos "antígeno asociado a cáncer " o "antígeno de tumor" o "antígeno de trastorno proliferativo" o "antígeno asociado con un trastorno proliferativo" se refiere indistintamente a una molécula (típicamente proteína, carbohidrato o lípido) que se expresa preferentemente en la superficie de un célula cancerosa, ya sea totalmente o como un fragmento (por ejemplo, CMH/péptido), en comparación con una célula normal, y que es útil para la orientación preferencial de un agente farmacológico a la célula cancerosa. En algunas realizaciones, un antígeno tumoral es un marcador expresado por células normales y células cancerosas, por ejemplo, un marcador de linaje, por ejemplo, CD19 en las células B. En ciertos aspectos, los antígenos tumorales de la presente invención se derivan de, cánceres que incluyen pero no se limitan a melanoma primario o metastásico, timoma, linfoma, sarcoma, cáncer de

pulmón, cáncer de hígado, linfoma no Hodgkin, linfoma de Hodgkin, leucemias, cáncer de útero, cáncer cervical, cáncer de vejiga, cáncer de riñón y adenocarcinomas tales como cáncer de mama, cáncer de próstata, cáncer de ovario, cáncer de páncreas, y similares. En algunas realizaciones, el antígeno tumoral es un antígeno que es común a un trastorno proliferativo específico. En algunas formas de realización, un antígeno asociado al cáncer es una molécula de superficie celular que se sobreexpresa en una célula de cáncer en comparación con una célula normal, por ejemplo, 1-vez más expresión, sobreexpresión de 2 veces, sobreexpresión 3 veces o más en comparación a una célula normal. En algunas modalidades, un antígeno asociado al cáncer es una molécula de superficie celular que se sintetiza de forma inapropiada en la célula cancerosa, por ejemplo, una molécula que contiene deleciones, adiciones o mutaciones en comparación con la molécula expresada en una célula normal. En algunas modalidades, un antígeno asociado al cáncer se expresa exclusivamente en la superficie celular de una célula cancerosa, por completo o como un fragmento (por ejemplo, MHC / péptido), y no se sintetiza o se expresa en la superficie de una célula normal. En algunas modalidades, los CARs de la presente invención incluyen CARs que comprenden un dominio de unión a antígeno (por ejemplo, anticuerpo o fragmento de anticuerpo) que se une a un péptido presentado al CMH. Normalmente, los péptidos derivados de proteínas endógenas llenan los bolsillos del complejo mayor de histocompatibilidad (CMH) de clase I, y son reconocidos por los receptores de células T (TCR) en los linfocitos TCD8 +. Los complejos del CMH de clase I se expresan de forma constitutiva por todas las células nucleadas. En el cáncer, los complejos de MHC específicos del virus y/o un péptido específico de tumor representan una clase única de blancos de superficie de células para la inmunoterapia. Los anticuerpos similares a TCR que se dirigen a los péptidos derivados de antígenos virales o tumorales en el contexto de antígeno leucocitario humano (HLA) -A1 o HLA-A2 se han descrito (véase, por ejemplo, Sastry et al., J Virol. 2011 85(5):1935-1942; Sergeeva et al., Bood, 2011 117(16):4262-4272; Verma et al., J Immunol 2010 184(4):2156-2165; Willemsen et al., Gene Ther 2001 8(21) :1601-1608 ; Dao et al., Sci Transl Med 2013 5(176) :176ra33 ; Tassev et al., Cancer Gene Ther 2012 19(2):84-100). Por ejemplo, el anticuerpo similar a TCR se puede identificar a partir del cribado de una biblioteca, tal como una biblioteca de muestra de fagos de scFv humano.

La frase "enfermedad asociada con la expresión de CD19" incluye, pero no se limita a, una enfermedad asociada con la expresión de CD19 (por ejemplo, CD19 de tipo silvestre o mutante) o condición asociada con las células que expresan, o en cualquier momento expresaron

CD19 (por ejemplo, CD19 de tipo silvestre o mutante) incluyendo, por ejemplo, enfermedades proliferativas tales como el cáncer o un tumor maligno o una afección precancerosa tal como una mielodisplasia, un síndrome mielodisplásico o una preleucemia; o una indicación relación con el cáncer asociada con las células que expresan CD19. Para evitar dudas, una enfermedad asociada con la expresión de CD19 puede incluir una condición asociada con las células que no expresan actualmente CD19, por ejemplo, porque la expresión CD19 se ha inhibido, por ejemplo, debido al tratamiento con una molécula diana de CD19, por ejemplo, un CAR CD19, pero que a la vez expresa CD19. En un aspecto, un cáncer asociado con la expresión de CD19 es un cáncer hematológico. En un aspecto, el cáncer hematológico es una leucemia o un linfoma. En un aspecto, un cáncer asociado con la expresión de CD19 incluye tipos de cáncer y tumores malignos, incluyendo, pero no limitado a, por ejemplo, uno o más leucemias agudas incluyendo, pero no limitado a, por ejemplo, leucemia linfoide aguda de células B (LLA B), leucemia aguda linfoide de células T (LLA T), leucemia linfoide aguda (LLA); una o más leucemias crónicas incluyendo, pero no limitado a, por ejemplo, leucemia mielógena crónica (LMC), la leucemia linfoide crónica (LLC). Cánceres adicionales o condiciones hematológicas asociadas con la expresión de CD19 comprenden, pero no se limitan a, por ejemplo, leucemia prolinfocítica de células B, neoplasia blástica plasmocitoide de células dendríticas, el linfoma de Burkitt, linfoma difuso de células B grandes, linfoma folicular, leucemia de células pilosas, pequeña por células o una gran linfoma de células foliculares, las condiciones linfoproliferativas malignas, linfoma MALT, linfoma de células del manto (LCM), linfoma de la zona marginal, mieloma múltiple, mielodisplasia y el síndrome mielodisplásico, el linfoma no de Hodgkin, linfoma de Hodgkin, linfoma plasmablástico, neoplasia plasmocitoide de células dendríticas, macroglobulinemia de Waldenstrom, y "preleucemia", que es una colección diversa de condiciones hematológicas unidas por la producción ineficaz (o displasia) de glóbulos mieloides, y similares. Otras enfermedades asociadas con la expresión de CD19 incluyen, pero no se limitan a, cánceres, tumores malignos, condiciones precancerosas o enfermedades proliferativas asociadas con la expresión de CD19 por ejemplo, atípicas y/o no clásico. Las indicaciones no relacionadas con cáncer asociadas con la expresión de CD19 incluyen, pero no se limitan a, por ejemplo, enfermedad autoinmune, (por ejemplo, lupus), trastornos inflamatorios (alergia y el asma) y trasplante. En algunas realizaciones, las células que expresan CD19, o en cualquier momento expresaron, ARNm de CD19. En una realización, las células que expresan CD19producen una proteína CD19 (por ejemplo, de tipo silvestre o mutante), y la proteína CD19 puede estar

presente en niveles normales o niveles reducidos. En una realización, las células que expresan CD19 produjeron niveles detectables de una proteína CD19 en un punto, y posteriormente no se producen ninguna proteína CD19 sustancialmente detectable.

El término " modificaciones conservadoras de secuencia " se refiere a las modificaciones de aminoácidos que no afectan de manera significativa o alteran las características de unión del anticuerpo o fragmento de anticuerpo que contiene la secuencia de aminoácidos. Tales modificaciones conservativas incluyen sustituciones de aminoácidos, adiciones y deleciones. Las modificaciones pueden ser introducidas en un anticuerpo o fragmento de anticuerpo de la invención mediante técnicas estándar conocidas en la técnica, tales como mutagénesis dirigida al sitio y mutagénesis mediada por PCR. Las sustituciones de aminoácidos conservativas son aquellas en las que el residuo de aminoácido se reemplaza con un residuo de aminoácido que tiene una cadena lateral similar. Las familias de residuos de aminoácidos que tienen cadenas laterales similares han sido definidas en la técnica. Estas familias incluyen aminoácidos con cadenas secundarias básicas (por ejemplo, lisina, arginina, histidina), cadenas laterales ácidas (por ejemplo, ácido aspártico, ácido glutámico), cadenas laterales polares no cargadas (por ejemplo, glicina, asparagina, glutamina, serina, treonina, tirosina, cisteína, triptófano), cadenas laterales no polares (por ejemplo, alanina, valina, leucina, isoleucina, prolina, fenilalanina, metionina), cadenas laterales beta ramificadas (por ejemplo, treonina, valina, isoleucina) y cadenas laterales aromáticas (por ejemplo, tirosina, fenilalanina, triptófano, histidina). Por lo tanto, uno o más residuos de aminoácidos dentro de un CAR de la invención pueden ser reemplazados por otros residuos de aminoácidos de la misma familia de cadena lateral y el CAR alterado puede ser probado usando los ensayos funcionales descritos en este documento.

El término "estimulación", se refiere a una respuesta primaria inducida por la unión de una molécula de estimulación (por ejemplo, un complejo TCR/CD3 o CAR) con su ligando cognado (o antígeno tumoral en el caso de un CAR) mediando de este modo un evento de transducción de señales, tal como, pero no limitado a, la transducción de señales a través de la transducción de señal o complejo TCR / CD3 a través del receptor NK apropiado o de los dominios de señalización del CAR. La estimulación puede mediar la expresión alterada de ciertas moléculas.

El término "molécula estimuladora," se refiere a una molécula expresada por una célula inmune, por ejemplo, células T, células NK, o células B) que proporciona la(s) secuencia(s) de

señalización citoplasmática que regulan la activación de la célula inmune de una manera estimuladora para al menos algún aspecto de la vía de señalización de las células inmunes. En un aspecto, la señal es una señal primaria que se inicia, por ejemplo, con la unión de un complejo TCR/CD3 con una molécula del CMH cargado con péptido, y que conduce a la mediación de una respuesta de células T, incluyendo, pero no limitado a la proliferación, activación, diferenciación, y similares. Una secuencia primaria citoplasmática de señalización (también referida como un "dominio primario de señalización") que actúa de una manera estimuladora puede contener un motivo de señalización que se conoce como grupo de inmunoreceptor de activación basada en tirosina o ITAM. Ejemplos de un ITAM que contiene la secuencia de señalización citoplasmática que es de uso particular en la invención incluyen, pero no se limita a, los derivados de CD3 zeta, común gamma de FcR (FCER1G), Fc gamma gamma RIIa, FcR beta (Fc Epsilon R1b), CD3 gamma, CD3 delta, CD3 epsilon, CD79a, CD79b, DAP10, DAP12 y. En un CAR específico de la invención, el dominio de señalización intracelular en cualquiera o más CARs de la invención comprende una secuencia de señalización intracelular, por ejemplo, una secuencia primaria de señalización de CD3 zeta. En un CAR específico de la invención, la secuencia primaria de señalización de CD3 zeta es la secuencia proporcionada como SEQ ID NO: 17, o los residuos equivalentes de una especie no humana, por ejemplo, ratón, roedor, mono y similares. En un CAR específico de la invención, la secuencia de señalización primaria de CD3-zeta es la secuencia que se proporciona en la SEC ID NO: 43, o los residuos equivalentes de una especie no humana, por ejemplo, ratón, roedor, mono y similares.

El término "célula presentadora de antígeno" o "CPA" se refiere a una célula del sistema inmune tal como una célula accesoria (por ejemplo, una célula B, una célula dendrítica, y similares) que muestra un antígeno extraño acomplejado con los principales complejos de histocompatibilidad (CMHs) en su superficie. Las células T pueden reconocer estos complejos usando sus receptores de células T (TCR). Las CPA procesan antígenos y los presentan a las células T.

"Célula efectora inmune", como ese término se usa en el presente documento, se refiere a una célula que está implicada en una respuesta inmune, por ejemplo, en la promoción de una respuesta efectora inmune. Los ejemplos de células efectoras inmunes incluyen las células T, por ejemplo, células T alfa/beta y células T gamma/delta, células B, células asesinas naturales (NK), células T asesinas naturales (NK-T), mastocitos, y fagocitos derivados de mieloide.

"Función efectora inmune o respuesta efectora inmune", como se usa ese término en el presente documento, se refiere a la función o la respuesta, por ejemplo, de una célula efectora inmune, que mejora o promueve un ataque inmune de una célula diana. Por ejemplo, una función o respuesta efectora inmune se refiere una propiedad de una T o célula NK que promueve la muerte o la inhibición del crecimiento o la proliferación, de una célula diana. En el caso de una célula T, la estimulación primaria y la co-estimulación son ejemplos de la función efectora inmune o respuesta.

El término “función efectora”se refiere a una función especializada de una célula. La función efectora de una célula T, por ejemplo, puede ser una actividad citolítica, o una actividad colaboradora que incluye la secreción de citoquinas.

Un "dominio de señalización intracelular", como se utiliza el término en el presente documento, se refiere a una porción intracelular de una molécula. El dominio de señalización intracelular puede generar una señal que promueve una función efectora inmune de la célula que contiene CAR, por ejemplo, una célula TCAR. Los ejemplos de la función efectora inmune, por ejemplo, en una célula TCAR, incluyen la actividad citolítica y la actividad auxiliar, incluyendo la secreción de citoquinas. En formas de realización, el dominio intracelular de la señal es la porción de la proteína que transduce la señal de la función efectora y dirige la célula para realizar una función especializada. Mientras que todo el dominio de señalización intracelular se puede emplear, en muchos casos, no es necesario el uso de toda la cadena. En la medida en que se utiliza una porción truncada del dominio de señalización intracelular, tales porciones truncadas pueden ser usadas en lugar de la cadena intacta, siempre que se transduce la señal de la función efectora. El dominio de señalización intracelular así término se entiende que incluye cualquier parte truncada del dominio de señalización intracelular suficiente para transducir la señal de la función efectora.

En una realización, el dominio de señalización intracelular puede comprender un dominio primario de señalización intracelular. Los principales dominios de señalización intracelular de ejemplo incluyen aquellos derivado de las moléculas responsables de la estimulación primaria, o simulación dependiente de antígeno. En una realización, el dominio de señalización intracelular puede comprender un dominio intracelular coestimulador. Los dominios coestimuladoras de señalización intracelular ejemplares incluyen a los derivados de moléculas responsables de las señales coestimuladoras, o la estimulación independiente de antígeno. Por ejemplo, en el caso de

un CAR, un dominio primaria de señalización intracelular puede comprender una secuencia citoplásmica de un receptor de células T, y un dominio de señalización intracelular coestimulador puede comprender la secuencia citoplasmática del co-receptor o molécula coestimuladora.

Un dominio primario de señalización intracelular puede comprender un motivo de señalización que se conoce como un grupo de inmunoreceptor de activación basado en tirosina o ITAM. Ejemplos de ITAM que contiene secuencias de señalización citoplasmáticas primarias incluyen, pero no se limitan a aquellos derivados de CD3 zeta, FcR gamma, común gamma de FcR (FCER1G), Fc gamma gamma RIIa, FcR beta (Fc Epsilon R1b), CD3 gamma, CD3 delta, CD3 epsilon, CD22, CD79a, CD79b, CD278 ("ICOS"), FcεRI, CD66d, CD32, DAP10 y DAP12.

El término "zeta" o, alternativamente, "cadena zeta", "CD3-zeta" o "TCR-zeta" se define como la proteína proporcionada como GenBank Acc. No. BAG36664.1, o los residuos equivalentes de una especie no humana, por ejemplo, ratón, roedor, mono y similares, y un "dominio estimulante zeta" o, alternativamente, un "dominio de estimulación CD3-zeta" o un " TCR-zeta dominio estimulante "se define como los residuos de aminoácidos del dominio citoplásmico de la cadena zeta, o derivados funcionales de los mismos, que son suficientes para transmitir una señal inicial funcionalmente necesaria para la activación de células T. En un aspecto, el dominio citoplásmico de zeta comprende los residuos 52 a 164 de GenBank Acc. Nº BAG36664.1 o los residuos equivalentes de una especie no humana, por ejemplo, ratón, roedor, mono y similares, que son ortólogos funcionales de los mismos. En un aspecto, el "dominio estimulante zeta" o un "dominio de estimulación CD3-zeta" es la secuencia proporcionada como SEC ID NO: 17. En un aspecto, el "dominio estimulante zeta" o un "dominio de estimulación CD3-zeta" es la secuencia proporcionada como SEC ID NO: 43.

El término "molécula coestimuladora" se refiere a la molécula de fijación análoga sobre una célula T que se une específicamente con un ligando coestimulador, mediando de ese modo una respuesta coestimuladora por la célula T, tal como, pero no limitado a, la proliferación. Las moléculas coestimuladoras son moléculas de la superficie celular distintas de los receptores de antígeno o sus ligandos que contribuyen a una respuesta inmune eficiente. Las moléculas coestimuladoras incluyen, pero no se limitan a una molécula del CMH de clase I, proteínas del receptor de TNF, las proteínas de tipo inmunoglobulina, receptores de citocinas, integrinas,

moléculas de señalización de activación linfocítica (proteínas SLAM), activación de receptores de células NK, BTLA, un receptor de ligando Toll, OX40, CD2 , CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a / CD18), el 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LUZ, HVEM (LightR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alfa, CD8beta, beta IL2R, gamma IL2R, alfa IL7R, ITGA4, Vla1, CD49a, ITGA4, IA4 , CD49d, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D , NKG2C, TNFR2, TRANCE / RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Táctil), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69 , SLAMF6 (NTB-a, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG / CBP, CD19a, y un ligando se une específicamente con CD83.

Un dominio de señalización intracelular coestimulador se refiere a la porción intracelular de una molécula coestimuladora.

El dominio de señalización intracelular puede comprender toda la parte intracelular, o todo el dominio de señalización intracelular nativa, de la molécula de la que se deriva, o un fragmento funcional o derivado del mismo.

El término "de 4-1BB" se refiere a un miembro de la superfamilia de TNFR con una secuencia de aminoácidos proporcionada como GenBank Acc. Nº AAA62478.2, o los residuos equivalentes de una especie no humana, por ejemplo, ratón, roedor, mono y similares; y un "dominio coestimulador de 4-1BB" se define como los residuos de aminoácidos 214-255 de GenBank acceso No. AAA62478.2, o los residuos equivalentes de una especie no humana, por ejemplo, ratón, roedor, mono y similares. En un aspecto, el "dominio coestimulador de 4-1BB" es la secuencia proporcionada como SEC ID NO: 16 o los residuos equivalentes de una especie no humana, por ejemplo, ratón, roedor, mono y similares.

El término "codificar" se refiere a la propiedad inherente de las secuencias específicas de nucleótidos en un polinucleótido, como un gen, un ADNc, o un ARNm, para servir como plantillas para la síntesis de otros polímeros y macromoléculas en procesos biológicos que tienen ya sea una secuencia definida de nucleótidos (por ejemplo, ARNr, ARNt y ARNm) o una secuencia definida de aminoácidos y las propiedades biológicas resultantes de los mismos. Por lo tanto, un gen, ADNc, o ARN, codifica una proteína si la transcripción y la traducción del

ARNm correspondiente a ese gen produce la proteína en una célula u otro sistema biológico. Tanto la cadena codificante, por lo general la secuencia de nucleótidos de la cual es idéntica a la secuencia de ARNm y se proporciona en listados de secuencia, y la cadena no codificante, utilizada como molde para la transcripción de un gen o ADNc, puede denominarse como que codifica la proteína u otro producto de ese gen o ADNc.

A menos que se especifique lo contrario, una "secuencia de nucleótidos que codifica una secuencia de aminoácidos" incluye todas las secuencias de nucleótidos que son versiones degeneradas una de la otra y que codifican la misma secuencia de aminoácidos. La frase secuencia de nucleótidos que codifica una proteína o un ARN también pueden incluir intrones en la medida en que la secuencia de nucleótidos que codifica la proteína puede contener un intrón(es)en alguna versión.

Los términos "cantidad eficaz" o "cantidad terapéuticamente eficaz" se utilizan indistintamente en la presente memoria, y se refieren a una cantidad de un compuesto, la formulación, material o composición, tal como se describe en el presente documento que es eficaz para conseguir un resultado biológico particular.

El término "endógeno" se refiere a cualquier material de o producido en un organismo, célula, tejido o sistema.

El término "exógeno" se refiere a cualquier material introducido desde o producido fuera de un organismo, célula, tejido o sistema.

El término "expresión" se refiere a la transcripción y/o traducción de una secuencia de nucleótidos particular dirigida por un promotor.

El término "vector de transferencia" se refiere a una composición de materia que comprende un ácido nucleico aislado y que puede ser utilizado para entregar el ácido nucleico aislado al interior de una célula. Numerosos vectores son conocidos en la técnica incluyendo, pero no limitado a, los polinucleótidos lineales, polinucleótidos asociados con compuestos iónicos o anfifílicos, plásmidos y virus. Por lo tanto, el término "vector de transferencia" incluye un plásmido de replicación autónoma o un virus. El término también debe interpretarse para incluir, además, compuestos no plásmidos y no virales que facilitan la transferencia de ácido nucleico en células, tales como, por ejemplo, un compuesto de polilisina, liposomas, y similares. Ejemplos de vectores de transferencia virales incluyen, pero no se limitan a, vectores

adenovirales, vectores de virus adeno-asociados, vectores retrovirales, vectores lentivirales, y similares.

El término "vector de expresión" se refiere a un vector que comprende un polinucleótido recombinante que comprende secuencias de control de expresión unidas operativamente a una secuencia de nucleótidos a expresar. Un vector de expresión comprende suficientes elementos que actúan en cis para la expresión; otros elementos para la expresión pueden ser suministrados por la célula hospedera o en un sistema de expresión in vitro. Los vectores de expresión incluyen todos los conocidos en la técnica, incluyendo cósmidos, plásmidos (por ejemplo, desnudos o contenidos en liposomas) y virus (por ejemplo, lentivirus, retrovirus, adenovirus y virus adeno-asociados) que incorporan el polinucleótido recombinante.

El término "lentivirus" se refiere a un género de la familia Retroviridae. Los lentivirus son únicos entre los retrovirus por ser capaces de infectar células que no se dividen; que pueden entregar una cantidad significativa de información genética en el ADN de la célula hospedera, por lo que son uno de los métodos más eficaces de un vector de suministro de gen. HIV, SIV, y FIV son todos ejemplos de lentivirus.

El término "vector lentiviral" se refiere a un vector derivado de al menos una porción de un genoma de lentivirus, incluyendo especialmente un vector lentiviral de auto-inactivación según se dispone en Milone et al., Mol. Ther. 17 (8): 1453-1464 (2009). Otros ejemplos de vectores de lentivirus que pueden ser utilizados en la práctica clínica, incluyen pero no se limitan a, por ejemplo, la tecnología LENTIVECTOR® de suministro de genes de Oxford BioMedica, el sistema vector LENTIMAX ™ de Lentigen y similares. También están disponibles tipos no clínicos de vectores lentivirales y serían conocidos por un experto en la técnica.

El término "homólogo" o "identidad" se refiere a la identidad de secuencia de la subunidad entre dos moléculas poliméricas, por ejemplo, entre dos moléculas de ácido nucleico, tales como, dos moléculas de ADN o dos moléculas de ARN, o entre dos moléculas de polipéptido. Cuando una posición de la subunidad en ambas de las dos moléculas está ocupada por la misma subunidad monomérica; por ejemplo, si una posición en cada una de dos moléculas de ADN está ocupada por adenina, entonces son homólogas o idénticas en esa posición. La homología entre dos secuencias es una función directa del número de posiciones coincidentes u homólogas; por ejemplo, si la mitad (por ejemplo, cinco posiciones en un polímero de diez subunidades de longitud) de las posiciones en dos secuencias son homólogas, las dos secuencias

son 50% homólogas; si el 90% de las posiciones (por ejemplo, 9 de 10), se emparejan u homólogas, las dos secuencias son 90% homólogas.

Las formas "humanizadas" de anticuerpos no humanos (por ejemplo, murinos) son inmunoglobulinas quiméricas, cadenas de inmunoglobulinas o fragmentos de las mismas (tales como Fv, Fab, Fab', $F(ab')_2$ u otras subsecuencias de unión a antígeno de los anticuerpos) que contienen una secuencia mínima derivada de inmunoglobulina no humana. En su mayor parte, los anticuerpos humanizados y fragmentos de anticuerpos de los mismos son inmunoglobulinas humanas (anticuerpo receptor o fragmento de anticuerpo) en la que losresiduos de una región determinante de la complementariedad (CDR) del receptor se sustituyen por residuos de una CDR de una especie no humana (anticuerpo donante) tal como ratón, rata o conejo que tiene la especificidad, afinidad y capacidad deseada. En algunos casos, la región marco Fv (FR) de residuos de la inmunoglobulina humana se sustituyen por los correspondientes residuos no humanos. Además, un fragmento de anticuerpo/anticuerpo humanizado puede comprender residuos que no se encuentran ni en el anticuerpo receptor ni en las secuencias CDR o marco importadas. Estas modificaciones pueden perfeccionar y optimizar el rendimiento del anticuerpo o fragmento. En general, el anticuerpo o fragmento de anticuerpo humanizado del mismo comprenderá sustancialmente todos de al menos uno, y típicamente dos, dominios variables, en los que todas o sustancialmente todas las regiones CDR corresponden a las de una inmunoglobulina no humana y todas o una porción significativa de las regiones FR son las de una secuencia de inmunoglobulina humana. El anticuerpo o fragmento de anticuerpo humanizado puede comprender también al menos una porción de una región constante de inmunoglobulina (Fc), típicamente la de una inmunoglobulina humana. Para más detalles, véase Jones et al, Nature, 321:. 522-525, 1986; Reichmann y otros, Nature, 332: 323-329, 1988;. Presta, Curr. Op. Struct. Biol., 2: 593-596, 1992.

"Completamente humano" se refiere a una inmunoglobulina, tal como un anticuerpo o fragmento de anticuerpo, en donde la molécula es de origen humano o consiste en una secuencia de aminoácidos idéntica a una forma humana del anticuerpo o inmunoglobulina.

El término "aislado" significa alterado o removido del estado natural. Por ejemplo, un ácido nucleico o un péptido de forma natural presente en un animal vivo no está "aislado", pero el mismo ácido nucleico o péptido parcial o completamente separado de los materiales coexistentes de su estado natural está "aislado". Un ácido nucleico aislado o proteína puede

existir en forma sustancialmente purificada, o puede existir en un ambiente no nativo tal como, por ejemplo, una célula hospedera.

En el contexto de la presente invención, se utilizan las siguientes abreviaturas para las bases de ácidos nucleicos que se presentan comúnmente. "A" se refiere a la adenosina, "C" se refiere a la citosina, "G" se refiere a guanosina, "T" se refiere a la timidina, y "T" se refiere a uridina.

El término "unido operativamente" o "control transcripcional" se refiere al enlace funcional entre una secuencia reguladora y una secuencia de ácido nucleico heteróloga que resulta en la expresión de este último. Por ejemplo, una primera secuencia de ácido nucleico está unida operativamente con una segunda secuencia de ácido nucleico cuando la primera secuencia de ácido nucleico se coloca en una relación funcional con la segunda secuencia de ácido nucleico. Por ejemplo, un promotor está unido operativamente a una secuencia codificante si el promotor afecta a la transcripción o expresión de la secuencia codificante. Las secuencias de ADN unidas operativamente pueden ser contiguas entre sí y, por ejemplo, cuando es necesario unir dos regiones codificantes de proteína, están en el mismo marco de lectura.

El término administración "parenteral" de una composición inmunogénica incluye, por ejemplo, la administración subcutánea (s.c.), intravenosa (i.v.), intramuscular (i.m.), o técnicas de inyección, intratumoral, o infusión intraesternal.

El término "ácido nucleico" o "polinucleótido" se refiere a los ácidos desoxirribonucleico (ADN) o ribonucleico (ARN) y polímeros de los mismos en forma mono- o bicatenaria. El término “ácido nucleico” incluye un gen, ADNc, o un ARNm. En una modalidad, la molécula de ácido nucléico es sintética (por ejemplo, químicamente sintetizada o recombinante). A menos que se limite específicamente, el término abarca ácidos nucleicos que contienen análogos o derivados de nucleótidos naturales que tienen propiedades de unión similares al ácido nucleico de referencia y se metabolizan de una manera similar a nucleótidos de origen natural. A menos que se indique lo contrario, una secuencia particular de ácido nucleico abarca también implícitamente variantes modificadas de manera conservadora del mismo (por ejemplo, sustituciones de codones degenerados), alelos, ortólogos, SNPs, y secuencias complementarias, así como la secuencia indicada explícitamente. Específicamente, las sustituciones de codones degenerados se pueden conseguir mediante la generación de secuencias en las que la tercera posición de uno o más seleccionados (o todos) los codones está sustituido con de base mixta y/o

residuos desoxiinosina (Batzer et al, Nucleic Acid Res. 19:. 5081 (1991); Ohtsuka et al, J. Biol Chem 260: 2605-2608 (1985); y Rossolini et al, Mol Cell Probes 8: 91-98 (1994)).

Los términos "péptido", "polipéptido" y "proteína" se utilizan indistintamente, y se refieren a un compuesto formado por residuos de aminoácidos unidos covalentemente por enlaces peptídicos. Una proteína o péptido debe contener al menos dos aminoácidos, y no de limitación se coloca en el número máximo de aminoácidos que pueden comprender la secuencia de un péptido o de proteína. Los polipéptidos incluyen cualquier péptido o proteína que comprende dos o más aminoácidos unidos entre sí por enlaces peptídicos. Tal como se utiliza aquí, el término se refiere tanto a cadenas cortas, que también comúnmente se hace referencia en la técnica como péptidos, oligopéptidos y oligómeros, por ejemplo, y a cadenas más largas, que generalmente se hace referencia en la técnica como proteínas, de las cuales hay muchos tipos. Los "Polipéptidos" incluyen, por ejemplo, fragmentos biológicamente activos, polipéptidos sustancialmente homólogos, oligopéptidos, homodímeros, heterodímeros, las variantes de polipéptidos, polipéptidos modificados, derivados, análogos, proteínas de fusión, entre otros. Un polipéptido incluye un péptido natural, un péptido recombinante, o una combinación de los mismos.

El término "promotor" se refiere a una secuencia de ADN reconocida por la maquinaria sintética de la célula, o maquinaria sintética introducida, requerida para iniciar la transcripción específica de una secuencia de polinucleótido.

El término "promotor / secuencia reguladora" se refiere a una secuencia de ácido nucleico que se requiere para la expresión de un producto génico operativamente unido a la secuencia promotora/reguladora. En algunos casos, esta secuencia puede ser la secuencia promotora central y en otros casos, esta secuencia también puede incluir una secuencia potenciadora y otros elementos reguladores que son necesarios para la expresión del producto génico. La secuencia promotora/ reguladora puede ser, por ejemplo, una que expresa el producto génico de una manera específica de tejido.

El término promotor "constitutivo" se refiere a una secuencia de nucleótidos que, cuando se une operativamente con un polinucleótido que codifica o especifica un producto génico, provoca que el producto del gen que se produce en una célula bajo la mayoría o todas las condiciones fisiológicas de la célula.

El término "inducible" promotor se refiere a una secuencia de nucleótidos que, cuando se une operativamente con un polinucleótido que codifica o especifica un producto génico, provoca que el producto del gen que se produce en una célula sustancialmente solo cuando está presente en un inductor que corresponde al promotor en la célula.

El término promotor "específico de tejido" se refiere a una secuencia de nucleótidos que, cuando se une operativamente con un polinucleótido que codifica o es especificado por un gen, provoca que el producto del gen que se produce en una célula sustancialmente solo si la célula es una célula del tipo de tejido que corresponde al promotor.

El término " enlazador flexible polipéptido " o "enlazador" como se usa en el contexto de un scFv se refiere a un enlazador peptídico que consiste en los aminoácidos tales como residuos de glicina y/o serina usados solos o en combinación, para enlazar las regiones variables de las cadenas ligera y pesada. En una realización, el enlazador flexible polipéptido es un enlazador Ser/Gly y comprende la secuencia de aminoácidos $(Gly\text{-}Gly\text{-}Gly\text{-}Ser)_n$, donde n es un entero positivo igual o mayor que 1. Por ejemplo, n= 1, n= 2, n = 3. n = 4, n = 5, n = 6, n = 7, n = 8, n = 9 y n = 10 (SEQ ID NO: 105). En una realización, los enlazadores flexibles polipeptídicos incluyen, pero no se limitan a, $(Gly_4\ Ser)_4$ (SEQ ID NO: 106) o $(Gly_4\ Ser)_3$ (SEQ ID NO: 107). En otra realización, los enlazadores incluyen múltiples repeticiones de (Gly_2Ser), (GlySer) o (Gly_3Ser) (SEQ ID NO: 108). También se incluyen dentro del alcance de la invención los enlazadores descritos en WO2012/138475, que se incorpora aquí por referencia.

Tal como se usa en este documento, una tapa 5' (también denominado una tapa de ARN, una tapa 7-metilguanosina ARN o una tapa de ARN m7G) es un nucleótido de guanina modificado que se ha añadido a la "parte delantera" o 5' de un ARN mensajero eucariota poco después del inicio de la transcripción. La tapa 5 'consiste en un grupo terminal que está vinculado al primer nucleótido transcrito. Su presencia es importante para el reconocimiento por el ribosoma y la protección contra RNasas. Además la tapa está acoplado a la transcripción, y se produce de manera co-transcripcional, de manera que cada uno influye en el otro. Poco después del inicio de la transcripción, el extremo 5 'del ARNm se sintetiza está obligado por un complejo sintetizador de la tapa asociado a la ARN polimerasa. Este complejo enzimático cataliza las reacciones químicas que se requieren para la limitación de ARNm. La síntesis procede como una reacción bioquímica de varios pasos. El resto de la limitación puede ser modificado para modular la funcionalidad del ARNm tales como su estabilidad o eficacia de la traducción.

En la presente memoria, "en el ARN transcrito in vitro" se refiere al ARN, por ejemplo ARNm, que se ha sintetizado in vitro. Generalmente, el ARN transcrito in vitro en que se genera a partir de un vector de transcripción in vitro. El vector de transcripción in vitro comprende una plantilla que se utiliza para generar el ARN transcrito in vitro.

Como se usa en este documento, un "poli (A)" es una serie de adenosinas unidos por poliadenilación al ARNm. En algunas modalidades de un constructo para la expresión transitoria, la poliA es de entre 50 y 5.000, (SEQ ID NO: 28), mayor que 64, popr ejemplo, mayor que 100, por ejemplo más que 300 o 400. Las secuencias de poli (A) pueden ser modificadas química o enzimáticamente para modular la funcionalidad del ARNm como la localización, la estabilidad o la eficiencia de la traducción.

Como se usa en este documento, "poliadenilación" se refiere a la unión covalente de un resto poliadenilil, o su variante modificada, a una molécula de ARN mensajero. En los organismos eucariotas, la mayoría de ARN mensajero (ARNm) las moléculas se poliadenilan en el extremo 3'. El 3'poli (A) de la cola es una secuencia larga de nucleótidos de adenina (a menudo varios cientos) añadida a la pre-ARNm a través de la acción de una enzima, la polimerasa de poliadenilato. En eucariotas superiores, se añade el poli (A) de la cola en las transcripciones que contienen una secuencia específica, la señal de poliadenilación. La cola de poli (A) y la proteína unida ayuda en la protección del ARNm de la degradación por exonucleasas. La poliadenilación también es importante para terminación de la transcripción, la exportación del ARNm desde el núcleo, y la traducción. La poliadenilación ocurre en el núcleo inmediatamente después de la transcripción de ADN en ARN, pero, además, también puede ocurrir más tarde en el citoplasma. Después que la transcripción se ha terminado, la cadena de ARNm se escinde mediante la acción de un complejo de endonucleasa asociada a la ARN polimerasa. El sitio de escisión se caracteriza generalmente por la presencia de la secuencia de bases AAUAAA cerca del sitio de escisión. Después de que el ARNm se ha escindido, los residuos de adenosina se añaden al extremo libre 3' en el sitio de escisión.

Como se usa en este documento, "transitoria" se refiere a la expresión de un transgén no integrado por un período de horas, días o semanas, en el que el período de tiempo de la expresión es menor que el período de tiempo para la expresión del gen si se integran en el genoma o están contenidos dentro de un plásmido replicón estable en la célula hospedera.

El término "vía de transducción de señales" se refiere a la relación bioquímica entre una

variedad de moléculas de transducción de señales que desempeñan un papel en la transmisión de una señal de una porción de una célula a otra parte de una célula. La frase "receptor de superficie celular" incluye moléculas y complejos de moléculas capaces de recibir una señal y la transmisión de señal a través de la membrana de una célula.

El término "sujeto" pretende incluir organismos vivos en los que una respuesta inmune puede ser obtenida (por ejemplo, mamíferos, humanos).

El término, una célula "sustancialmente purificada" se refiere a una célula que está esencialmente libre de otros tipos de células. Una célula sustancialmente purificada se refiere también a una célula que ha sido separada de otros tipos de células con las que se asocia normalmente en su estado de origen natural. En algunos casos, una población de células sustancialmente purificada se refiere a una población homogénea de células. En otros casos, este término se refiere simplemente a la célula que se ha separado de las células con las que están asociadas de forma natural en su estado natural. En algunos aspectos, las células se cultivan in vitro. En otros aspectos, las células no se cultivan in vitro.

El término "terapéutico" tal como se usa aquí, significa un tratamiento. Un efecto terapéutico se obtiene por reducción, supresión, remisión, o la erradicación de un estado de enfermedad.

El término "profilaxis", como se usa en este documento significa la prevención o el tratamiento de protección para un estado de enfermedad o enfermedad.

En el contexto de la presente invención, "antígeno tumoral" o "antígeno de trastorno hiperproliferativo" o "antígeno asociado con un trastorno hiperproliferativo" se refiere a antígenos que son comunes a trastornos hiperproliferativos específicos. En ciertos aspectos, los antígenos de trastorno hiperproliferativo de la presente invención se derivan de, cánceres que incluyen pero no se limitan a melanoma primario o metastásico, timoma, linfoma, sarcoma, cáncer de pulmón, cáncer de hígado, linfoma no de Hodgkin, linfoma de Hodgkin, leucemias, cáncer uterino, cáncer cervical, cáncer de vejiga, cáncer de riñón y adenocarcinomas tales como cáncer de mama, cáncer de próstata, cáncer de ovario, cáncer de páncreas, y similares.

El término "transfectada" o "transformado" o "transducidas" se refiere a un proceso por el cual el ácido nucleico exógeno se transfiere o se introduce en la célula hospedera. Una célula "transfectada" o "transformada" o "transducida" es una célula que ha sido transfectada,

transformada o transducida con ácido nucleico exógeno. La célula incluye la célula sujeto primaria y su progenie.

Un sujeto "responde" para el tratamiento si un parámetro de un cáncer (por ejemplo, un cáncer hematológico, por ejemplo, el crecimiento de células de cáncer, la proliferación y/o supervivencia) en el sujeto es retardado o reducido en una cantidad detectable, por ejemplo, aproximadamente 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% o más según se determina por cualquier medida adecuada, por ejemplo, en masa, recuento de células o el volumen. En un ejemplo, un sujeto responde al tratamiento si el sujeto experimenta una esperanza de vida extendida en alrededor de 5%, 10%, 20%, 30%, 40%, 50% o más allá de la esperanza de vida prevista si no se administra el tratamiento. En otro ejemplo, un sujeto responde al tratamiento, si el sujeto tiene un aumento de la supervivencia libre de enfermedad, supervivencia global o aumento del tiempo hasta la progresión. Varios métodos se pueden utilizar para determinar si un paciente responde a un tratamiento que incluye, por ejemplo, los criterios proporcionados por guías de práctica clínica de la NCCN en Oncología (NCCN Guidelines®). Por ejemplo, en el contexto de B-ALL, una respuesta completa o respuesta completa, puede incluir uno o más de: <5% blastocitos de BM,> 1000 neutrófilos / ANC (/ µl). > 100.000 plaquetas (/ µl) sin blastocitos circulantes o enfermedad extramedular (sin linfadenopatía, esplenomegalia, la piel / infiltración de goma / masa testicular / afectación del SNC), el trilinaje de hematopoyesis, y no se repitan durante 4 semanas. Una respuesta parcial puede implicar una o más de> 50% de reducción en el blastocitos de BM,> 1000 neutrófilos / ANC (/µl). > 100.000 plaquetas (/ µl). Un no-respondedor puede mostrar el progreso de la enfermedad, por ejemplo,> 25% en blastos deBM.

"Refractario", como se usa aquí se refiere a una enfermedad, por ejemplo, cáncer, que no responde a un tratamiento. En formas de realización, un cáncer refractario puede ser resistente a un tratamiento antes o en el inicio del tratamiento. En otras realizaciones, el cáncer refractario puede volverse resistente durante un tratamiento. Un cáncer resistente al tratamiento también se llama un cáncer resistente.

El término "recaída" tal como se utiliza aquí, se refiere a la reaparición de un cáncer después de un período inicial de respuesta (por ejemplo, la respuesta completa o respuesta parcial). El período inicial de la capacidad de respuesta puede implicar el nivel de las células de

cáncer que caen por debajo de un cierto umbral, por ejemplo, por debajo de 20%, 1%, 10%, 5%, 4%, 3%, 2%, o 1%. La reaparición puede implicar el nivel de células de cáncer de aumento por encima de un cierto umbral, por ejemplo, por encima de 20%, 1%, 10%, 5%, 4%, 3%, 2%, o 1%. Por ejemplo, por ejemplo, en el contexto de B-ALL, la reaparición puede implicar, por ejemplo, una reaparición de blastos en la sangre, médula ósea (> 5%), o cualquier sitio extramedular, después de una respuesta completa. Una respuesta completa, en este contexto, puede implicar <5% blastocitos en BM. Más en general, en una realización, una respuesta (por ejemplo, respuesta completa o respuesta parcial) puede implicar la ausencia de detectable MRD (enfermedad residual mínima). En una realización, el período inicial de la capacidad de respuesta tiene una duración de al menos 1, 2, 3, 4, 5, o 6 días; al menos 1, 2, 3, o 4 semanas; al menos 1, 2, 3, 4, 6, 8, 10, o 12 meses; o al menos 1, 2, 3, 4, o 5 años.

En algunas realizaciones, una terapia que incluye un inhibidor de CD19, por ejemplo, una terapia CAR CD19, pueden sufrir una recaída o refractarios al tratamiento. La recaída o resistencia pueden ser causados por la pérdida de CD19 (por ejemplo, una mutación de pérdida de antígeno) u otra alteración CD19 que reduce el nivel de CD19 (por ejemplo, causada por selección clonal de clones CD19-negativo). Un cáncer que alberga dicha pérdida o alteración CD19 se denomina aquí como un "cáncer de CD19-negativo" o un "cáncer recidivante-CD19 negativa"). Se entenderá que un cáncer CD19-negativas no necesita tener la pérdida de 100% de CD19, pero una reducción suficiente para reducir la eficacia de una terapia de CD19 de tal manera que las recaídas del cáncer o se vuelve refractaria. En algunas realizaciones, un CD19-negativas cáncer resulta de una terapia CAR CD19.

El término "se une específicamente" se refiere a un anticuerpo, o un ligando, que reconoce y se une con una pareja de unión (por ejemplo, un antígeno tumoral estimuladora) proteína presente en una muestra, pero que el anticuerpo o ligando no reconoce sustancialmente o se une otra moléculas en la muestra.

Tal como se utiliza aquí, el término "sal farmacéuticamente aceptable" se refiere a aquellas sales que son, dentro del alcance del juicio médico, adecuados para uso en contacto con los tejidos de los sujetos sin excesiva toxicidad, irritación, respuesta alérgica y similares, y son acorde con una relación riesgo/beneficio razonable. Las sales farmacéuticamente aceptables son bien conocidos en la técnica. Por ejemplo, Berge et al. describe sales farmacéuticamente aceptables en detalle en J. Pharmaceutical Sciences (1977) 66: 1-19.

"Receptor quimérico de antígeno regulable (RCAR)", como se usa ese término en el presente documento, se refiere a un conjunto de polipéptidos, típicamente dos en las realizaciones más simples, que cuando en una célula RCARX, proporciona la célula RCARX con especificidad para una célula diana, típicamente una célula de cáncer, y con generación de señales intracelulares regulable o la proliferación, que puede optimizar una propiedad de efector inmune de la célula RCARX. Una célula RCARX se basa al menos en parte, en un dominio de unión para proporcionar especificidad a una célula diana que comprende el antígeno unido por el dominio de unión a antígeno de antígeno. En una realización, un RCAR incluye un interruptor de dimerización que, en la presencia de una molécula de dimerización, se puede acoplar un dominio de señalización intracelular al antígeno dominio de unión.

"Anclaje de membrana" o "dominio tethering membrana", como ese término se usa en este documento, se refiere a un polipéptido o resto, por ejemplo, un grupo miristoilo, suficiente para anclar un dominio extracelular o intracelular de la membrana plasmática.

"Dominio interruptor," tal como ese término se utiliza en el presente documento, por ejemplo, cuando se hace referencia a un RCAR, se refiere a una entidad que, típicamente una entidad basada en polipéptido, que, en presencia de una molécula de la dimerización, se asocia con otro dominio interruptor. La asociación da como resultado un acoplamiento funcional de una primera entidad vinculada a, por ejemplo, fusionado a, un primer dominio de conmutación, y una segunda entidad vinculada a, por ejemplo, fusionado a, un segundo dominio de conmutación. Un primero y segundo dominio interruptor se denominan colectivamente como un interruptor de dimerización. En formas de realización, el primer y segundo dominios de conmutación son los mismos que el uno al otro, por ejemplo, que son polipéptidos que tienen la misma secuencia de aminoácidos primaria, y se denominan colectivamente como un interruptor de homodimerización. En formas de realización, el primer y segundo dominios de conmutación son diferentes una de otra, por ejemplo, que son polipéptidos que tienen diferentes secuencias de aminoácidos primaria, y se denominan colectivamente como un interruptor de heterodimerización. En formas de realización, el interruptor es intracelular. En formas de realización, el interruptor es extracelular. En formas de realización, el dominio de interruptor es una entidad basada en el polipéptido, por ejemplo, FKBP o basado en FRB, y la molécula de dimerización es pequeña molécula, por ejemplo, un rapalogo. En formas de realización, el dominio de interruptor es una entidad basada en polipéptido, por ejemplo, un scFv que se une un

péptido myc, y la molécula de dimerización es un polipéptido, un fragmento de la misma, o un multímero de un polipéptido, por ejemplo, un ligando myc o multímeros de un ligando myc que se unen a uno o más scFv myc. En formas de realización, el dominio de interruptor es una entidad basada en el polipéptido, por ejemplo, receptor myc, y la molécula de dimerización es un anticuerpo o fragmentos de los mismos, por ejemplo, anticuerpo myc.

"Molécula de dimerización", como se usa ese término en el presente documento, por ejemplo, cuando se hace referencia a un RCAR, se refiere a una molécula que promueve la asociación de un primer dominio interruptor con un segundo dominio de conmutación. En formas de realización, la molécula de dimerización no se produce de forma natural en el sujeto, o no se produce en concentraciones que resultarían en la dimerización significativo. En formas de realización, la molécula de dimerización es una molécula pequeña, por ejemplo, rapamicina o un rapalogo, por ejemplo, RAD001.

El término "dosis potenciadora inmunológica baja" cuando se usa en conjunción con un inhibidor de mTOR, por ejemplo, un inhibidor de mTOR alostérico, por ejemplo, RAD001 o rapamicina, o un inhibidor de mTOR catalítico, se refiere a una dosis de inhibidor de mTOR que parcialmente, pero no totalmente, inhibe la actividad de mTOR, por ejemplo, medida por la inhibición de la actividad de la quinasa P70 S6. Los métodos para evaluar la actividad de mTOR, por ejemplo, por la inhibición de P70 S6 quinasa, se discuten en este documento. La dosis es insuficiente para dar lugar a la supresión inmune completa, pero es suficiente para mejorar la respuesta inmune. En una realización, la dosis potenciadora inmunológica baja de los resultados de inhibidores de mTOR en una disminución en el número de células de PD-1 T positivas y/o un aumento en el número de células T PD-1 negativas, o un aumento en la proporción de células T PD-1 negativas / células T PD-1positivas. En una realización, la dosis potenciadora inmunológica baja es la dosis de los resultados de inhibidores de mTOR en un aumento en el número de células T vírgenes. En una realización, la dosis potenciadora inmunológica baja, es la dosis de los resultados de inhibidores de mTOR en uno o más de los siguientes:

un aumento en la expresión de uno o más de los siguientes marcadores: $CD62L^{alto}$, $CD127^{alto}$, CD27 +, y BCL2, por ejemplo, en las células T de memoria, por ejemplo, precursores de células T de memoria;

una disminución en la expresión de KLRG1, por ejemplo, en las células T de

memoria, por ejemplo, precursores de células T de memoria; y

un aumento en el número de precursores de células T de memoria, por ejemplo, las células con uno cualquiera o una combinación de las siguientes características: aumento de $CD62L^{alto}$, Aumento de $CD127^{alto}$, el aumento de CD27 +, disminución KLRG1, y el aumento de BCL2;

en el que se presenta cualquiera de los cambios descritos anteriormente, por ejemplo, al menos transitoriamente, por ejemplo, en comparación con un sujeto no tratado.

Rangos: a lo largo de esta descripción, los diversos aspectos de la invención pueden ser presentados en un formato de intervalo. Debe entenderse que la descripción en formato de rango es meramente por conveniencia y brevedad, y no debe interpretarse como una limitación inflexible sobre el alcance de la invención. En consecuencia, la descripción de un rango debe considerarse que tiene específicamente dado a conocer todos los subintervalos posibles, así como valores numéricos individuales dentro de ese rango. Por ejemplo, la descripción de un intervalo tal como de 1 a 6 se debe considerar por tener subintervalos específicamente descritos tales como 1-3, 1-4, 1-5, 2-4, 2-6, de 3 a 6 etc., así como los números individuales dentro de ese intervalo, por ejemplo, 1, 2, 2,7, 3, 4, 5, 5,3, y 6.Como otro ejemplo, un rango tal como 95 a 99% de identidad, incluye algo con 95%, 96%, 97%, 98% o 99% de identidad, e incluye los subintervalos tales como 96-99%, 96-98%, 96- 97%, 97-99%, 97-98% y 98-99% de identidad. Esto se aplica independientemente de la amplitud del rango.

Descripción

Inhibidores de CD19 y dominios de unión

Este documento presenta composiciones de materia y métodos de uso para el tratamiento de una enfermedad como el cáncer usando receptores quiméricos de antígeno (CAR) de CD19. Los métodos incluyen, entre otros, la administración de un CAR de CD19 descrito en el presente documento en combinación con otro agente, tal como un inhibidor de células B. Los métodos también incluyen, por ejemplo, administrar un CAR de CD19 descrito en el presente documento para el tratamiento de un linfoma, tal como un linfoma de Hodgkin.

En un aspecto, la invención proporciona un número de receptores quiméricos de antígeno

(CAR) que comprenden un anticuerpo o un fragmento de anticuerpo modificado para unirse específicamente a una proteína CD19. En un aspecto, la invención proporciona una célula (por ejemplo, una célula T) modificada para expresar un CAR, donde la célula T CAR ("TCAR") exhibe una propiedad antitumoral. En un aspecto, una célula se transforma con el CAR y el CAR se expresa en la superficie celular. En algunas modalidades, la célula (por ejemplo, una célula T) se transduce con un vector viral que codifica un CAR. En algunas modalidades, el vector viral es un vector retroviral. En algunas modalidades, el vector viral es un vector lentiviral. En algunas de dichas modalidades, la célula puede expresar el CAR de forma estable. En otra modalidad, la célula (por ejemplo, una célula T) se transfecta con un ácido nucleico, por ejemplo, ARNm, ADNc o ADN, que codifica un CAR. En algunas de dichas modalidades, la célula puede expresar el CAR de forma transitoria.

En un aspecto, la porción de unión a la proteína anti-CD19 del CAR es un fragmento de anticuerpo scFv. En un aspecto, dichos fragmentos de anticuerpo son funcionales en tanto que retienen la afinidad de unión equivalente, por ejemplo, unen el mismo antígeno con una afinidad comparable a la del anticuerpo de IgG del cual se derivan. En un aspecto, dichos fragmentos de anticuerpo son funcionales en tanto que proporcionan una respuesta biológica que puede incluir, de manera enunciativa más no limitativa, la activación de una respuesta inmune, la inhibición del origen de transducción de señales de su antígeno blanco, la inhibición de la actividad quinasa, y similares, como lo entenderá un experto en la materia. En un aspecto, el dominio de unión a antígeno anti-CD19 del CAR es un fragmento de anticuerpo scFv que es humanizado en comparación con la secuencia murina del scFv del cual se deriva. En un aspecto, la secuencia del scFv murino parental es el constructo de CAR19 proporcionada en la publicación PCT WO2012/079000 y presentada en el presente documento como SEQ ID NO.: 59. En una modalidad, el dominio de unión anti-CD19 es un scFv descrito en WO2012/079000 y proporcionado en SEQ ID NO.: 59, o una secuencia al menos 95 %, por ejemplo, entre 95 % y 99 %, idéntica a la misma. En una modalidad, el dominio de unión anti-CD19 es parte de un constructo de CAR proporcionado en la publicación PCT WO2012/079000 y presentado en el presente documento como SEQ ID NO.: 58, o una secuencia al menos 95 %, por ejemplo, entre 95 % y 99 %, idéntica a la misma. En una modalidad, el dominio de unión anti-CD19 comprende al menos una (por ejemplo, 2, 3, 4, 5 o 6) CDR seleccionadas de la **Tabla 4** y/o la **Tabla 5**.

En algunos aspectos, los anticuerpos de la invención se incorporan a un receptor quimérico de antígeno (CAR). En un aspecto, el CAR comprende la secuencia de polipéptido proporcionada como SEQ ID NO.: 12 en la publicación PCT WO2012/079000, y presentada en el presente documento como SEQ ID NO.: 58, donde el dominio scFv está sustituido por una o más secuencias seleccionadas de entre SEQ ID NO.: 1-12. En un aspecto, los dominios scFv de SEQ ID NO.: 1-12 son variantes humanizadas del dominio scFv de SEQ ID NO.: 59, que es un fragmento scFv de origen murino que se une específicamente a CD19 humana. La humanización de este scFv murino puede ser deseable para el entorno clínico, donde los residuos específicos de ratón pueden inducir una respuesta al antígeno humano anti-murino (HAMA) en pacientes que reciben tratamiento con TCAR19, por ejemplo, tratamiento con células T transducidas con el constructo de CAR19.

En un aspecto, la porción de unión a la proteína anti-CD19, por ejemplo, scFv humanizado, del CAR de la invención está codificada por un transgén cuya secuencia ha sido sometida a optimización de codones para expresión en una célula de mamífero. En un aspecto, todo el constructo de CAR de la invención está codificado por un transgén cuya secuencia completa ha sido sometida a optimización de codones para expresión en una célula de mamífero. La optimización de codones se refiere al descubrimiento de que la frecuencia de aparición de codones sinónimos (es decir, codones que codifican para el mismo aminoácido) en la codificación de ADN está sesgada en diferentes especies. Dicha degeneración de codones permite la codificación de un polipéptido idéntico por una variedad de secuencias de nucleótidos. Una variedad de métodos de optimización de codones se conoce en la técnica, e incluyen, por ejemplo, métodos descritos en al menos las Patentes de Estados Unidos No. 5,786,464 y 6,114,148.

En un aspecto, el CAR19 humanizado comprende la porción scFv proporcionada en la SEQ ID NO.: 1. En un aspecto, el CAR19 humanizado comprende la porción scFv proporcionada en la SEQ ID NO.: 2. En un aspecto, el CAR19 humanizado comprende la porción scFv proporcionada en la SEQ ID NO.: 3. En un aspecto, el CAR19 humanizado comprende la porción scFv proporcionada en la SEQ ID NO.: 4. En un aspecto, el CAR19 humanizado comprende la porción scFv proporcionada en la SEQ ID NO.: 5. En un aspecto, el CAR19 humanizado comprende la porción scFv proporcionada en la SEQ ID NO.: 6. En un aspecto, el CAR19 humanizado comprende la porción scFv proporcionada en la SEQ ID NO.: 7.

En un aspecto, el CAR19 humanizado comprende la porción scFv proporcionada en la SEQ ID NO.: 8. En un aspecto, el CAR19 humanizado comprende la porción scFv proporcionada en la SEQ ID NO.: 9. En un aspecto, el CAR19 humanizado comprende la porción scFv proporcionada en la SEQ ID NO.: 10. En un aspecto, el CAR19 humanizado comprende la porción scFv proporcionada en la SEQ ID NO.: 11. En un aspecto, el CAR19 humanizado comprende la porción scFv proporcionada en la SEQ ID NO.: 12.

En un aspecto, los CAR de la invención combina un dominio de unión a antígeno de un anticuerpo específico con una molécula de señalización intracelular. Por ejemplo, en algunos aspectos, la molécula de señalización intracelular incluye, de manera enunciativa mas no limitativa, los módulos de señalización de la cadena CD3 zeta, 4-1BB y CD28, y combinaciones de los mismos. En un aspecto, el CAR de CD19 comprende un vehículo seleccionado de la secuencia proporcionada en una o más SEQ ID NO.: 31 - 42. En un aspecto, el CAR de CD19 comprende la secuencia proporcionada en SEQ ID NO.: 31. En un aspecto, el CAR de CD19 comprende la secuencia proporcionada en SEQ ID NO.: 32. En un aspecto, el CAR de CD19 comprende la secuencia proporcionada en SEQ ID NO.: 33. En un aspecto, el CAR de CD19 comprende la secuencia proporcionada en SEQ ID NO.: 34. En un aspecto, el CAR de CD19 comprende la secuencia proporcionada en SEQ ID NO.: 35. En un aspecto, el CAR de CD19 comprende la secuencia proporcionada en SEQ ID NO.: 36. En un aspecto, el CAR de CD19 comprende la secuencia proporcionada en SEQ ID NO.: 37. En un aspecto, el CAR de CD19 comprende la secuencia proporcionada en SEQ ID NO.: 38. En un aspecto, el CAR de CD19 comprende la secuencia proporcionada en SEQ ID NO.: 39. En un aspecto, el CAR de CD19 comprende la secuencia proporcionada en SEQ ID NO.: 40. En un aspecto, el CAR de CD19 comprende la secuencia proporcionada en SEQ ID NO.: 41. En un aspecto, el CAR de CD19 comprende la secuencia proporcionada en SEQ ID NO.: 42.

Por lo tanto, en un aspecto, el dominio de unión a antígeno comprende un anticuerpo o un fragmento de anticuerpo humanizado. En una modalidad, el dominio de unión anti-CD19 humanizado comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena ligera (LC CDR1), la región 2 determinante de la complementariedad de cadena ligera (LC CDR2), la región 3 determinante de la complementariedad de cadena ligera (LC CDR3) de un dominio de unión anti-CD19 murino o humanizado descrito en el presente documento, y/o una o más (por ejemplo, las tres) de la región

1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión anti-CD19 murino o humanizado descrito en el presente documento, por ejemplo, un dominio de unión anti-CD19 humanizado que comprende una o más, por ejemplo, las tres, LC CDR y una o más, por ejemplo, las tres, HC CDR. En una modalidad, el dominio de unión anti-CD19 humanizado comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión anti-CD19 murino o humanizado descrito en el presente documento, por ejemplo, el dominio de unión anti-CD19 humanizado tiene dos regiones variables de cadena pesada, cada una de las cuales comprende una HC CDR1, una HC CDR2 y una HC CDR3 descritas en el presente documento. En una modalidad, el dominio de unión anti-CD19 humanizado comprende una región variable de cadena ligera humanizada descrita en el presente documento (por ejemplo, en la **Tabla 2**) y/o una región variable de cadena pesada humanizada descrita en el presente documento (por ejemplo, en la **Tabla 2**). En una modalidad, el dominio de unión anti-CD19 humanizado comprende una región variable de cadena pesada humanizada descrita en el presente documento (por ejemplo, en la **Tabla 2**), por ejemplo, al menos dos regiones variables de cadena pesada humanizadas descritas en el presente documento (por ejemplo, en la **Tabla 2**). En una modalidad, el dominio de unión anti-CD19 es un scFv que comprende una cadena ligera y una cadena pesada de una secuencia de aminoácidos de las **Tabla 2**. En una modalidad, el dominio de unión anti-CD19 (por ejemplo, un scFv) comprende: una región variable de cadena ligera que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena ligera proporcionada en la **Tabla 2**, o una secuencia con 95-99 % de identidad frente una secuencia de aminoácidos de la **Tabla 2**; y/o una región variable de cadena pesada que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena pesada proporcionada en la **Tabla 2**, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de la **Tabla 2** En una

modalidad, el dominio de unión anti-CD19 humanizado comprende una secuencia seleccionada de un grupo que consiste en SEQ ID NO.: 1, SEQ ID NO.: 2, SEQ ID NO.: 3, SEQ ID NO.: 4, SEQ ID NO.: 5, SEQ ID NO.: 6, SEQ ID NO.: 7, SEQ ID NO.: 8, SEQ ID NO.: 9, SEQ ID NO.: 10, SEQ ID NO.: 11 y SEQ ID NO.: 12, o una secuencia con 95-99 % de identidad frente a las mismas. En una modalidad, la secuencia de ácido nucleico que codifica el dominio de unión anti-CD19 humanizado comprende una secuencia seleccionada de un grupo que consiste en SEQ ID NO.: 61, SEQ ID NO.: 62, SEQ ID NO.: 63, SEQ ID NO.: 64, SEQ ID NO.: 65, SEQ ID NO.: 66, SEQ ID NO.: 67, SEQ ID NO.: 68, SEQ ID NO.: 70, SEQ ID NO.: 71 y SEQ ID NO.: 72, o una secuencia con 95-99 % de identidad frente a las mismas. En una modalidad, el dominio de unión anti-CD19 humanizado es un scFv, y una región variable de cadena ligera que comprende una secuencia de aminoácidos descrita en el presente documento, por ejemplo, en la **Tabla 2**, se une a una región variable de cadena pesada que comprende una secuencia de aminoácidos descrita en el presente documento, por ejemplo, en la **Tabla 2**, a través de un enlazador, por ejemplo, un enlazador descrito en el presente documento. En una modalidad, el dominio de unión anti-CD19 humanizado incluye un enlazador $(Gly_4\text{-}Ser)n$, en el que n es 1, 2, 3, 4, 5 o 6, preferiblemente 3 o 4 (SEQ ID NO.: 53). La región variable de cadena ligera y la región variable de cadena pesada de un scFv pueden estar, por ejemplo, en cualquiera de las siguientes orientaciones: región variable de cadena ligera-enlazador-región variable de cadena pesada o región variable de cadena pesada-enlazador-región variable de cadena ligera.

En un aspecto, la porción del dominio de unión a antígeno comprende una o más secuencias seleccionadas de SEQ ID NO.: 1-12. En un aspecto, el CAR humanizado se selecciona de una o más secuencias seleccionadas de SEQ ID NO.: 31-42. En algunos aspectos, un anticuerpo no humano es humanizado, donde secuencias o regiones específicas del anticuerpo se modifican para aumentar la similitud con un anticuerpo, o un fragmento del mismo, producido de manera natural en un ser humano.

En una modalidad, La molécula de CAR comprende un dominio de unión a antígeno que comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena ligera (LC CDR1), la región 2 determinante de la complementariedad de cadena ligera (LC CDR2), la región 3 determinante de la complementariedad de cadena ligera (LC CDR3) de un dominio de unión anti-CD19 murino o humanizado descrito en el presente documento, y/o una o más (por ejemplo, las tres) de la región

1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión anti-CD19 murino o humanizado descrito en el presente documento, por ejemplo, un dominio de unión anti-CD19 humanizado que comprende una o más, por ejemplo, las tres, LC CDR y una o más, por ejemplo, las tres, HC CDR. En una modalidad, el dominio de unión anti-CD19 humanizado comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión anti-CD19 murino o humanizado descrito en el presente documento, por ejemplo, el dominio de unión anti-CD19 humanizado tiene dos regiones variables de cadena pesada, cada una de las cuales comprende una HC CDR1, una HC CDR2 y una HC CDR3 descritas en el presente documento.

En un aspecto, el dominio de unión anti-CD19 se caracteriza por unas propiedades funcionales particulares de un anticuerpo o de un fragmento de anticuerpo. Por ejemplo, en un aspecto, la porción de una composición de CAR d ela invención que comprende un dominio de unión a antígeno se une específicamente a CD19 humano. En un aspecto, la invención se refiere a un dominio de unión a antígeno que comprende un anticuerpo o fragmento de anticuerpo, en el que el dominio de unión a anticuerpo se une específicamente a una proteína CD19 o fragmento de la misma, donde el anticuerpo o fragmento de anticuerpo comprende una cadena variable ligera y/o una cadena variable pesada que incluye una secuencia de aminoácidos de SEQ ID NO.: 1-12 o SEQ ID NO: 59. En un aspecto, la porción del dominio de unión a antígeno comprende una secuencia de aminoácidos seleccionada de SEQ ID NO.: 1-12 o SEQ ID NO: 59. En ciertos aspectos, el scFv es contiguo y está en el mismo marco de lectura que una secuencia líder. En un aspecto, la secuencia líder es la secuencia del polipéptido proporcionada como SEQ ID NO.: 13.

En un aspecto, la porción del CAR que comprende el dominio de unión a antígeno comprende un dominio de unión a antígeno que se dirige a CD19. En un aspecto, el dominio de unión a antígeno se dirige a CD19 humana. En un aspecto, el dominio de unión a antígeno del CAR tiene la misma especificidad de unión o una especificidad de unión similar a la del fragmento scFv FMC63 descrito en Nicholson et al. Mol. Immun. 34 (16-17): 1157-1165

(1997). En una modalidad, el dominio de unión a antígeno del CAR incluye el fragmento scFv que se describe en Nicholson et al. Mol. Immun. 34 (16-17): 1157-1165 (1997). En un aspecto, la porción del CAR que comprende el dominio de unión a antígeno comprende un dominio de unión a antígeno que se dirige a un antígeno de células B, por ejemplo, un antígeno de células B humano. Una molécula de anticuerpo CD19 puede ser, por ejemplo, una molécula de anticuerpo (por ejemplo, una molécula de anticuerpo anti-CD19 humanizado) descrita en WO2014/153270, el cual se incluye en su totalidad en el presente documento a manera de referencia. WO2014/153270 también describe métodos para someter a ensayo la unión y la eficacia de diversos constructos de TCAR.

En una modalidad, el dominio de unión anti-CD19 comprende una región variable de cadena ligera murina descrita en el presente documento (por ejemplo, en la **Tabla 3**) y/o una región variable de cadena pesada murina descrita en el presente documento (por ejemplo, en la **Tabla 3**). En una modalidad, el dominio de unión anti-CD19 es un scFv que comprende una cadena ligera murina y una cadena pesada murina de una secuencia de aminoácidos de la **Tabla 3**. En una modalidad, el dominio de unión anti-CD19 (por ejemplo, un scFv) comprende: una región variable de cadena ligera que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena ligera proporcionada en la **Tabla 3**, o una secuencia con 95-99 % de identidad frente una secuencia de aminoácidos de la **Tabla 3**; y/o una región variable de cadena pesada que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena pesada proporcionada en la **Tabla 3**, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de la **Tabla 3** En una modalidad, el dominio de unión anti-CD19 comprende una secuencia de SEQ ID NO.: 59, o una secuencia con 95-99 % de identidad frente a la misma. En una modalidad, el dominio de unión anti-CD19 es un scFv, y una región variable de cadena ligera que comprende una secuencia de aminoácidos descrita en el presente documento, por ejemplo, en la **Tabla 3**, se une a una región variable de cadena pesada que comprende una secuencia de aminoácidos descrita en este documento, por ejemplo, en la **Tabla 3**, a través de un enlazador, por ejemplo, un enlazador descrito en el presente documento. En una modalidad, el dominio de unión anti-CD19 incluye un enlazador $(Gly_4\text{-}Ser)n$, en el que n es 1, 2,

3, 4, 5 o 6, preferiblemente 3 o 4 (SEQ ID NO.: 53). La región variable de cadena ligera y la región variable de cadena pesada de un scFv pueden estar, por ejemplo, en cualquiera de las siguientes orientaciones: región variable de cadena ligera-enlazador-región variable de cadena pesada o región variable de cadena pesada-enlazador-región variable de cadena ligera.

Además, la presente invención proporciona (entre otras cosas) composiciones de CAR de CD19, opcionalmente en combinación con un inhibidor de células B, y su uso en medicamentos o métodos para tratar, entre otras enfermedades, cáncer o cualquier tumor maligno o enfermedades autoinmunes que involucran células o tejidos que expresan CD19.

En un aspecto, el CAR de la invención se puede usar para erradicar células normales que expresan CD19, y por lo tanto se puede usar como una terapia de acondicionamiento celular previa al trasplante de células. En un aspecto, la célula normal que expresa CD19 es una célula madre normal que expresa CD19 y el trasplante de células es un trasplante de células madre.

En un aspecto, la invención proporciona una célula (por ejemplo, una célula T) modificada para expresar un receptor quimérico de antígeno (CAR), donde la célula que expresa CAR, por ejemplo, célula T de CAR ("TCAR") exhibe una propiedad antitumoral. Un antígeno preferido es CD19. En un aspecto, el dominio de unión a antígeno del CAR comprende un fragmento de anticuerpo anti-CD19 parcialmente humanizado. En un aspecto, el dominio de unión a antígeno del CAR comprende un fragmento de anticuerpo anti-CD19 parcialmente humanizado que comprende un scFv. En consecuencia, la invención proporciona (entre otras cosas) un CAR de CD19 que comprende un dominio de unión anti-CD19 humanizado y ha sido modificado en una célula efectora inmune, por ejemplo, una célula T o una célula NK, y los métodos de su uso para terapia adoptiva con NK.

En un aspecto, el CAR, por ejemplo, CAR de CD19, comprende al menos un dominio intracelular seleccionado del grupo de un dominio de señalización de CD137 (4-1BB), un dominio de señalización de CD28, un dominio de señalización de CD3 zeta, y cualquier combinación de los mismos. En un aspecto, el CAR, por ejemplo, el CAR de CD19, comprende al menos un dominio de señalización intracelular de una o más moléculas coestimuladoras diferentes de CD137 (4-1BB) o CD28.

La presente invención abarca, de manera enunciativa más no limitativa, un constructo de ADN recombinante que comprende secuencias que codifican un CAR, donde el CAR

comprende un anticuerpo o fragmento de anticuerpo que se une específicamente a CD19, CD10, CD20, CD22, CD34, CD123, FLT-3, o ROR1, por ejemplo, CD19 humano, CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1, donde la secuencia del fragmento de anticuerpo es contigua y está en el mismo marco de lectura de una secuencia de ácido nucleico que codifica un dominio de señalización intracelular. El dominio de señalización intracelular puede comprender un dominio coestimulador de señalización y/o un dominio primario de señalización, por ejemplo, una cadena de zeta. El dominio coestimulador de señalización se refiere a una porción del CAR que comprende al menos una porción del dominio intracelular de una molécula coestimuladora. En una modalidad, el dominio de unión a antígeno es un anticuerpo o fragmento de anticuerpo murino descrito en el presente documento. En una modalidad, el dominio de unión a antígeno es un anticuerpo o fragmento de anticuerpo humanizado.

En aspectos específicos, un constructo de CAR de la invención comprende un dominio scFv seleccionado del grupo que consiste en SEQ ID NO.: 31-12, donde el scFv puede estar precedido por una secuencia líder opcional tal como la proporcionada en SEQ ID NO.: 13, y seguido por una secuencia de bisagra opcional tal como la proporcionada en SEQ ID NO.:14 o SEQ ID NO.: 45 o SEQ ID NO.: 47 o SEQ ID NO.: 49, una región transmembrana tal como la proporcionada en SEQ ID NO.: 15, un dominio de señalización intracelular que incluye SEQ ID NO.: 16 o SEQ ID NO.: 51 y una secuencia de CD3 zeta que incluye SEQ ID NO.: 17 o SEQ ID NO.: 43, donde los dominios son contiguos y están en el mismo marco de lectura para formar una proteína de fusión única. También se incluye en la invención (entre otras cosas) una secuencia de nucleótidos que codifica el polipéptido de cada uno de los fragmentos scFv seleccionados del grupo que consiste en SEQ NO.: 1, SEQ ID NO.: 2, SEQ ID NO.: 3, SEQ ID NO.: 4, SEQ ID NO.: 5, SEQ IS NO.: 6, SEQ ID NO.: 7, SEQ ID NO.: 8, SEQ ID NO.: 9, SEQ ID NO.: 10, SEQ ID NO.: 11, SEQ ID NO.: 12 y SEQ ID NO.: 59. También se incluye en la invención (entre otras cosas) una secuencia de nucleótidos que codifica el polipéptido de cada uno de los fragmentos scFv seleccionados del grupo que consiste en SEQ NO.: 1, SEQ ID NO.: 2, SEQ ID NO.: 3, SEQ ID NO.: 4, SEQ ID NO.: 5, SEQ IS NO.: 6, SEQ ID NO.: 7, SEQ ID NO.: 8, SEQ ID NO.: 9, SEQ ID NO.: 10, SEQ ID NO.: 11, SEQ ID NO.: 12 y SEQ ID NO.: 59, y cada uno de los dominios de SEQ ID NO.: 13 a 17, además de una proteína de fusión a CAR de CD19 codificada de la invención. En un aspecto, un ejemplo de constructo de CAR de CD19 comprende una secuencia líder opcional, un dominio de unión a antígeno extracelular, una bisagra, un dominio transmembrana y un dominio estimulador intracelular. En un aspecto, un

ejemplo de constructo de CAR de CD19 comprende una secuencia líder opcional, un dominio de unión a antígeno extracelular, una bisagra, un dominio transmembrana, un dominio coestimulador intracelular y un dominio estimulador intracelular. En algunas modalidades, constructos de CAR de CD19 específicos que contienen dominios scFv humanizados de la invención se proporcionan como SEQ ID NOS: 31-42, o un dominio scFv murino se proporciona como SEQ ID NO.: 59.

Secuencias de CAR de longitud completa también se proporcionan en el presente documento como SEQ ID NO.: 31-42 y 58, tal como se muestra en la **Tabla 2** y la **Tabla 3**.

Un ejemplo de secuencia líder se proporciona como SEQ ID NO.: 13. Un ejemplo de secuencia de bisagra/espaciador se proporciona como SEQ ID NO.: 14 o SEQ ID NO.: 45 o SEQ ID NO.: 47 o SEQ ID NO.: 49. Un ejemplo de secuencia de dominio transmembrana se proporciona como SEQ ID NO.: 15. Un ejemplo de secuencia de dominio de señalización intracelular de la proteína 4-1BB se proporciona como SEQ ID NO.: 16. Un ejemplo de secuencia de dominio de señalización intracelular de CD27 se proporciona como SEQ ID NO.: 51. Un ejemplo de secuencia de dominio de CD3 zeta se proporciona como SEQ ID NO.: 17 o SEQ ID NO.: 43. Estas secuencias se pueden usar, por ejemplo, en combinación con un scFv que reconoce una o más de CD19, CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1.

Las secuencias ejemplares de diferentes fragmentos scFv y otros componentes de automóviles se proporcionan en este documento. Cabe mencionar que estos componentes de CAR (por ejemplo, de SEQ ID NO.: 121, o una secuencia de la **Tabla 2, 3, 6, 11A, 11B, 16 o 25**) sin una secuencia líder (por ejemplo, sin la secuencia de aminoácidos de SEQ ID NO.: 13 o una secuencia de nucleótidos de SEQ ID NO.: 54), también se proporcionan en el presente documento.

En algunas modalidades, las secuencias de CAR descritas en el presente documento contienen un cambio de residuo Q/K en el dominio de señalización del dominio coestimulador derivado de la cadena CD3 zeta.

En un aspecto, la presente invención abarca un constructo de ácido nucleico recombinante que comprende una molécula de ácido nucleico que codifica un CAR, donde la molécula de ácido nucleico comprende la secuencia de ácido nucleico que codifica un dominio de unión anti-CD19, por ejemplo, tal como el descrito en el presente documento, que es

contiguo y está en el mismo marco de lectura de la secuencia de ácido nucleico que codifica un dominio de señalización intracelular. En un aspecto, el dominio de unión anti-CD19 se selecciona de una o más de SEQ ID NO.: 1-12 y 58. En un aspecto, el dominio de unión anti-CD19 está codificado por un residuo de nucleótidos 64 a 813 de la secuencia proporcionada en una o más de SEQ ID NO.: 61-72 y 97. En un aspecto, el dominio de unión anti-CD19 está codificado por un residuo de nucleótidos 64 a 813 de SEQ ID NO.: 61. En un aspecto, el dominio de unión anti-CD19 está codificado por un residuo de nucleótidos 64 a 813 de SEQ ID NO.: 62. En un aspecto, el dominio de unión anti-CD19 está codificado por un residuo de nucleótidos 64 a 813 de SEQ ID NO.: 63. En un aspecto, el dominio de unión anti-CD19 está codificado por un residuo de nucleótidos 64 a 813 de SEQ ID NO.: 64. En un aspecto, el dominio de unión anti-CD19 está codificado por un residuo de nucleótidos 64 a 813 de SEQ ID NO.: 65. En un aspecto, el dominio de unión anti-CD19 está codificado por un residuo de nucleótidos 64 a 813 de SEQ ID NO.: 66. En un aspecto, el dominio de unión anti-CD19 está codificado por un residuo de nucleótidos 64 a 813 de SEQ ID NO.: 67. En un aspecto, el dominio de unión anti-CD19 está codificado por un residuo de nucleótidos 64 a 813 de SEQ ID NO.: 68. En un aspecto, el dominio de unión anti-CD19 está codificado por un residuo de nucleótidos 64 a 813 de SEQ ID NO.: 69. En un aspecto, el dominio de unión anti-CD19 está codificado por un residuo de nucleótidos 64 a 813 de SEQ ID NO.: 70. En un aspecto, el dominio de unión anti-CD19 está codificado por un residuo de nucleótidos 64 a 813 de SEQ ID NO.: 71. En un aspecto, el dominio de unión anti-CD19 está codificado por un residuo de nucleótidos 64 a 813 de SEQ ID NO.: 72.

Se proporcionan en la presente inhibidores de CD19 y terapiasde combinación. En algunas modalidades, el inhibidor de CD19 (por ejemplo, una terapia celular o un anticuerpo) se administra en combinación con un inhibidor de células B, por ejemplo, uno o más inhibidores de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, o ROR1. Un inhibidor de CD19 incluye pero no s elimita a una célula que expresa un CAR-CD19, por ejemplo una célula T CAR CD19, o un anticuerpo anti-CD19 (por ejemplo, un anticuerpo anti-CD19 mono o biespecífico) o un fragmento o conjugado del mismo. En una modlaidad, el inhibidor de CD19 se administra en cobinación con un inhibidor de células B, por ejemplo, una célula que expresa CAR descrita en el presente documento.

La presente divulgación describe un gran número de células que expresan CAR de

CD19. Por ejemplo, en algunas modalidades, un inhibidor de CD19 incluye una célula que expresa un CAR anti-CD19, por ejemplo, TCAR, por ejemplo, una célula que expresa un constructo de CAR anti-CD19 descrita en la **Tabla 2,** o codificada por un CAR de unión a CD19 que comprende un scFv, CDR o cadenas VH y VL descritos en las **Tablas 2, 4** o **5**. Por ejemplo, una célula que expresa un CAR anti-CD19, por ejemplo, TCAR, es una célula generada a través de la adaptación de un CAR de CD19 (que comprende un dominio de unión a CD19) en una célula (por ejemplo, una célula T o célula NK), por ejemplo, para la administración en combinación con una célula que expresa un CAR descrita en el presente documento. El presente documento también proporciona métodos de uso de las células que expresan CAR descritas en el presente documento para la terapia adoptiva.

En una modalidad, un dominio d eunión a antígeno comprende una, dos, tres, (por ejemplo las tres) CDRs de cadena pesada HC CDR1, HC CDR2 y HC CDR3, de un anticuerpo listado en el presente documento, por ejemplo en la **Tabla 2, 4 o 5** y/o una, dos, tres (por ejemplo, las tres) CDRs de cadena ligera LC CDR1, LC CDR2 y LC CDR3, de un anticuerpo listado en el presente documento, por ejemplo en la **Tabla 2, 4 o 5**. En una modalidad el dominio de unión al antígeno comprende una región variable de la cadena pesada y/o una región variable de la cadena ligera de un anticuerpo enunciaso o descrito en el presente documento.

En una modalidad, el dominio de unión a CD19 (por ejemplo, un scFv) comprende: una región variable de cadena ligera que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena ligera proporcionada en la **Tabla 2**, o una secuencia con 95-99 % de identidad frente una secuencia de aminoácidos de la **Tabla 2**; y/o una región variable de cadena pesada que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena pesada proporcionada en la **Tabla 2**, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de la **Tabla 2**. En algunas modalidades, el dominio de unión a CD19 comprende una o más CDR (por ejemplo, una de cada una de HC CDR1, CDR2 HC, HC CDR3, LC CDR1, LC CDR2 y LC CDR3) de la **Tabla 4** o la **Tabla 5**, o CDR que tienen una, dos, tres, cuatro, cinco o seis modificaciones (por ejemplo, sustituciones) de una o más de las CDR.

Ejemplos de anticuerpos anti-CD19 o fragmentos o conjugados de los mismos incluyen, de manera enunciativa mas no limitativa, SAR3419 (Sanofi), MEDI-551 (MedImmune LLC), Combotox, DT2219ARL (Masonic Cancer Center), MOR-208 (también llamado XmAb-5574; MorphoSys), XmAb-5871 (Xencor), MDX-1342 (Bristol-Myers Squibb), SGN-CD19A (Seattle Genetics), y AFM11 (Affimed Terapéutica). Véase, por ejemplo, Hammer. MAbs. 4.5 (2012): 571–77. Blinatomomab es un anticuerpo biespecífico compuesto de dos scFv, uno que se une a CD19 y uno que se une a CD3. Blinatomomab dirige las células T para que ataquen las células cancerosas. Véase, por ejemplo, Hammer et al.; Identificador de Ensayo Clínico No. NCT00274742 y NCT01209286. MEDI-551 es un anticuerpo humanizado anti-CD19 modificado con Fc para mejorar la citotoxicidad mediada por células dependiente de anticuerpos (ADCC). Véase, por ejemplo, Hammer et al.; e Identificador de Ensayo Clínico No. NCT01957579. Combotox es una mezcla de inmunotoxinas que se unen a CD19 y CD22. Las inmunotoxinas se componen de fragmentos de anticuerpo scFv fusionados a una cadena A de la ricina desglicosilada. Véase, por ejemplo, Hammer et al.; y Herrera et al. J. Pediatr. Hematol. Oncol. 31.12(2009): 936-41; Schindler et al. Br. J. Haematol. 154.4 (2011):471-6. DT2219ARL es una inmunotoxina biespecífica dirigido a CD19 y CD22, que comprende dos scFv y una toxina de la difteria truncada. Véase, por ejemplo, Hammer et al.; e Identificador de Ensayo Clínico No. NCT00889408. SGN-CD19A es un conjugado anticuerpo-fármaco (ADC) compuesto de un anticuerpo monoclonal humanizado anti-CD19 enlazado a un agente de destrucción celular citotóxico sintético, monometil auristatina F (MMAF). Véase, por ejemplo, Hammer et al.; e Identificador de Ensayo Clínico No. NCT01786096 y NCT01786135. SAR3419 es un conjugado anticuerpo-fármaco anti-CD19 (ADC) que comprende un anticuerpo monoclonal humanizado anti-CD19 conjugado a un derivado de maitansina través de un enlazador escindible. Véase, por ejemplo, Younes et al. J. Clin. Oncol. 30.2 (2012): 2776-82; Hammer et al.; Identificador de Ensayo Clínico No. NCT00549185; y Blanc et al. Clin Cancer Res. 2011;17: 6448-58. XmAb-5871 es un anticuerpo anti-CD19 humanizado y modificado con Fc. Véase, por ejemplo, Hammer et al. MDX-1342 es un anticuerpo anti-CD19 humano, modificado con Fc y mejorado con ADCC. Véase, por ejemplo, Hammer et al. En algunas modalidades, la molécula de anticuerpo es una molécula biespecífica anti-CD19 y anti-CD3. Por ejemplo, AFM11 es un anticuerpo biespecífico que se dirige a CD19 y CD3. Véase, por ejemplo, Hammer et al.; e Identificador de Ensayo Clínico No. NCT02106091. En algunas modalidades, un anticuerpo anti-CD19 descrito en el presente documento se conjuga o se une de

otra manera a un agente terapéutico, por ejemplo, un agente quimioterapéutico, una vacuna de péptido (tal como la descrita en Izumoto et al. 2008 J Neurosurg 108: 963-971), un agente inmunosupresor o un agente inmunoablativo, por ejemplo, ciclosporina, azatioprina, metotrexato, micofenolato, FK506, CAMPATH, anticuerpo anti-CD3, citoxina, fludarabina, rapamicina, ácido micofenólico, esteroides, FR901228 o citoquinas.

Ejemplos de moléculas de anticuerpo anti-CD19 (incluyendo anticuerpos o fragmentos o conjugados de los mismos) puede incluir un scFv, CDR, o las cadenas VH y VL descritas en las **Tablas 2, 4 o 5**. En una modalidad, la molécula de anticuerpo de unión a CD19 comprende: una región variable de cadena ligera que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena ligera proporcionada en la **Tabla 2**, o una secuencia con 95-99 % de identidad frente una secuencia de aminoácidos de la **Tabla 2**; y/o una región variable de cadena pesada que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena pesada proporcionada en la **Tabla 2**, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de la **Tabla 2** En algunas modalidades, la molécula de anticuerpo de unión a CD19 comprende una o más CDR (por ejemplo, una de cada una de HC CDR1, CDR2 HC, HC CDR3, LC CDR1, LC CDR2 y LC CDR3) de la **Tabla 4** o la **Tabla 5**, o CDR que tienen una, dos, tres, cuatro, cinco o seis modificaciones (por ejemplo, sustituciones) de una o más de las CDR. La molécula de anticuerpo puede ser, por ejemplo, una molécula aislada de anticuerpo.

En una realización, un dominio de unión a antígeno para CD19 es una porción de unión a antígeno, por ejemplo, las CDRs, de un dominio de unión a antígeno que se describen en una tabla en el presente documento. En una realización, un dominio de unión a antígeno de CD19 puede ser de cualquier CAR CD19, por ejemplo, LG-740; Patente de Estados Unidos. Nº 8.399.645; Patente de Estados Unidos. Nº 7.446.190; Xu et al., Leuk Lymphoma. 2013 54 (2): 255-260 (2012); Cruz et al, Blood 122 (17): 2965-2973 (2013);. . Brentjens et al, Blood, 118 (18): 4.817 hasta 4.828 (2011); Kochenderfer y otros, Blood 116 (20):. 4099-102 (2010); Kochenderfer et al, Blood 122 (25): 4129-39 (2013); y 16 de la célula Annu Meet Am Soc Gen

Ther (ASGCT) (mayo 15-18 de Salt Lake City) 2013, Abst 10, cada una de las cuales se incorpora aquí como referencia en su totalidad.

En una realización, la célula T CAR que se une específicamente a CD19 tiene la designación USAN de TISAGENLECLEUCEL-T. CTL019 se hace mediante una modificación de genes de las células T está mediada por la inserción estable a través de la transducción con una auto-inactivación, vector de replicación deficiente Lentiviral (LV) que contiene el transgén CTL019 bajo el control del promotor alfa EF-1. CTL019 puede ser una mezcla de células T positivas y negativas de transgenes que se entregan al sujeto sobre la base del porcentaje de las células transgén T positivas.

En un aspecto, la secuencia de ácido nucleico de un constructo de CAR de la invención se selecciona de uno o más de las SEQ ID NOS: 85-96. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 85. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 86. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 87. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 88. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 89. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 90. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 91. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 92. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 93. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 94. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 95. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 96. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 97. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 98. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR es la SEQ ID NO: 99.

Inhibidores de CD20 y dominios de unión

Tal como se usa en el presente documento, el término "CD20" se refiere a un determinante antigénico que se conocer por ser detectable en células B. CD20 humano también

se conoce como miembro 1 de la subfamilia A con 4 dominios transmembranarios (MS4A1). Las secuencias de aminoácidos y de ácido nucleico humanas y de ratón se pueden encontrar en bases de datos públicas, tales como GenBank, UniProt y Swiss-Prot. Por ejemplo, la secuencia de aminoácidos de CD20 humano se puede encontrar en los No. de Acceso NP_690605.1 y NP_068769.2, y la secuencia de nucleótidos que codifica las variantes de transcripción 1 y 3 de CD20 humano se puede encontrar en los No. de Acceso NM_152866.2 y NM_021950.3, respectivamente. Como se usa en el presente documento, "CD20" incluye proteínas que comprenden mutaciones, por ejemplo, mutaciones puntuales, fragmentos, inserciones, deleciones y variantes de corte y empalme de CD20 de tipo silvestre de extensión completa. En un aspecto, la porción de unión a antígeno del CAR reconoce y se une a un antígeno dentro del dominio extracelular de la proteína CD20. En un aspecto, la proteína CD20 se expresa en una célula cancerosa.

En algunos aspectos, la presente invención proporciona un inhibidor de o un dominio de unión a CD20, por ejemplo, un inhibidor de CD20 o un dominio de unión como se describe en el presente documento. La divulgación también proporciona un ácido nucléico que codifica el dominio de unión a CD20, o un CAR que comprende el dominio de unión a CD20. Un inhibidor de CD20 invluye, pero no está limitado a una célula que expresa un CAR CD20, por ejemplo, una célula TCAR CD20 o un anticuerpo anti-CD20 (por ejemplo, un anticuerpo mono o biespecífico anti-CD20) o un fragmento del mismo. La composición también puede comprender un segundo agente, por ejemplo una célula que expresa un CAR anti CD19 o un dominio de unión a CD19. Los agentes pueden estar, por ejemplo, codificados por un único ácido nucléico o por diferentes pacidos nucleícos.

En algunos aspectos, un inhibidor de CD20 o un dominio de unión, es administrado como una monoterapia. En algunos aspectos, el inhibidor de CD20 o un dominio de unión se administra en combinación con un segundo agente tal como una célula que expresa un CAR anti CD19. En una modalidad, el inhibidor de CD20 se administra en combinación con un inhibidor de CD19, por ejemplo, una célula que expresa un CAR CD19, por ejemplo, una célula que expresa un CAR que se describe en el presente documento, por ejemplo, una célula que expresa un CAR que comprende un dominio de unión de anticuerpo que es murino, humano o humanizado.

Células que expresan CAR-CD20, por ejemplo, TCARs

En una modalidad, la molécula de anticuerpo CD20 comprende: una región variable de cadena ligera que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena ligera proporcionada en la **Tabla 15A o 15B ,** o una secuencia con 95-99 % de identidad frente una secuencia de aminoácidos de la **Tabla 15A o 15B**; y/o una región variable de cadena pesada que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena pesada proporcionada en la Tabla **14A o 14B**, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de la Tabla **14A o 14B**. En una modalidad, la molécula de anticuerpo CD20 comprende una o más (por ejemplo, dos o las tres) de la región 1 determinante de la complementariedad de cadena ligera (LC CDR1), la región 2 determinante de la complementariedad de cadena ligera (LC CDR2), la región 3 determinante de la complementariedad de cadena ligera (LC CDR3) de un dominio de unión a CD20 descrito en el presente documento, y/o una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión a CD20 descrito en el presente documento, por ejemplo, un dominio de unión a CD20 que comprende una o más, por ejemplo, las tres, LC CDR y una o más, por ejemplo, las tres, HC CDR. Estos CDR pueden ser, por ejemplo, las de la **Tabla 12A o 12B** y/o la **Tabla 13**, o una secuencia sustancialmente idéntica a las mismas. En una modalidad, la molécula de anticuerpo CD20 comprende una o más CDR (por ejemplo, una HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 o LC CDR3) que comprende una secuencia de aminoácidos que tiene una, dos, tres, cuatro, cinco, o seis modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de la **Tabla 12A o 12B** y/o la **Tabla 13.** La molécula de anticuerpo puede ser, por ejemplo, una molécula de anticuerpo aislada.

En una modalidad, el dominio de unión a CD20 (por ejemplo, un scFv) comprende: una región variable de cadena ligera que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena ligera proporcionada en la **Tabla 15A o 15B,** o una secuencia con 95-99 % de identidad frente una secuencia de aminoácidos de la **Tabla 15A o 15B**; y/o una región variable de cadena pesada que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena pesada proporcionada en la **Tabla 14A o 14B**, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de la **Tabla 14A o 14B**.

En una modalidad, el dominio de unión a CD20 comprende una o más (por ejemplo, dos o las tres) de la región 1 determinante de la complementariedad de cadena ligera (LC CDR1), la región 2 determinante de la complementariedad de cadena ligera (LC CDR2), la región 3 determinante de la complementariedad de cadena ligera (LC CDR3) de un dominio de unión a CD20 descrito en el presente documento, y/o una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión a CD20 descrito en el presente documento, por ejemplo, un dominio de unión a CD20 que comprende una o más, por ejemplo, las tres, LC CDR y una o más, por ejemplo, las tres, HC CDR. Estos CDR pueden ser, por ejemplo, las de la **Tabla 12A o 12B** y/o la **Tabla 13**, o una secuencia sustancialmente idéntica a las mismas. En una modalidad, el dominio de unión a CD20 (por ejemplo, un scFv) comprende una o más CDR (por ejemplo, una HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 o LC CDR3) que comprenden una secuencia de aminoácidos que tiene una, dos, tres, cuatro, cinco o seis modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de la **Tabla 12A o 12B** y/o la **Tabla 13.**

En algunas modalidades, el CAR comprende un anticuerpo o fragmneto de anticuerpo que incluye un dominio de unión a CD20, un dominio trasmembrana y un dominio de señalización intracelular. El dominio de unión a CD20 puede comprender una o más región 1

determinante de la complementariedad de la cadena ligera (LC CDR1), región 2 determinante de la complementariedad de la cadena ligera (LC CDR2) y región 3 determinante de la complementariedad de la cadena ligera (LC CDR3) de cualquier secuencia de aminoácidos del dominio de unión de la cadena ligera a CD20 listada en la **Tabla 13, 15A o 15B,** y una o más región 1 determinante de la complementariedad de la cadena pesada (HC CDR1), región 2 determinante de la complementariedad de la cadena pesada (HC CDR2) y región 3 determinante de la complementariedad de la cadena pesada (HC CDR3) de cualquier secuencia de aminoácidos del dominio de unión de la cadena pesada a CD20 listada en la **Tabla 12A o 12B, 14A o 14B.**

En una modalidad, el dominio de unión a CD20 comprende seis CDR (por ejemplo, una de cada una de HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 y LC CDR3) de cualquiera de CAR20-1, CAR20-2, CAR20 -3, CAR20-4, CAR20-5, CAR20-6, CAR20-7, CAR20-8, CAR20-9, CAR20-10, CAR20-11, CAR20-12, CAR20-13, CAR20-14, CAR20-15 o CAR20-16, o una secuencia sustancialmente idéntica a las mismas. En una modalidad, el dominio de unión a CD20 comprende tres CDR (por ejemplo, una de cada una de HC CDR1, HC CDR2 y HC CDR3, o una de cada una de LC CDR1, LC CDR2 y LC CDR3) de cualquiera de CAR20-1, CAR20-2, CAR20-3, CAR20-4, CAR20-5, CAR20-6, CAR20-7, CAR20-8, CAR20-9, CAR20-10, CAR20-11, CAR20-12, CAR20-13, CAR20-14, CAR20-15 o CAR20-16, o una secuencia sustancialmente idéntica a las mismas.

En una modalidad, el dominio de unión a CD20 comprende una región variable de cadena ligera descrita en el presente documento (por ejemplo, en la **Tabla 15A o 15B**) y/o una región variable de cadena pesada descrita en el presente documento (por ejemplo, en la Tabla **14A o 14B**), o una secuencia substancialmente idéntica a las mismas. En una modalidad, el dominio de unión a CD20 (por ejemplo, un scFv) comprende: una región variable de cadena ligera que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena ligera proporcionada en la **Tabla 15A o 15B**, o una secuencia con 95-99 % de identidad frente una secuencia de aminoácidos de la **Tabla 15A o 15B**; y/o una región variable de cadena pesada que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones)

de una secuencia de aminoácidos de una región variable de cadena pesada proporcionada en la **Tabla 14A o 14B**, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de la **Tabla 14A o 14B.**

Otras modalidades incluyen una secuencia de nucleótidos que codifica un polipéptido descrito en esta sección. Por ejemplo, otras modalidades incluyen una secuencia de nucleótidos que codifica un polipéptido de cualquiera de las Tablas 11-15. Por ejemplo, la secuencia de nucleótidos puede comprender un constructo de CAR o scFv de la **Tabla 11A-15B**. El nucleótido puede codificar una VH de la **Tabla 14**, una VL de la **Tabla 15**, o ambas. El nucleótido puede codificar una o más de (por ejemplo, dos o tres de) VH CDR1, VH CDR2 o VH CDR3 de la **Tabla 12A o 12B** y/o el nucleótido puede codificar una o más de (por ejemplo, dos o tres de) VL CDR1, VL CDR2 o VL CDR3 de la **Tabla 13**. La secuencia de nucleótidos también puede incluir uno o más de, por ejemplo, todos los dominios de SEQ ID NO.: 13, 14, 15, 16, 17 y 51.

En otro aspecto, el presente documento proporciona una población de células que expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD20. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de CD20. En una modalidad, la población de células que expresan CAR incluye, por ejemplo, una primera célula que expresa un CAR (por ejemplo, un CAR de CD19, un CAR de ROR1, un CAR de CD20 o un CAR de CD22), que incluye un dominio primario de señalización intracelular, y una segunda célula que expresa un CAR (por ejemplo, un CAR de CD19, un CAR de ROR1, un CAR de CD20 o un CAR de CD22)), que incluye un dominio secundario de señalización.

El CAR de CD20 puede también comprender uno o más de un dominio transmembrana, por ejemplo, un dominio transmembrana como se describe en el presente documento, un dominio de señalización inatracelular, por ejemplo, un dominio de señalización intracelular como se describe en el presente documento, un dominio coestimulador, por ejemplo, un dominio coestimulador como se describe en el presente documento, una secuencia líder, por ejemplo, una secuencia líder como se describe en el presente documento, o una bisagra, por ejemplo, una bisagra como se describe en el presente documento.

Ejemplos de anticuerpos anti-CD20 incluyen, de manera enunciativa más no limitativa,

rituximab, ofatumumab, ocrelizumab, veltuzumab, obinutuzumab, TRU-015 (Trubion Pharmaceuticals), ocaratuzumab y Pro131921 (Genentech). Véase, por ejemplo, Lim et al. Haematologica. 95.1 (2010): 135-43.

En algunas modalidades, el anticuerpo anti-CD20 comprende rituximab. Rituximab es un anticuerpo monoclonal humano/de ratón quimérico IgG1 kappa que se une a CD20 y causa la citólisis de una célula que expresa CD20, por ejemplo, como se describe en www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf. En algunas modalidades, el rituximab se puede usar para tratar tumores malignos de células B, tales como linfoma no Hodgkin (NHL) (por ejemplo, NHL folicular, linfoma difuso de células B grandes) y leucemia linfocítica crónica (LLC). En otras modalidades, el rituximab se puede usar para tratar enfermedades autoinmunes, tales como artritis reumatoide, esclerosis múltiple, lupus eritematoso sistémico, polineuropatía desmielinizante inflamatoria crónica, anemia autoinmune, anemia hemolítica autoinmune, aplasia pura de células rojas, púrpura trombocitopénica idiopática (ITP), síndrome de Evans, vasculitis, enfermedades ampollosas de la piel, diabetes mellitus tipo 1, síndrome de Sjogren, encefalitis de receptor anti-NMDA y enfermedad de Devic, oftalmopatía de Graves y pancreatitis autoinmune. En algunas modalidades, se puede usar rituximab para tratar el rechazo de trasplantes.

En algunas modalidades, el rituximab se administra por vía intravenosa, por ejemplo, como una infusión intravenosa. Por ejemplo, cada infusión proporciona aproximadamente 500-2000 mg (por ejemplo, aproximadamente 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1100, 1100-1200, 1200-1300, 1300-1400, 1400-1500, 1500-1600, 1600-1700, 1700-1800, 1800-1900, o 1900-2000 mg) de rituximab.

En algunas modalidades, el rituximab se administra a una dosis entre 150 mg/m^2 y 750 mg/m^2, por ejemplo, aproximadamente 150-175 mg/m^2, 175-200 mg/m^2, 200-225 mg/m^2, 225-250 mg/m^2, 250-300 mg/m^2, 300-325 mg/m^2, 325-350 mg/m^2, 350-375 mg/m^2, 375-400 v, 400-425 mg/m^2, 425-450 mg/m^2, 450-475 mg/m^2, 475-500 mg/m^2, 500-525 mg/m^2, 525-550 mg/m^2, 550-575 mg/m^2, 575-600 mg/m^2, 600-625 mg/m^2, 625-650 mg/m^2, 650-675 mg/m^2, or 675-700 mg/m^2, donde m^2 indica el área de superficie corporal del sujeto.

En algunas modalidades, el rituximab se administra en un intervalo de dosificación de al menos 4 días, por ejemplo, 4, 7, 14, 21, 28, 35 días o más. Por ejemplo, el rituximab se administra en un intervalo de dosificación de al menos 0,5 semanas, por ejemplo, 0,5, 1, 2, 3, 4,

5, 6, 7, 8 semanas o más.

En algunas modalidades, el rituximab se administra a una dosis e intervalo de dosificación descritos en el presente documento durante un periodo de tiempo, por ejemplo, al menos 2 semanas, por ejemplo, al menos 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 semanas o más. Por ejemplo, el rituximab se administra a una dosis e intervalo de dosificación descritos en el presente documento para un total de al menos 4 dosis por ciclo de tratamiento (por ejemplo, al menos 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 o más dosis por ciclo de tratamiento).

En algunos aspectos, el anticuerpo anti-CD20 comprende ofatumumab. Ofatumumab es un anticuerpo monoclonal humano IgG1k anti-CD20 con un peso molecular de aproximadamente 149 kDa. Por ejemplo, ofatumumab se genera usando la tecnología de hibridoma y de ratón transgénico, y se expresa y se purifica a partir de una línea celular murina recombinante (NS0). Véase, por ejemplo, www.accessdata.fda.gov/drugsatfda_docs/label/2009/125326lbl.pdf; e Identificadores de Ensayo Clínico No. NCT01363128, NCT01515176, NCT01626352 y NCT01397591.

El ofatumumab se puede usar para tratar enfermedades tales como LLC, linfoma no Hodgkin (LNH) (por ejemplo, LNH folicular y DLBCL), leucemia prolinfocítica de células B, leucemia linfoblástica aguda (LLA), linfoma de células del manto, artritis reumatoide y esclerosis múltiple.

En algunas modalidades, el ofatumumab se administra como una infusión intravenosa. Por ejemplo, cada infusión proporciona aproximadamente 150-3000 mg (por ejemplo, aproximadamente 150-200, 200-250, 250-300, 300-350, 350-400, 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1200, 1200-1400, 1400-1600, 1600-1800, 1800-2000, 2000-2200, 2200-2400, 2400-2600, 2600-2800 o 2800-3000 mg) de ofatumumab.

En algunas modalidades, el ofatumunab se administra a un intervalo de dosificación de al menos 4 días, por ejemplo, 4, 7, 14, 21, 28, 35 días o más. Por ejemplo, el ofatumunab se administra en un intervalo de dosificación de al menos 1 semana, por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 26, 28, 20, 22, 24, 26, 28, 30 semanas o más.

En algunas modalidades, el ofatumumab se administra a una dosis e intervalo de

dosificación descritos en el presente documento durante un periodo de tiempo, por ejemplo, al menos 1 semana, por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 26, 28, 30, 40, 50, 60 semanas o más, o 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 meses o más, o 1, 2, 3, 4, 5 años o más. Por ejemplo, el ofatumumab se administra a una dosis e intervalo de dosificación descritos en el presente documento para un total de al menos 2 dosis por ciclo de tratamiento (por ejemplo, al menos 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20 o más dosis por ciclo de tratamiento).

En algunos aspectos, el anticuerpo anti-CD20 comprende ocrelizumab. Ocrelizumab es un anticuerpo monoclonal anti-CD20 humanizado, por ejemplo, como se describe en los Identificadores de Ensayos Clínicos No. NCT00077870, NCT01412333, NCT00779220, NCT00673920, NCT01194570, y Kappos et al. Lancet. 19.378 (2011): 1779-87. Por ejemplo, el ocrelizumab se puede usar para tratar enfermedades tales como la artritis reumatoide, la esclerosis múltiple y el lupus.

En algunas modalidades, el ocrelizumab se administra como una infusión intravenosa. Por ejemplo, cada infusión proporciona aproximadamente 50-2000 mg (por ejemplo, aproximadamente 50-100, 100-150, 150-200, 200-250, 250-300, 300-350, 350-400, 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1100, 1100-1200, 1200-1300, 1300-1400, 1400-1500, 1500-1600, 1600-1700, 1700-1800, 1800-1900 o 1900-2000 mg) de ocrelizumab.

En algunas modalidades, el ocrelizumab se administra en un intervalo de dosificación de al menos 7 días, por ejemplo, 7, 14, 21, 28, 35 días o más. Por ejemplo, el ocrelizumab se administra en un intervalo de dosificación de al menos 1 semana, por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 26, 28, 20, 22, 24, 26, 28, 30 semanas o más.

En algunas modalidades, el ocrelizumab se administra a una dosis e intervalo de dosificación descritos en el presente documento durante un periodo de tiempo, por ejemplo, al menos 2 semanas, por ejemplo, al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 26, 28, 30, 40, 50, 60 semanas o más, o 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 meses o más, o 1, 2, 3, 4, 5 años o más. Por ejemplo, el ocrelizumab se administra a una dosis e intervalo de dosificación descritos en el presente documento para un total de al menos 4 dosis por ciclo de tratamiento (por ejemplo, al menos 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20 o más dosis por ciclo de tratamiento).

En algunos aspectos, el anticuerpo anti-CD20 comprende veltuzumab. Veltuzumab es un anticuerpo monoclonal humanizado contra CD20. Véase, por ejemplo, Identificadores de Ensayos Clínicos No. NCT00547066, NCT00546793, NCT01101581, y Goldenberg et al. Leuk Lymphoma. 51(5) (2010): 747-55. Por ejemplo, el veltuzumab se puede usar para el tratamiento de NHL (por ejemplo, DLBCL, linfoma folicular), LLC y enfermedades autoinmunes tales como Púrpura Trombocitopénica Inmune (PTI).

En algunas modalidades, el veltuzumab se administra por vía subcutánea o intravenosa, por ejemplo, como una infusión intravenosa. En algunas modalidades, el veltuzumab se administra a una dosis de 50-800 mg/m^2, por ejemplo, aproximadamente 50-60, 60-70, 70-80, 80-90, 90-100, 100-110, 110-120, 120-130, 130-140, 140-150, 150-160, 160-170, 170-180, 180-190, 190-200, 200-225, 225-250, 250-275, 275-300, 300-325, 325-350, 350-375, 375-400, 400-425, 425-450, 450-475, 475-500, 500-525, 525-550, 550-575, 575-600, 600-625, 625-650, 650-675, 675-700, 700-725, 725-750, 750-775 o 775-800 mg/m^2. En algunas modalidades, se administra una dosis de 50-400 mg, por ejemplo, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375 o 400 mg de veltuzumab.

En algunas modalidades, el veltuzumab se administra en un intervalo de dosificación de al menos 7 días, por ejemplo, 7, 14, 21, 28, 35 días o más. Por ejemplo, el veltuzumab se administra en un intervalo de dosificación de al menos 1 semana, por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 26, 28, 20, 22, 24, 26, 28, 30 semanas o más.

En algunas modalidades, el veltuzumab se administra a una dosis e intervalo de dosificación descritos en el presente documento durante un periodo de tiempo, por ejemplo, al menos 2 semanas, por ejemplo, al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 26, 28, 30, 40, 50, 60 semanas o más, o 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 meses o más, o 1, 2, 3, 4, 5 años o más. Por ejemplo, el veltuzumab se administra a una dosis e intervalo de dosificación descritos en el presente documento para un total de al menos 4 dosis por ciclo de tratamiento (por ejemplo, al menos 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20 o más dosis por ciclo de tratamiento).

En algunos aspectos, el anticuerpo anti-CD20 comprende GA101. GA101 (también llamado obinutuzumab o RO5072759) es un anticuerpo monoclonal anti-CD20 humanizado y modificado mediante glico-ingeniería. Por ejemplo, GA101 se puede usar para tratar enfermedades tales como tumores malignos linfoides de células B, por ejemplo, LLC, linfoma

no Hodgkin (NHL) y linfoma difuso de células B grandes (DLBCL). Véase, por ejemplo, Robak. Curr. Opin. Investig. Drugs. 10.6 (2009): 588-96; Identificador de Ensayo Clínico No.: NCT01995669, NCT01889797, NCT02229422, y NCT01414205; y www.accessdata.fda.gov/drugsatfda_docs/label/2013/125486s000lbl.pdf.

En algunas modalidades, GA101 se administra por vía intravenosa, por ejemplo, como una infusión intravenosa. Por ejemplo, cada infusión proporciona aproximadamente 100-3000 mg (por ejemplo, aproximadamente 10-150, 150-200, 200-250, 250-500, 300-350, 350-400, 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1200, 1200-1400, 1400-1600, 1600-1800, 1800-2000, 2000-2200, 2200-2400, 2400-2600, 2600-2800 o 2800-3000 mg) de GA101.

En algunas modalidades, GA101 se administra en un intervalo de dosificación de al menos 7 días, por ejemplo, 7, 14, 21, 28, 35 días o más. Por ejemplo, GA101 se administra en un intervalo de dosificación de al menos 1 semana, por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 26, 28, 20, 22, 24, 26, 28, 30 semanas o más. Por ejemplo, GA101 se administra en un intervalo de dosificación de al menos 1 mes, por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 o más meses. En algunas modalidades, GA101 se administra en un intervalo de dosificación de 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 o 14 días.

En algunas modalidades, GA101 se administra a una dosis e intervalo de dosificación descritos en el presente documento durante un periodo de tiempo, por ejemplo, al menos 1 semana, por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 26, 28, 30, 40, 50, 60 semanas o más, o 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 meses o más, o 1, 2, 3, 4, 5 años o más. Por ejemplo, GA101 se administra a una dosis e intervalo de dosificación descritos en el presente documento para un total de al menos 2 dosis por ciclo de tratamiento (por ejemplo, al menos 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20 o más dosis por ciclo de tratamiento).

En algunos aspectos, el anticuerpo anti-CD20 comprende AME-133v. AME-133V (también llamado LY2469298 o ocaratuzumab) es un anticuerpo monoclonal IgG1 humanizado contra CD20 con afinidad aumentada por el receptor FcRIIIa y actividad mejorada de citotoxicidad celular dependiente de anticuerpos (ADCC) en comparación con el rituximab. Véase, por ejemplo, Robak et al. BioDrugs 25.1(2011): 13-25. En algunas realizaciones, AME-133V se puede usar para el tratamiento de cánceres como el NHL, por ejemplo, linfoma

folicular. Véase, por ejemplo, Forero-Torres et al. Clin Cancer Res. 18.5(2012): 1395-403.

En algunos aspectos, el anticuerpo anti-CD20 comprende PRO131921. PRO131921 es un anticuerpo monoclonal anti-CD20 humanizado diseñado para tener una mejor unión a FcRIIIa y una actividad mejorada de ADCC en comparación con el rituximab. Véase, por ejemplo, Robak et al. BioDrugs 25.1(2011): 13-25; y Casulo et al. Clin Immunol. 154.1(2014): 37-46. En algunas modalidades, PRO131921 se puede usar para el tratamiento de NHL. Véase, por ejemplo, el Identificador de Ensayo Clínico No. NCT00452127. En algunas modalidades, PRO131921 se administra por vía intravenosa, por ejemplo, como una infusión intravenosa. En algunas modalidades, PRO131921 se administra a una dosis entre 15 mg/m^2 y 1000 mg/m^2, por ejemplo, aproximadamente 15-20, 20-25, 25-30, 30-35, 35-40, 40-45, 45-50, 50-55, 55-60, 60-65, 65-70, 70-75, 75-80, 80-85, 85-90, 90-95, 95-100, 100-125, 125-150, 150-175, 175-200, 200-226, 225-250, 250-300, 300-325, 325-350, 350-375, 375-400, 400-425, 425-450, 450-475, 475-500, 500-525, 525-550, 550-575, 575-600, 600-625, 625-650, 650-675, 675-700, 700-725, 725-750, 750-775, 775-800, 800-825, 825-850, 850-875, 875-900, 900-925, 925-950, 950-975 o 975-1000 mg/m^2, donde m^2 indica el área de superficie corporal del sujeto.

En algunos aspectos, el anticuerpo anti-CD20 comprende TRU-015. TRU-015 es una proteína de fusión anti-CD20 derivada de dominios de un anticuerpo contra CD20. TRU-015 es más pequeña que los anticuerpos monoclonales, pero conserva las funciones efectoras mediadas por Fc. Véase, por ejemplo, Robak et al. BioDrugs 25.1(2011): 13-25. TRU-015 un fragmento variable de cadena simple anti-CD20 (scFv) unido a los dominios de la bisagra de IgG1, CH2 y CH3, pero carece de los dominios CH1 y CL. En algunas modalidades, TRU-015 se puede usar para el tratamiento de linfomas de células B y la artritis reumatoide. En algunas modalidades, TRU-015 se administra por vía intravenosa, por ejemplo, como una infusión intravenosa. En algunas modalidades, TRU-015 se administra a una dosis de 0,01-30 mg/kg, por ejemplo, 0,01-0,015; 0,015-0,05; 0,05-0,15; 0,15-0,5; 0,5-1, 1-1,5; 1,5-2,5; 2,5-5; 5-10; 10-15; 15-20; 20-25; o 25-30 mg/kg de peso corporal. En algunas modalidades, TRU-015 se administra en un intervalo de dosificación de al menos 1 día, por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 o 14 días. Véase, por ejemplo, Burger et al. Clin Ther. 30.10 (2008): 1806-16.

En algunas modalidades, un anticuerpo anti-CD20 descrito en el presente documento se conjuga o se une de otra manera a un agente terapéutico, por ejemplo, un agente quimioterapéutico (por ejemplo, citoxan, fludarabina, inhibidor de histona deacetilasa, agente de

desmetilación, vacuna de péptidos, antibiótico anti-tumor, inhibidor de tirosina quinasa, agente alquilante, anti-microtúbulo o agente anti-mitótico, anticuerpo CD20 o conjugado anticuerpo-fármaco de CD20 descrito en el presente documento), un agente anti-alérgico, un agente anti-náuseas (o anti-emético), un analgésico, o un agente citoprotector descrito en el presente documento.

Inhibidores de CD22 y dominios de unión

Tal como se usa en el presente documento, el término "CD22" se refiere a un determinante antigénico que se conocer por ser detectable en células precursoras de leucemia. Las secuencias de aminoácidos y de ácido nucleico humanas y de ratón se pueden encontrar en bases de datos públicas, tales como GenBank, UniProt y Swiss-Prot. Por ejemplo, las secuencias de aminoácidos de las isoformas 1-5 de CD22 humano se pueden encontrar en los No. de Acceso NP 001762.2, NP 001172028.1, NP 001172029.1, NP 001172030.1 y NP 001265346.1, respectivamente, y la secuencia de nucleótidos que codifica las variantes de 1-5 de CD22 humano se puede encontrar en los No. de Acceso NM 001771.3, NM 001185099.1, NM 001185100.1, NM 001185101.1 y NM 001278417.1, respectivamente. Como se usa en el presente documento, "CD22" incluye proteínas que comprenden mutaciones, por ejemplo, mutaciones puntuales, fragmentos, inserciones, deleciones y variantes de corte y empalme de CD22 de tipo silvestre de extensión completa. En un aspecto, la porción de unión a antígeno del CAR reconoce y se une a un antígeno dentro del dominio extracelular de la proteína CD22. En un aspecto, la proteína CD22 se expresa en una célula cancerosa.

En algunos aspectos, la presente invención proporciona un inhibidor de o un dominio de unión a CD22, por ejemplo, un inhibidor de CD22 o un dominio de unión como se describe en el presente documento. La divulgación también proporciona un ácido nucléico que codifica el dominio de unión a CD22, o un CAR que comprende el dominio de unión a CD22. Un inhibidor de CD22 invluye, pero no está limitado a una célula que expresa un CAR CD22, por ejemplo, una célula TCAR CD22 o un anticuerpo anti-CD22 (por ejemplo, un anticuerpo mono o biespecífico anti-CD22) o un fragmento del mismo. La composición también puede comprender un segundo agente, por ejemplo una célula que expresa un CAR anti CD19 o un dominio de unión a CD19. Los agentes pueden estar, por ejemplo, codificados por un único ácido nucléico o por diferentes pacidos nucleícos.

En algunos aspectos, un inhibidor de CD22 o un dominio de unión, es administrado como una monoterapia. En algunos aspectos, el inhibidor de CD22 o un dominio de unión se administra en combinación con un segundo agente tal como una célula que expresa un CAR anti CD19. En una modalidad, el inhibidor de CD22 se administra en combinación con un inhibidor de CD19, por ejemplo, una célula que expresa un CAR CD19, por ejemplo, una célula que expresa un CAR que se describe en el presente documento, por ejemplo, una célula que expresa un CAR que comprende un dominio de unión de anticuerpo que es murino, humano o humanizado.

Células que expresan CAR-CD22, por ejemplo, TCARs

En una modalidad, el inhibidor de CD22 es una célula que expresa un CAR de CD22, por ejemplo, un CAR de CD22 que comprende un dominio de unión a CD22 y que está diseñado en una célula (por ejemplo, células T o células NK) para administración en combinación con una célula que expresa un CAR de CD19, por ejemplo, TCAR, y métodos para su uso en terapia adoptiva.

En otro aspecto, la presente invención proporciona una población de células que expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD22. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de CD22. En una modalidad, la población de células que expresan CAR incluye, por ejemplo, una primera célula que expresa un CAR (por ejemplo, un CAR de CD19 o un CAR de CD22), que incluye un dominio primario de señalización intracelular, y una segunda célula que expresa un CAR (por ejemplo, un CAR de CD19 o un CAR de CD22)), que incluye un dominio secundario de señalización.

En un aspecto, el CAR de CD22 comprende una secuencia líder opcional (por ejemplo, una secuencia líder opcional descrita en el presente documento), un dominio de unión a antígeno extracelular, una bisagra (por ejemplo, una bisagra descrita en el presente documento), un dominio transmembrana (por ejemplo, un dominio transmembrana descrito en el presente documento) y un dominio estimulador intracelular (por ejemplo, un dominio estimulador

intracelular descrito en el presente documento). En un aspecto, un ejemplo de constructo de CAR de CD22 comprende una secuencia líder opcional (por ejemplo, una secuencia líder opcional descrita en el presente documento), un dominio de unión a antígeno extracelular, una bisagra, un dominio transmembrana, un dominio coestimulador intracelular (por ejemplo, un dominio coestimulador intracelular descrito en el presente documento) y un dominio estimulador intracelular.

En un aspecto, el dominio de unión a CD22 comprende la porción scFv de una secuencia de aminoácidos (o codificada por una secuencia de nucleótidos) proporcionada en cualquiera de SEQ ID NO.: 200-428. En un aspecto, el dominio de unión a CD22 comprende la porción scFv proporcionada en cualquiera de SEQ ID NO.: 203, 209, 215, 221, 227, 232, 238, 244, 250, 256, 262, 268, 274, 280, 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, 400, 406, 412, 418 o 423.

En aspectos específicos, un constructo de CAR de la invención comprende un dominio scFv seleccionado del grupo que consiste en SEQ ID NO.: 203, 209, 215, 221, 227, 232, 238, 244, 250, 256, 262, 268, 274, 280, 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, 400, 406, 412, 418 o 423, donde l scFv puede estar precedido por una secuencia líder opcional tal como la proporcionada en SEQ ID NO.: 13, y seguido por una secuencia de bisagra opcional tal como la proporcionada en SEQ ID NO.:14 o SEQ ID NO.: 45 o SEQ ID NO.: 47 o SEQ ID NO.: 49, una región transmembrana tal como la proporcionada en SEQ ID NO.: 15, un dominio de señalización intracelular que incluye SEQ ID NO.: 16 o SEQ ID NO.: 51 y una secuencia de CD3 zeta que incluye SEQ ID NO.: 17 o SEQ ID NO.: 43, por ejemplo, donde los dominios son contiguos y están en el mismo marco de lectura para formar una proteína de fusión única. En algunas modalidades, el dominio scFv es un dominio scFv humano seleccionado del grupo que consiste en SEQ ID NO.: 203, 209, 215, 221, 227, 232, 238, 244, 250, 256, 262, 268, 274, 280, 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, 400, 406, 412, 418 o 423.

La invención también incluye una secuencia de nucleótidos que codifica el polipéptido de cada uno de los fragmentos scFv seleccionados del grupo que consiste en SEQ ID NO.: 203, 209, 215, 221, 227, 232, 238, 244, 250, 256, 262, 268, 274, 280, 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, 400, 406, 412, 418 o 423. La invención también incluye una secuencia de nucleótidos que codifica el polipéptido de cada uno

de los fragmentos scFv seleccionados del grupo que consiste en SEQ ID NO.: 203, 209, 215, 221, 227, 232, 238, 244, 250, 256, 262, 268, 274, 280, 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, 400, 406, 412, 418 o 423, y cada uno de los dominios de SEQ ID NOS: 13-17, además del CAR de CD22 codificado de la invención.

En algunas modalidades, las secuencias de CAR de CD22 de extensión completa también se proporcionan en el presente documento como SEQ ID NO.: 207, 213, 219, 225, 230, 236, 242, 248, 254, 260, 266, 272, 278, 284, 290, 296, 302, 308, 314, 320, 326, 332, 338, 344, 350, 356, 362, 368, 374, 380, 386, 392, 398, 404, 410, 416, 422 o 427, tal como se muestra en la **Tabla 6A o 6B**.

En un aspecto, la presente invención abarca un constructo de ácido nucleico recombinante que comprende una molécula de ácido nucleico que codifica un CAR, donde la molécula de ácido nucleico comprende la secuencia de ácido nucleico que codifica un dominio de unión a CD22, por ejemplo, tal como el descrito en el presente documento, por ejemplo, que es contiguo y está en el mismo marco de lectura que la secuencia de ácido nucleico que codifica un dominio de señalización intracelular. En un aspecto, el dominio de unión a CD22 se selecciona de una o más SEQ ID NO.: 203, 209, 215, 221, 227, 232, 238, 244, 250, 256, 262, 268, 274, 280, 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, 400, 406, 412, 418 o 423. En un aspecto, la presente invención abarca un constructo de ácido nucleico recombinante que comprende una molécula de ácido nucleico que codifica un CAR, donde la molécula de ácido nucleico comprende una secuencia de ácido nucleico que codifica un dominio de unión a CD22, donde la secuencia es contigua y está en el mismo marco de lectura que la secuencia de ácido nucleico que codifica un dominio de señalización intracelular. Un ejemplo de dominio de señalización intracelular que se puede usar en el CAR incluye, de manera enunciativa mas no limitativa, uno o más dominios de señalización intracelular, por ejemplo, CD3 zeta, CD28, 4-1BB y similares. En algunos casos, el CAR puede comprender cualquier combinación de CD3 zeta, CD28, 4-1BB y similares.

En un aspecto, la secuencia de ácido nucleico de un constructo de CAR de la invención comprende el constructo de CAR de una o más de SEQ ID NO.: 200, 208, 214, 220, 226, 231, 237, 243, 249, 255, 261, 267, 273, 279, 285, 291, 297, 303, 309, 315, 321, 327, 333, 339, 345, 351, 357, 363, 369, 375, 381, 387, 393, 399, 405, 411, 417, 422 o 428. En un aspecto, la secuencia de ácido nucleico de un constructo de CAR de la invención comprende una secuencia

que codifica scFv de una o más SEQ ID NO.: 204, 210, 216, 222, 116, 233, 239, 245, 251, 257, 263, 269, 275, 281, 287, 293, 299, 305, 311, 317, 323, 329, 335, 341, 347, 353, 359, 365, 371, 377, 383, 389, 395, 401, 407, 413, 117 o 424.

En algunos casos, es beneficioso para el dominio de unión a antígeno ser derivado de la misma especie en la que el CAR será usado. Por ejemplo, para uso en seres humanos, puede ser beneficioso para el dominio de unión a antígeno del CAR comprender residuos humanos o humanizados para el dominio de unión a antígeno de un anticuerpo o fragmento de anticuerpo. Por lo tanto, en un aspecto, el dominio de unión a antígeno comprende un anticuerpo o un fragmento de anticuerpo humano. En una modalidad, el dominio de unión a CD22 humano comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena ligera (LC CDR1), la región 2 determinante de la complementariedad de cadena ligera (LC CDR2), la región 3 determinante de la complementariedad de cadena ligera (LC CDR3) de un dominio de unión a CD22 humano descrito en el presente documento, y/o una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión a CD22 humano descrito en el presente documento, por ejemplo, un dominio de unión a CD22 humano que comprende una o más, por ejemplo, las tres, LC CDR y una o más, por ejemplo, las tres, HC CDR. En una modalidad, el dominio de unión a CD22 humano comprende una o más (por ejemplo, las tres) de la región 1 determinante de la complementariedad de cadena pesada (HC CDR1), la región 2 determinante de la complementariedad de cadena pesada (HC CDR2), la región 3 determinante de la complementariedad de cadena pesada (HC CDR3) de un dominio de unión a CD22 humano descrito en el presente documento, por ejemplo, el dominio de unión a CD22 humano tiene dos regiones variables de cadena pesada, cada una de las cuales comprende una HC CDR1, una HC CDR2 y una HC CDR3 descritas en el presente documento. En una modalidad, el dominio de unión a CD22 humano comprende una región variable de cadena ligera humana descrita en el presente documento (por ejemplo, en la **Tabla 6A, 6B, 10A o 10B**) y/o una región variable de cadena pesada humana descrita en el presente documento (por ejemplo, en la **Tabla 6A, 6B, 9A o 9B**). En una modalidad, el dominio de unión a Cd22 humano comprende una región variable de cadena pesada humana descrita en el presente documento (por ejemplo, en la **Tabla 6A, 6B, 9A o 9B**), por ejemplo, al menos dos regiones variables de cadena

pesada humanas descritas en el presente documento (por ejemplo, en la **Tabla 6A, 8B, 9A o 9B**). En una modalidad, el dominio de unión a CD22 es un scFv que comprende una cadena ligera y una cadena pesada de una secuencia de aminoácidos de las **Tabla 6A, 6B, 9A, 9B, 10A o 10B**. En una modalidad, el dominio de unión a CD22 (por ejemplo, un scFv) comprende: una región variable de cadena ligera que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena ligera proporcionada en la **Tabla 6A, 6B, 10A o 10B**, o una secuencia con 95-99 % de identidad frente una secuencia de aminoácidos de la **Tabla 6A, 6B, 10A o 10B**; y/o una región variable de cadena pesada que comprende una secuencia de aminoácidos que tiene al menos una, dos o tres modificaciones (por ejemplo, sustituciones), pero no más de 30, 20 o 10 modificaciones (por ejemplo, sustituciones) de una secuencia de aminoácidos de una región variable de cadena pesada proporcionada en la **Tabla 6A, 6B, 9A o 9B**, o una secuencia con 95-99 % de identidad frente a una secuencia de aminoácidos de la **Tabla 6A, 6B, 9A o 9B** En una modalidad, el dominio de unión a CD22 comprende una secuencia seleccionada del grupo que consiste en SEQ ID NO.: 203, 209, 215, 221, 227, 232, 238, 244, 250, 256, 262, 268, 274, 280, 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, 400, 406, 412, 418 o 423, o una secuencia con 95-99 % de identidad frente a la misma. En una modalidad, el dominio de unión a CD22 humano es un scFv, y una región variable de cadena ligera que comprende una secuencia de aminoácidos descrita en el presente documento, por ejemplo, en la **Tabla 6A, 6B, 10A o 10B**, está fijada a una región variable de cadena pesada que comprende una secuencia de aminoácidos descrita en el presente documento, por ejemplo, en la **Tabla 6A, 6B, 9A o 9B**, a través de un enlazador, por ejemplo, un enlazador descrito en el presente documento. En una modalidad, el dominio de unión a CD22 humano incluye un enlazador (Gly_4-Ser)n, en el que n es 1, 2, 3, 4, 5 o 6, por ejemplo 3 o 4 (SEQ ID NO.: 53). La región variable de cadena ligera y la región variable de cadena pesada de un scFv pueden estar, por ejemplo, en cualquiera de las siguientes orientaciones: región variable de cadena ligera-enlazador-región variable de cadena pesada o región variable de cadena pesada-enlazador-región variable de cadena ligera.

En un aspecto, el dominio de unión a CD22 se distingue por características o propiedades funcionales particulares de un anticuerpo o fragmento de anticuerpo. Por ejemplo, en un aspecto, la porción de una composición de CAR de la invención que comprende un dominio de unión a

antígeno une específicamente CD22 humana o a un fragmento de la misma. En un aspecto, la invención se refiere a un dominio de unión a antígeno que comprende un anticuerpo o fragmento de anticuerpo, en el que el dominio de unión a anticuerpo se une específicamente a una proteína CD22 o fragmento de la misma, donde el anticuerpo o fragmento de anticuerpo comprende una cadena variable pesada que incluye una secuencia de aminoácidos de cualquiera de SEQ ID NO. 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737 o 738, y/o una cadena variable ligera que incluye una secuencia de aminoácidos de cualquiera de SEQ ID NO. 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776 o 777. En ciertos aspectos, el scFv es contiguo y está en el mismo marco de lectura que una secuencia líder. En un aspecto, la secuencia líder es la secuencia del polipéptido proporcionada como SEQ ID NO.: 13.

En algunas modalidades, el CAR comprende un anticuerpo o fragmneto de anticuerpo que incluye un dominio de unión a CD22, un dominio trasmembrana y un dominio de señalización intracelular. El dominio de unión a CD22 puede comprender una o más región 1 determinante de la complementariedad de la cadena ligera (LC CDR1), región 2 determinante de la complementariedad de la cadena ligera (LC CDR2) y región 3 determinante de la complementariedad de la cadena ligera (LC CDR3) de cualquier secuencia de aminoácidos del dominio de unión de la cadena ligera a CD22 listada en la **Tabla 8A, 8b, 10A o 10B,** y una o más región 1 determinante de la complementariedad de la cadena pesada (HC CDR1), región 2 determinante de la complementariedad de la cadena pesada (HC CDR2) y región 3 determinante de la complementariedad de la cadena pesada (HC CDR3) de cualquier secuencia de aminoácidos del dominio de unión de la cadena pesada a CD22 listada en la **Tabla 7A, 7B, 7C, 9A o 9B.**

En un aspecto, el dominio de unión a CD22 es un fragmento, por ejemplo, un fragmento variable de cadena única (scFv). En un aspecto, el dominio de unión a CD22 es un Fv, un Fab, un (Fab')2 o un anticuerpo híbrido bi-funcional (por ejemplo, bi-específico) (por ejemplo, Lanzavecchia et al., Eur. J. Immunol. 17, 105 (1987)). En un aspecto, los anticuerpos y fragmentos de los mismos de la invención se unen a una proteína CD22 o a un fragmento de la misma con afinidad natural o aumentada.

En algunos casos, un scFv humano se puede derivar de una biblioteca de expresión.

En una modalidad, el dominio de unión a CD22, por ejemplo, scFv, comprende al menos una mutación tal que el scFv mutado confiere una mayor estabilidad al constructo de TCAR22. En otra modalidad, el dominio de unión a CD22, por ejemplo, scFv, comprende al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 mutaciones como resultado de, por ejemplo, el proceso de humanización, tales que el scFv mutado confiere una mayor estabilidad al constructo de TCAR22.

En un aspecto, la presente invención contempla modificaciones de la secuencia de aminoácidos de partida del anticuerpo o fragmento (por ejemplo, scFv) que generan moléculas funcionalmente equivalentes. Por ejemplo, el VH o VL de un dominio de unión a CD22, por ejemplo, scFv, comprendido en el CAR, se puede modificar para retener al menos aproximadamente 70 %, 71 %, 72 %, 73 %, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 % de identidad de la región marco VH o VL de partida del dominio de unión a CD22, por ejemplo, scFv. La presente invención contempla modificaciones en todo el constructo de CAR, por ejemplo, modificaciones en una o más secuencias de aminoácidos de los diversos dominios del constructo de CAR con el fin de generar moléculas funcionalmente equivalentes. El constructo de CAR se puede modificar para retener al menos aproximadamente 70 %, 71 %, 72 %, 73 %, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 % de identidad del constructo de CAR de partida.

En una modalidad, el dominio de unión a CD22 comprende seis CDR (por ejemplo, una de cada una de HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2 y LC CDR3) de cualquiera de CAR22-1, CAR22-2, CAR22-3, CAR22-4, CAR22-5, CAR22-6, CAR22-7, CAR22-8, CAR22-9, CAR22-10, CAR22-11, CAR22-12, CAR22-13, CAR22-14, CAR22-15, o CAR22-16, CAR22-17, CAR22-18, CAR22-19, CAR22-20, CAR22-21, CAR22-22, CAR22-23, CAR22-24, CAR22-25, CAR22-26, CAR22-27, CAR22-28, CAR22-29, CAR22-30, CAR22-31, CAR22-32, CAR22-33, CAR22-34, CAR22-35, CAR22-36, CAR22-37 o CAR22-38 (por ejemplo, tal como se describe en la **Tabla 7A , 7B, 7C, 8A y/o 8B**), o una secuencia sustancialmente idéntica a las mismas. En una modalidad, el dominio de unión a CD22 comprende tres CDR (por ejemplo, una de cada una de HC CDR1, HC CDR2 y HC CDR3, y una de cada una de LC CDR1, LC CDR2 y LC CDR3) de cualquiera de CAR22-1, CAR22-2,

CAR22-3, CAR22-4, CAR22-5, CAR22-6, CAR22-7, CAR22-8, CAR22-9, CAR22-10, CAR22-11, CAR22-12, CAR22-13, CAR22-14, CAR22-15, o CAR22-16, CAR22-17, CAR22-18, CAR22-19, CAR22-20, CAR22-21, CAR22-22, CAR22-23, CAR22-24, CAR22-25, CAR22-26, CAR22-27, CAR22-28, CAR22-29, CAR22-30, CAR22-31, CAR22-32, CAR22-33, CAR22-34, CAR22-35, CAR22-36, CAR22-37 o CAR22-38 (por ejemplo, tal como se describe en la **Tabla 7A , 7B, 7C, 8A y/o 8B**), o una secuencia sustancialmente idéntica a las mismas.

Otras modalidades incluyen una secuencia de nucleótidos que codifica un polipéptido descrito en esta sección. Por ejemplo, otras modalidades incluyen una secuencia de nucleótidos que codifica un polipéptido de **cualquiera de las Tablas 6A-10B**. Por ejemplo, la secuencia de nucleótidos puede comprender un constructo de CAR o scFv de la **Tabla 6A o 6B**. El nucleótido puede codificar una VH de la **Tabla 9A o 9B**, una VL de la **Tabla 10 A o 10B**, o ambas. El nucleótido puede codificar una o más de (por ejemplo, dos o tres de) VH CDR1, VH CDR2 o VH CDR3 de la **Tabla 7A, 7B o 7C** y/o el nucleótido puede codificar una o más de (por ejemplo, dos o tres de) VL CDR1, VL CDR2 o VL CDR3 de la **Tabla 8A o 6B**. La secuencia de nucleótidos también puede incluir uno o más de, por ejemplo, todos los dominios de SEQ ID NO.: 13, 14, 15, 16, 17 y 51.

El CAR de CD22 puede también comprender uno o más de un dominio transmembrana, por ejemplo, un dominio transmembrana como se describe en el presente documento, un dominio de señalización inatracelular, por ejemplo, un dominio de señalización intracelular como se describe en el presente documento, un dominio coestimulador, por ejemplo, un dominio coestimulador como se describe en el presente documento, una secuencia líder, por ejemplo, una secuencia líder como se describe en el presente documento, o una bisagra, por ejemplo, una bisagra como se describe en el presente documento.

En una modalidad, el inhibidor de CD22 es un inhibidor de CD22 descrito en el presente documento. El inhibidor de CD22 puede ser, por ejemplo, un anticuerpo anti-CD22 (por ejemplo, un anticuerpo monoespecífico o biespecífico anti-CD22), una molécula pequeña o un TCAR de CD22. En algunas modalidades, el anticuerpo anti-CD22 se conjuga o se une de otra manera a un agente terapéutico. Ejemplos de agentes terapéuticos incluyen, por ejemplo, agentes disruptivos de microtúbulos (*por ejemplo,* monometil auristatina E) y toxinas (*por ejemplo,* toxina de la difteria o exotoxina de Pseudomonas A, ricina). En una modalidad, el inhibidor de

CD22 se administra en combinación con un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD19, por ejemplo, una célula que expresa un CAR descrita en el presente documento, por ejemplo, una célula que expresa un CAR que comprende un dominio de unión a anticuerpo que es murino, humano o humanizado.

En una modalidad, el anticuerpo anti-CD22 se selecciona de una toxina dirigida al ligando biespecífico de anti-CD19/CD22 (por ejemplo, dos ligandos scFv, reconociendo CD19 y CD22, enlazados a los primeros 389 aminoácidos de la toxina de difteria (DT), DT 390, por ejemplo, DT2219ARL); conjugado MMAE-anticuerpo monoclonal anti-CD22 (por ejemplo, DCDT2980S); scFv de un anticuerpo anti-CD22 RFB4 fusionado a un fragmento de exotoxina de Pseudomonas A (por ejemplo, BL22); conjugado-cadena A de la ricina desglicosilada anti-CD19/anti-CD22 (por ejemplo, Combotox); anticuerpo monoclonal anti-CD22 humanizado (por ejemplo, epratuzumab); o la porción Fv de un anticuerpo anti-CD22 covalentemente unido a un fragmento 38 KDa de exotoxina de Pseudomonas A (por ejemplo, moxetumomab pasudotox).

En una modalidad, el anticuerpo anti-CD22 es una toxina dirigida al ligando biespecífico de anti-CD19/CD22 (por ejemplo, DT2219ARL) y la toxina dirigida al ligando biespecífico de anti-CD19/CD22 se administra a una dosis de 1 μg/kg, 2 μg/kg, 3 μg/kg, 4 μg/kg, 5 μg/kg, 6 μg/kg, 7 μg/kg, 8 μg/kg, 9 μg/kg, 10 μg/kg, 11 μg/kg, 12 μg/kg, 13 μg/kg, 14 μg/kg,15 μg/kg, 20 μg/kg, 25 μg/kg, 30 μg/kg, 40 μg/kg, 60 μg/kg, 80 μg/kg, 100 μg/kg, 120 μg/kg, 140 μg/kg, 160 μg/kg, 180 μg/kg, 200 μg/kg, 220 μg/kg, 250 μg/kg, 300 μg/kg, 350 μg/kg, 400 μg/kg, 450 μg/kg, 500 μg/kg, 600 μg/kg, 700 μg/kg, 800 μg/kg, 900 μg/kg, 1 mg/kg (por ejemplo, 30 μg/kg, 40 μg/kg, 60 μg/kg o 80 μg/kg) durante un periodo de tiempo, por ejemplo, cada 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 o más días. En algunas modalidades, la toxina dirigida al ligando biespecífico de anti-CD19/CD22 se administra mediante infusión intravenosa.

En una modalidad, el anticuerpo anti-CD22 es BL22, y el BL22 se administra a una dosis de aproximadamente 1 μg/kg, 2 μg/kg, 3 μg/kg, 4 μg/kg, 5 μg/kg, 6 μg/kg, 7 μg/kg, 8 μg/kg, 9 μg/kg, 10 μg/kg, 11 μg/kg, 12 μg/kg, 13 μg/kg, 14 μg/kg,15 μg/kg, 20 μg/kg, 25 μg/kg, 30 μg/kg, 40 μg/kg, 60 μg/kg, 80 μg/kg, 100 μg/kg, 120 μg/kg, 140 μg/kg, 160 μg/kg, 180 μg/kg, 200 μg/kg, 220 μg/kg, 250 μg/kg, 300 μg/kg, 350 μg/kg, 400 μg/kg, 450 μg/kg, 500 μg/kg, 600 μg/kg, 700 μg/kg, 800 μg/kg, 900 μg/kg, 1 mg/kg (por ejemplo, 3 μg/kg, 30 μg/kg, 40 μg/kg o 50 μg/kg) durante un período de tiempo, por ejemplo, cada 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 o más días En algunas modalidades, BL22 se administra diariamente, cada dos días, cada tres días

o cada cuarto día durante un período de tiempo, por ejemplo, durante un ciclo de 4 días, un ciclo de 6 días, un ciclo de 8 días, un ciclo de 10 días, un ciclo de 12 días, o un ciclo de 14 días. En una modalidad, se administran 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 o más ciclos de BL22. En algunas modalidades, BL22 se administra mediante infusión intravenosa.

En una modalidad, el anticuerpo anti-CD22 es un conjugado-cadena A de la ricina desglicosilada anti-CD19/anti-CD22 (por ejemplo, Combotox) y el conjugado-cadena A de la ricina desglicosilada anti-CD19/anti-CD22 se administra a una dosis de aproximadamente 500 $\mu g/m^2$, 600 $\mu g/m^2$, 700 $\mu g/m^2$, 800 $\mu g/m^2$, 900 $\mu g/m^2$, 1 mg/m^2, 2 mg/m^2, 3 mg/m^2, 4 mg/m^2, 5 mg/m^2, 6 mg/m^2 o 7 mg/m^2 durante un período de tiempo, por ejemplo, cada 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 o 12 o más días. En algunas modalidades, el conjugado-cadena A de la ricina desglicosilada anti-CD19/anti-CD22 se administra diariamente, cada dos días, cada tres días o cada cuarto día durante un período de tiempo, por ejemplo, durante un ciclo de 4 días, un ciclo de 6 días, un ciclo de 8 días, un ciclo de 10 días, un ciclo de 12 días, o un ciclo de 14 días (por ejemplo, cada dos días durante 6 días). En una modalidad, se administran 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 o más ciclos de conjugado-cadena A de la ricina desglicosilada anti-CD19/anti-CD22. En algunas modalidades, el conjugado-cadena A de la ricina desglicosilada anti-CD19/anti-CD22 se administra mediante infusión por vía intravenosa.

En una modalidad, el anticuerpo anti-CD22 es un anticuerpo monoclonal anti-CD22 humanizado (por ejemplo, epratuzumab) y el anticuerpo monoclonal anti-CD22 humanizado se administra a una dosis de aproximadamente 10 mg/m^2/semana, 20 mg/m^2/semana, 50 mg/m^2/semana, 100 mg/m^2/semana, 120 mg/m^2/semana, 140 mg/m^2/semana, 160 mg/m^2/semana, 180 mg/m^2/semana, 200 mg/m^2/semana, 220 mg/m^2/semana, 250 mg/m^2/semana, 260 mg/m^2/semana, 270 mg/m^2/semana, 280 mg/m^2/semana, 290 mg/m^2/semana, 300 mg/m^2/semana, 305 mg/m^2/semana, 310 mg/m^2/semana, 320 mg/m^2/semana, 325 mg/m^2/semana, 330 mg/m^2/semana, 335 mg/m^2/semana, 340 mg/m^2/semana, 345 mg/m^2/semana, 350 mg/m^2/semana, 355 mg/m^2/semana, 360 mg/m^2/semana, 365 mg/m^2/semana, 370 mg/m^2/semana, 375 mg/m^2/semana, 380 mg/m^2/semana, 385 mg/m^2/semana, 390 mg/m^2/semana, 400 mg/m^2/semana, 410 mg/m^2/semana, 420 mg/m^2/semana, 430 mg/m^2/semana, 440 mg/m^2/semana, 450 mg/m^2/semana, 460 mg/m^2/semana, 470 mg/m^2/semana, 480 mg/m^2/semana, 490 mg/m^2/semana, 500 mg/m^2/semana, 600 mg/m^2/semana, 700 mg/m^2/semana, 800

mg/m^2/semana, 900 mg/m^2/semana, 1 g/m^2/semana o 2 g/m^2/semana (por ejemplo, 360 mg/m^2/semana o 480 mg/m^2/semana) durante un período de tiempo, por ejemplo, cada 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 o más semanas. En algunas modalidades, una primera dosis es inferior a las dosis posteriores (por ejemplo, una primera dosis de 360 mg/m^2/semana, seguida de dosis posteriores de 370 mg/m^2/semana). En algunas modalidades, el anticuerpo monoclonal anti-CD22 humanizado se administra mediante infusión intravenosa.

En una modalidad, el anticuerpo anti-CD22 es moxetumomab pasudotox, y el moxetumomab pasudotox se administra a una dosis de aproximadamente 1 µg/kg, 2 µg/kg, 3 µg/kg, 4 µg/kg, 5 µg/kg, 6 µg/kg, 7 µg/kg, 8 µg/kg, 9 µg/kg, 10 µg/kg, 11 µg/kg, 12 µg/kg, 13 µg/kg, 14 µg/kg,15 µg/kg, 20 µg/kg, 25 µg/kg, 30 µg/kg, 40 µg/kg, 60 µg/kg, 80 µg/kg, 100 µg/kg, 120 µg/kg, 140 µg/kg, 160 µg/kg, 180 µg/kg, 200 µg/kg, 220 µg/kg, 250 µg/kg, 300 µg/kg, 350 µg/kg, 400 µg/kg, 450 µg/kg, 500 µg/kg (por ejemplo, 5 µg/kg, 10 µg/kg, 20 µg/kg, 30 µg/kg, 40 µg/kg o 50 µg/kg) durante un período de tiempo, por ejemplo, cada 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 o más días En algunas modalidades, el moxetumomab pasudotox se administra diariamente, cada dos días, cada tres días o cada cuarto día durante un período de tiempo, por ejemplo, durante un ciclo de 4 días, un ciclo de 6 días, un ciclo de 8 días, un ciclo de 10 días, un ciclo de 12 días, o un ciclo de 14 días (por ejemplo, cada dos días durante 6 días). En una modalidad, se administran 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 o más ciclos de moxetumomab pasudotox. En algunas modalidades, el moxetumomab pasudotox se administra mediante infusión intravenosa.

En una modalidad, una molécula de anticuerpo de CD22 comprende seis CDR (por ejemplo, una de cada una de HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, LC CDR3) de cualquiera de CAR22-1, CAR22-2, CAR22-3, CAR22-4, CAR22-5, CAR22-6, CAR22-7, CAR22-8, CAR22-9, CAR22-10, CAR22-11, CAR22-12, CAR22-13, CAR22-14, CAR22-15, o CAR22-16, CAR22-17, CAR22-18, CAR22-19, CAR22-20, CAR22-21, CAR22-22, CAR22-23, CAR22-24, CAR22-25, CAR22-26, CAR22-27, CAR22-28, CAR22-29, CAR22-30, CAR22-31, CAR22-32, CAR22-33, CAR22-34, CAR22-35, CAR22-36, CAR22-37 o CAR22-38 (por ejemplo, tal como se describe en la **Tabla 7A, 7B, 7C, 8A y/o 8B**), o una secuencia sustancialmente idéntica a las mismas. En una modalidad, una molécula de anticuerpo de CD22 comprende tres CDR (por ejemplo, una de cada una de HC CDR1, HC CDR2 y HC CDR3, y una de cada una de LC CDR1, LC CDR2 y LC CDR3) de cualquiera de CAR22-1,

CAR22-2, CAR22-3, CAR22-4, CAR22-5, CAR22-6, CAR22-7, CAR22-8, CAR22-9, CAR22-10, CAR22-11, CAR22-12, CAR22-13, CAR22-14, CAR22-15, o CAR22-16, CAR22-17, CAR22-18, CAR22-19, CAR22-20, CAR22-21, CAR22-22, CAR22-23, CAR22-24, CAR22-25, CAR22-26, CAR22-27, CAR22-28, CAR22-29, CAR22-30, CAR22-31, CAR22-32, CAR22-33, CAR22-34, CAR22-35, CAR22-36, CAR22-37 o CAR22-38 (por ejemplo, tal como se describe en la **Tabla 7A, 7B, 7C, 8A y/o 8B**), o una secuencia sustancialmente idéntica a las mismas. En una modalidad, una molécula de anticuerpo CD22 comprende una región variable de cadena pesada, una región variable de cadena ligera, o ambas de una región variable de cadena pesada y región variable de cadena pesada, o un scFv, tal como se describe en la **Tabla 6A o 6B**, o una secuencia sustancialmente idéntica a los mismos. En algunas modalidades, la molécula de anticuerpo CD22 es una molécula de anticuerpo aislada.

Inhibidores de ROR1

Tal como se usa en el presente documento, el término "ROR1" se refiere a un determinante antigénico que se conoce por ser detectable en células precursoras de leucemia. Las secuencias de aminoácidos y de ácido nucleico humanas y de ratón se pueden encontrar en bases de datos públicas, tales como GenBank, UniProt y Swiss-Prot. Por ejemplo, las secuencias de aminoácidos de los precursores de ROR1 humana isoformas 1 y 2 se pueden encontrar en los No. de Acceso NP_005003.2 y NP_001077061.1, respectivamente, y las secuencias de ARNm que las codifican se pueden encontrar en los No. de Acceso NM_005012.3 y NM_001083592.1, respectivamente. Como se usa en el presente documento, "ROR1" incluye proteínas que comprenden mutaciones, por ejemplo, mutaciones puntuales, fragmentos, inserciones, deleciones y variantes de corte y empalme de ROR1 de tipo silvestre de extensión completa. En un aspecto, la porción de unión a antígeno del CAR reconoce y se une a un antígeno dentro del dominio extracelular de la proteína ROR1. En un aspecto, la proteína ROR1 se expresa en una célula cancerosa.

El presente documento también proporciona inhibidores de ROR1 y terapias de combinación. Los inhibidores de ROR1 incluyen, de manera enunciativa mas no limitativa, células que expresan CAR, por ejemplo, TCAR, y anticuerpos anti-ROR (por ejemplo, un anticuerpo monoespecífico o biespecífico anti-ROR1) y fragmentos de los mismos. En algunas modalidades, los inhibidores anti-ROR1 se pueden usar para el tratamiento de tumores malignos de células B (por ejemplo, leucemias, tales como LLC, y linfomas de células B, tales como el

linfoma de células del manto; LLA; linfoma linfocítico pequeño; linfoma de células B de células marginales, y linfoma de Burkett) o cánceres epiteliales (por ejemplo, cáncer de mama, carcinoma de células renales, cáncer de pulmón, cáncer colorrectal, cáncer de ovario, y melanoma). En una modalidad, el inhibidor de CD20 se administra en combinación con un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD19, por ejemplo, una célula que expresa un CAR descrita en el presente documento, por ejemplo, una célula que expresa un CAR que comprende un dominio de unión a anticuerpo que es murino, humano o humanizado.

Un ejemplo de inhibidor anti-ROR1 se describe en Hudecek, et al. Clin. Cancer Res. 19.12(2013): 3153-64, que se incluye en el presente documento como referencia. Por ejemplo, un inhibidor de anti-ROR1 incluye los TCAR anti-ROR1 descritos en Hudecek et al. (por ejemplo, generados tal como se describe en Hudecek et al. en la página 3155, primer párrafo completo, que se incluye en el presente documento a manera de referencia). En otros ejemplos, un inhibidor de anti-ROR1 incluye un anticuerpo o fragmento del mismo que comprende las secuencias VH y/o VL de los anticuerpos monoclonales anti-ROR1 2A2 y R12 descritos en Hudecek et al. en el párrafo entre las páginas 3154-55; Baskar et al. MAbs 4(2012): 349–61; y Yang et al. PLoS ONE 6 (2011): e21018, que se incluye en el presente documento a manera de referencia.

En otras modalidades, un inhibidor de ROR1 incluye un anticuerpo o fragmento del mismo (por ejemplo, fragmento variable de cadena única (scFv)) que se dirige a ROR1, incluyendo aquellos descritos en US 2013/0101607, por ejemplo, SEQ ID NO.: 1 o 2 de US 2013/0101607, que se incluye en el presente documento a manera de referencia. En algunas modalidades, los fragmentos de anticuerpo anti-ROR1 (por ejemplo, scFv) se conjugan o se fusionan a una molécula biológicamente activa, por ejemplo, para formar un receptor quimérico de antígeno (CAR) que dirige células inmunitarias, por ejemplo, células T, para responder a células que expresan ROR1.

En algunas modalidades, un ejemplo de inhibidor de ROR1 incluye un anticuerpo monoclonal anti-ROR1 llamado UC-961 (Cirmtuzumab). Véase, por ejemplo, el Identificador de Ensayo Clínico No. NCT02222688. El cirmtuzumab se puede usar para tratar cánceres, tal como la leucemia linfocítica crónica (LLC), el cáncer de ovario y el melanoma. Véase, por ejemplo, Hojjat-Farsangi et al. PLoS One. 8(4): e61167; y NCT02222688.

En algunas modalidades, el cirmtuzumab se administra por vía intravenosa, por ejemplo, como una infusión intravenosa. Por ejemplo, cada infusión proporciona aproximadamente 700-7000 μg (por ejemplo, 700-750, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1500, 1500-2000, 2000-2500, 2500-3000, 3000-3500, 3500-4000, 4000-4500, 4500-5000, 5000-5500, 5500-6000, 6000-6500 o 6500-7000 μg) de cirmtuzumab. En otras modalidades, el cirmtuzumab se administra a una dosis de peso 10-100 μg/kg de peso corporal, por ejemplo, 10-15, 15-20, 20-25, 25-30, 30-35, 35-40, 40-45, 45-50, 50-55, 55-60, 60-65, 65-70, 70-75, 75-80, 80-85, 85-90, 90-95 o 95-100 μg/kg de peso corporal. En una modalidad, el cirmtuzumab se administra a una dosis inicial 15 μg/kg de peso corporal.

En algunas modalidades, el cirmtuzumab se administra en un intervalo de dosificación de al menos 7 días, por ejemplo, 7, 14, 21, 28, 35 días o más. Por ejemplo, el cirmtuzumab se administra en un intervalo de dosificación de al menos 1 semana, por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 26, 28, 20, 22, 24, 26, 28, 30 semanas o más.

En algunas modalidades, el cirmtuzumab se administra a una dosis e intervalo de dosificación descritos en el presente documento durante un periodo de tiempo, por ejemplo, al menos 1 semana, por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 26, 28, 30, 40, 50, 60 semanas o más, o 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 meses o más, o 1, 2, 3, 4, 5 años o más. Por ejemplo, el cirmtuzumab se administra a una dosis e intervalo de dosificación descritos en el presente documento para un total de al menos 2 dosis por ciclo de tratamiento (por ejemplo, al menos 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20 o más dosis por ciclo de tratamiento).

En algunas modalidades, el anticuerpo anti-ROR1 se conjuga o se une de otra manera a un agente terapéutico.

En algunas modalidades, un inhibidor de ROR1 incluye una célula que expresa un CAR anti-ROR1, por ejemplo, TCAR, por ejemplo, una célula que expresa un constructo de CAR anti-ROR1 o codificada por un CAR de unión a ROR1 que comprende un scFv, CDR, o cadenas VH y VL. Por ejemplo, una célula que expresa un CAR anti-ROR1, por ejemplo, TCAR, es una célula generada a través de la adaptación de un CAR de ROR1 (que comprende un dominio de unión a ROR1) en una célula (por ejemplo, una célula T o célula NK), por ejemplo, para la administración en combinación con una célula que expresa un CAR descrita en el presente documento. El presente documento también proporciona métodos de uso de las células que

expresan CAR descritas en el presente documento para la terapia adoptiva.

En otro aspecto, el presente documento proporciona una población de células que expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de ROR1. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de ROR1.

Inhibidores de CD123

CD123 también se conoce como la cadena alfa del receptor de interleuquina-3 (IL-3RA). El receptor de IL-3 (IL-3R) es un heterodímero compuesto de cadenas alfa y beta. IL-3R es un receptor de membrana. La cadena IL-3Rα es una glicoproteína de 360 residuos de aminoácidos. Anormalidades de CD123 se observan con frecuencia en algunos trastornos leucémicos. La CD123 se sobreexpresa en múltiples tumores malignos hematológicos, por ejemplo, leucemias mieloides agudas y linfoides B, neoplasia blástica de células dendríticas plasmocitoides (BPDCN) y la leucemia de células pilosas.

Tal como se usa en el presente documento, el término "CD123" se refiere a un determinante antigénico que se conoce por ser detectable en algunas células cancerosas hematológicas malignas, por ejemplo, células de leucemia. Las secuencias de aminoácidos y de ácido nucleico humanas y de ratón se pueden encontrar en bases de datos públicas, tales como GenBank, UniProt y Swiss-Prot. Por ejemplo, las secuencias de aminoácidos de CD123 humana se pueden encontrar en los No. de Acceso NP_002174.1 (isoforma precursora 1); NP_001254642.1 (isoforma precursora 2), y las secuencias de ARNm que las codifican se pueden encontrar en los No. de Acceso NM_002183.3 (variante 1).; NM_001267713.1 (variante 2). Como se usa en el presente documento, "CD123" incluye proteínas que comprenden mutaciones, por ejemplo, mutaciones puntuales, fragmentos, inserciones, deleciones y variantes corte y empalme de CD123 de tipo silvestre de extensión completa. En un aspecto, la porción de unión a antígeno del CAR reconoce y se une a un antígeno dentro del dominio extracelular de la proteína CD123. En un aspecto, la proteína CD123 se expresa en una célula cancerosa.

El presente documento proporciona inhibidores de CD123 y terapias de combinación. Los inhibidores de CD123 incluyen, de manera enunciativa mas no limitativa, moléculas

pequeñas, proteínas recombinantes, células que expresan CAR anti-CD123, por ejemplo, TCAR, y anticuerpos anti-CD10 (por ejemplo, un anticuerpo monoespecífico o biespecífico anti-CD123) y fragmentos de los mismos. En algunas modalidades, los inhibidores anti-CD123 se pueden usar para tratar un tumor maligno de células B descrito en el presente documento. En una modalidad, el inhibidor de CD123 se administra en combinación con un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD19, por ejemplo, una célula que expresa un CAR descrita en el presente documento, por ejemplo, una célula que expresa un CAR que comprende un dominio de unión a anticuerpo que es murino, humano o humanizado.

En una modalidad, el inhibidor de CD123 es una proteína recombinante, por ejemplo, que comprende el ligando natural (o un fragmento) del receptor de CD123. Por ejemplo, la proteína recombinante es SL-401 (también llamada DT388IL3; University of Texas Southwestern Medical Center), que es una proteína de fusión que comprende IL-3 humana fusionada a una toxina de la difteria truncada. Véase, por ejemplo, Testa et al. Biomark Res. 2014; 2: 4; e Identificador de Ensayo Clínico No. NCT00397579.

En otra modalidad, el inhibidor de CD123 es un anticuerpo anti-CD123 o fragmento del mismo. En una modalidad, el anticuerpo anti-CD123 o fragmento del mismo comprende un anticuerpo monoclonal, por ejemplo, un anticuerpo monoespecífico o biespecífico o fragmento del mismo. Por ejemplo, el anticuerpo anti-CD123 o fragmento del mismo comprende CSL360 (CSL Limited). CSL360 es un anticuerpo monoclonal quimérico recombinante que se une a CD123. En algunas modalidades, CSL360 se administra por vía intravenosa, por ejemplo, mediante una infusión intravenosa. Por ejemplo, CSL360 se administra a una dosis de 0,1-10 mg/kg, por ejemplo, de 0,1-0,5 mg/kg, 0,5-1 mg/kg, 1-5 mg/kg o 5-10 mg/kg. Véase, por ejemplo, Identificador de Ensayo Clínico No. NCT01632852; y Tesla et al.

En otra modalidad, el anticuerpo CD123 o fragmento del mismo comprende CSL362 (CSL Limited). CSL362 es un anticuerpo monoclonal humanizado que se dirige a CD123 y está optimizado para una mayor activación de la citotoxicidad mediada por células dependiente de anticuerpos (ADCC). En algunas modalidades, CSL362 se administra por vía intravenosa, por ejemplo, mediante una infusión intravenosa. En algunos ejemplos, CSL362 se administra a una dosis de 0,1-12 mg/kg, por ejemplo, de 0,1-0,2 mg/kg, 0,2-0,5 mg/kg, 0,5-1 mg/kg, 1-6 mg/kg o 6-12 mg/kg. Véase, por ejemplo, el Identificador de Ensayo Clínico No. NCT01632852.

En una modalidad, el anticuerpo CD123 o fragmento del mismo comprende un

anticuerpo biespecífico, por ejemplo, MGD006 (MacroGenics). MGD006 es un anticuerpo biespecífico que se dirige a CD123 y CD3. Véase, por ejemplo, el Identificador de Ensayo Clínico No. NCT02152956.

En algunas modalidades, el inhibidor de CD123 se conjuga o se une de otra manera a un agente terapéutico.

En algunas modalidades, un inhibidor de CD123 incluye una célula que expresa un CAR anti-CD123, por ejemplo, TCAR, por ejemplo, una célula que expresa un constructo de CAR anti-CD123 o codificada por un CAR de unión a CD123 que comprende un scFv, CDR o cadenas VH y VL. Por ejemplo, una célula que expresa un CAR anti-CD123, por ejemplo, TCAR, es una célula generada a través de la adaptación de un CAR de CD123 (que comprende un dominio de unión a CD123) en una célula (por ejemplo, una célula T o célula NK), por ejemplo, para la administración en combinación con una célula que expresa un CAR descrita en el presente documento. En una modalidad, el constructo de CAR anti-CD123 comprende una secuencia de scFv, por ejemplo, una secuencia de scFv proporcionada en US 2014/0322212 A1, el cual se incluye en el presente documento a manera de referencia. En una modalidad, el dominio de unión anti-CD123 es un scFv descrito en US 2014/0322212 A1. En una modalidad, el dominio de unión anti-CD123 es parte de un constructo de CAR proporcionado en el documento US 2014/0322212 A1. El presente documento también proporciona métodos de uso de las células que expresan CAR descritas en el presente documento para la terapia adoptiva.

En otro aspecto, el presente documento proporciona una población de células que expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD123. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de CD123.

Inhibidores de CD10

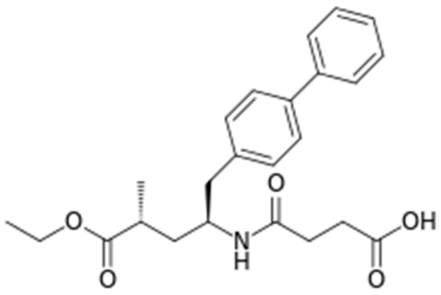
El grupo de diferenciación 10 (CD10) también se conoce como neprilisina, membrana metalo-endopeptidasa (MME), endopeptidasa neutra (NEP) y antígeno común de la leucemia linfoblástica aguda (CALA). CD10 es una enzima codificada por el gen metalo-endopeptidasa (MME). CD10 se expresa en células leucémicas de fenotipo pre-B y es un antígeno común de la

leucemia linfocítica aguda.

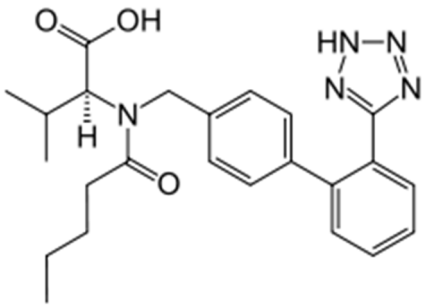
Tal como se usa en el presente documento, el término "CD10" se refiere a un determinante antigénico que se conoce por ser detectable en células de leucemia. Las secuencias de aminoácidos y de ácido nucleico humanas y de ratón se pueden encontrar en bases de datos públicas, tales como GenBank, UniProt y Swiss-Prot. Por ejemplo, las secuencias de aminoácidos de CD10 humano se pueden encontrar en los No. de Acceso NP_009218.2; NP_000893.2; NP_009219.2; NP_009220.2, y las secuencias de ARNm que las codifican se pueden encontrar en los No. de Acceso NM_007287.2 (variante 1bis); NM_000902.3 (variante 1); NM_007288.2 (variante 2a); NM_007289.2 (variante 2b). Como se usa en el presente documento, "CD10" incluye proteínas que comprenden mutaciones, por ejemplo, mutaciones puntuales, fragmentos, inserciones, deleciones y variantes corte y empalme de CD10 de tipo silvestre de extensión completa. En un aspecto, la porción de unión a antígeno del CAR reconoce y se une a un antígeno dentro del dominio extracelular de la proteína CD10. En un aspecto, la proteína CD10 se expresa en una célula cancerosa.

El presente documento también proporciona inhibidores de CD10 y terapias de combinación. Los inhibidores de CD10 incluyen, de manera enunciativa mas no limitativa, moléculas pequeñas, proteínas recombinantes, células que expresan CAR anti-CD10, por ejemplo, TCAR, y anticuerpos anti-CD10 (por ejemplo, un anticuerpo monoespecífico o biespecífico anti-CD10) y fragmentos de los mismos. En algunas modalidades, los inhibidores de anti-CD10 se pueden usar para tratar un tumor maligno de células B descrito en el presente documento. En una modalidad, el inhibidor de CD10 se administra en combinación con un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD19, por ejemplo, una célula que expresa un CAR descrita en el presente documento, por ejemplo, una célula que expresa un CAR que comprende un dominio de unión a anticuerpo que es murino, humano o humanizado.

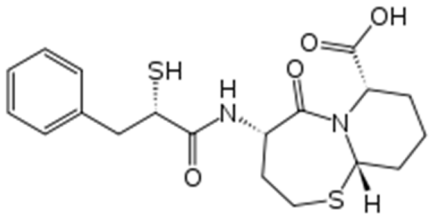
En una modalidad, el inhibidor de CD10 comprende sacubitril (AHU-377; Novartis) (ácido 4-{[(2*S*,4*R*)-1-(4-bifenilil)-5-etoxi-4-metil-5-oxo-2-pentanil]amino}-4-oxobutanoico), o una sal farmacéuticamente aceptable o un derivado del mismo. La estructura del sacubitril se muestra a continuación.



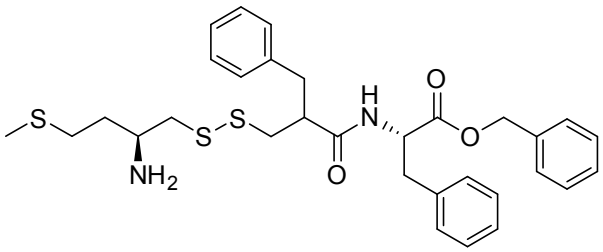
En otra modalidad, el inhibidor de CD10 comprende valsartán/sacubritril (LCZ696; Novartis) o una sal farmacéuticamente aceptable o un derivado del mismo. *Valsartán/sacubritril* es una combinación de fármacos que comprende una mezcla 1:1 de valsartán y sacubitril. La estructura de valsartán es (ácido (*S*)-3-metil-2-(*N*-{[2'-(2*H*-1,2,3,4-tetrazol-5-il)bifenil-4-il]metil}pentanamido)butanoico) se muestra a continuación.



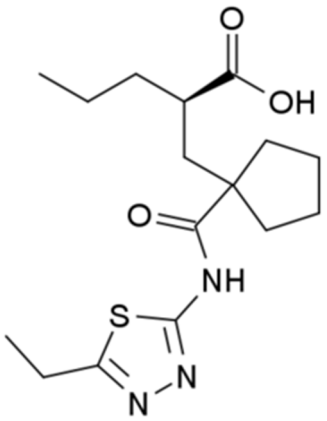
En una modalidad, el inhibidor de CD10 comprende omapatrilat (Bristol-Myers Squibb) (ácido (4*S*,7*S*,10a*S*)-5-oxo-4-{[(2*S*)-3-fenil-2- sulfanilpropanoil]amino}-2,3,4,7,8,9,10,10a-octahidropirido[6,1-*b*] [1,3]tiazepina-7-carboxílico), o una sal farmacéuticamente aceptable o un derivado del mismo. La estructura del omapatrilat se muestra a continuación.



En una modalidad, el inhibidor de CD10 comprende RB-101 (bencilo *N*-(3-{[(2*S*)-2-amino-4-(metiltio)butil]ditio}-2-bencilpropanoil)-L-fenilalaninato), o una sal farmacéuticamente aceptable o un derivado del mismo. La estructura de RB-101 se muestra a continuación.



En una modalidad, el inhibidor de CD10 comprende UK-414,495 (Pfizer) (ácido (R)-2-({1-[(5-etil-1,3,4-tiadiazol-2-il)carbamoil]ciclopentil}metil)valérico), o una sal farmacéuticamente aceptable o un derivado del mismo. La estructura de UK-414,495 se muestra a continuación.



En algunas modalidades, el inhibidor de CD10 se conjuga o se une de otra manera a un agente terapéutico.

En algunas modalidades, un inhibidor de CD10 incluye una célula que expresa un CAR anti-CD10, por ejemplo, TCAR, por ejemplo, una célula que expresa un constructo de CAR anti-CD10 o codificada por un CAR de unión a CD10 que comprende un scFv, CDR o cadenas VH y VL. Por ejemplo, una célula que expresa un CAR anti-CD10, por ejemplo, TCAR, es una célula generada a través de la adaptación de un CAR de CD10 (que comprende un dominio de unión a CD10) en una célula (por ejemplo, una célula T o célula NK), por ejemplo, para la administración en combinación con una célula que expresa un CAR descrita en el presente documento. El presente documento también proporciona métodos de uso de las células que expresan CAR descritas en el presente documento para la terapia adoptiva.

En otro aspecto, el presente documento proporciona una población de células que expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD10. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de CD10.

Inhibidores de CD34

El grupo de diferenciación 34 (CD34), también conocido como antígeno de células progenitoras hematopoyéticas CD34, es una glicoproteína de superficie celular que funciona como un factor de adhesión célula-célula. CD34 se expresa a veces en algunos tipos de cáncer/tumores, por ejemplo, sarcoma de parte blanda alveolar, LLA de células pre-B, LMA, LMA-M7, dermatofibrosarcoma protuberans, tumores del estroma gastrointestinal, fibroblastoma de células gigantes, sarcoma granulocítico, sarcoma de Kaposi, liposarcoma, histiocitoma fibroso maligno, tumores malignos de la vaina del nervio periférico, hemangiopericitomas mengingeales, meningiomas, neurofibromas, schwannomas y carcinoma papilar de tiroides.

Tal como se usa en el presente documento, el término "CD34" se refiere a un determinante antigénico que se conoce por ser detectable en células madre hematopoyéticas y algunas células cancerosas. Las secuencias de aminoácidos y de ácido nucleico humanas y de ratón se pueden encontrar en bases de datos públicas, tales como GenBank, UniProt y Swiss-Prot. Por ejemplo, las secuencias de aminoácidos de CD34 humana se pueden encontrar en los No. de Acceso NP_001020280.1 (isoforma precursora a); NP_001020280.1 (isoforma precursora b), y las secuencias de ARNm que las codifican se pueden encontrar en los No. de Acceso NM_001025109.1 (variante 1); NM_001773.2 (variante 2).c Como se usa en el presente documento, "CD34" incluye proteínas que comprenden mutaciones, por ejemplo, mutaciones puntuales, fragmentos, inserciones, deleciones y variantes de corte de CD34 de tipo silvestre de extensión completa. En un aspecto, la porción de unión a antígeno del CAR reconoce y se une a un antígeno dentro del dominio extracelular de la proteína CD34. En un aspecto, la proteína CD34 se expresa en una célula cancerosa.

El presente documento también proporciona inhibidores de CD34 y terapias de

combinación. Los inhibidores de CD34 incluyen, de manera enunciativa mas no limitativa, moléculas pequeñas, proteínas recombinantes, células que expresan CAR anti-CD34, por ejemplo, TCAR, y anticuerpos anti-CD34 (por ejemplo, un anticuerpo monoespecífico o biespecífico anti-CD34) y fragmentos de los mismos. En algunas modalidades, los inhibidores de anti-CD34 se pueden usar para tratar un tumor maligno de células B descrito en el presente documento. En una modalidad, el inhibidor de CD34 se administra en combinación con un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD19, por ejemplo, una célula que expresa un CAR descrita en el presente documento, por ejemplo, una célula que expresa un CAR que comprende un dominio de unión a anticuerpo que es murino, humano o humanizado.

En una modalidad, el inhibidor de CD34 comprende un anticuerpo o fragmento del mismo, por ejemplo, el anticuerpo monoclonal My-10 o un inmunoliposoma que comprende el anticuerpo monoclonal My-10, tal como se describe en Mercadal et al. Biochim. Biophys. Acta. 1371.1(1998): 17-23. En otras modalidades, el inhibidor de CD34 comprende un inmunoliposoma que contiene un medicamento contra el cáncer, por ejemplo, doxorrubicina, que se dirige a las células que expresan CD34, tal como se describe en Carrion et al. Life Sci. 75.3(2004): 313-28. En una modalidad, el inhibidor de CD34 comprende un anticuerpo monoclonal contra CD34 tal como se describe en Maleki et al. Hum. Antibodies. 22(2013): 1-8. En otra modalidad, el inhibidor de CD34 comprende un anticuerpo monoclonal que se dirige a CD34 tal como se describe en Maleki et al. Cell J. 16.3(2014): 361-66.

En algunas modalidades, el inhibidor de CD34 se conjuga o se une de otra manera a un agente terapéutico.

En algunas modalidades, un inhibidor de CD34 incluye una célula que expresa un CAR anti-CD34, por ejemplo, TCAR, por ejemplo, una célula que expresa un constructo de CAR anti-CD34 o codificada por un CAR de unión a CD34 que comprende un scFv, CDR o cadenas VH y VL. Por ejemplo, una célula que expresa un CAR anti-CD34, por ejemplo, TCAR, es una célula generada a través de la adaptación de un CAR de CD34 (que comprende un dominio de unión a CD34) en una célula (por ejemplo, una célula T o célula NK), por ejemplo, para la administración en combinación con una célula que expresa un CAR descrita en el presente documento. El presente documento también proporciona métodos de uso de las células que expresan CAR descritas en el presente documento para la terapia adoptiva.

En otro aspecto, el presente documento proporciona una población de células que expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD34. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de CD34.

Inhibidores de FLT-3

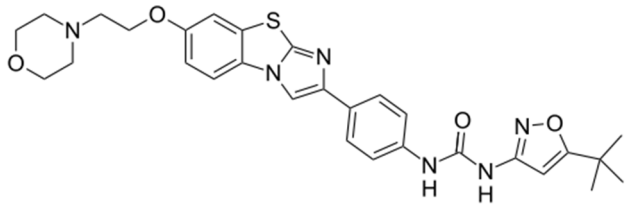
La tirosina quinasa 3 similar a fms (FLT-3), también llamada antígeno del grupo de diferenciación 135 (CD135), proteína tirosina quinasa de tipo receptor FLT3, o quinasa-2 de hígado fetal (Flk2), es una tirosina quinasa receptora. La FLT-3 es un receptor de citoquinas para el ligando, citoquina Flt3 ligando (Flt3L). La FLT-3 se expresa en la superficie de muchas células progenitoras hematopoyéticas y es importante para el desarrollo de linfocitos. El gen FLT3 está comúnmente mutado en la leucemia, por ejemplo, leucemia mieloide aguda (LMA).

Tal como se usa en el presente documento, el término "FLT-3" se refiere a un determinante antigénico que se conoce por ser detectable en células hematopoyéticas progenitoras y en algunas células cancerosas, por ejemplo, células de leucemia. Las secuencias de aminoácidos y de ácido nucleico humanas y de ratón se pueden encontrar en bases de datos públicas, tales como GenBank, UniProt y Swiss-Prot. Por ejemplo, las secuencias de aminoácidos de FLT-3 humana se puede encontrar en el No. de Acceso NP_004110.2 y las secuencias de ARNm que las codifican se pueden encontrar en el No. de Acceso NM_004119.2. Como se usa en el presente documento, "FLT-3" incluye proteínas que comprenden mutaciones, por ejemplo, mutaciones puntuales, fragmentos, inserciones, deleciones y variantes de corte de FLT-3 de tipo silvestre de extensión completa. En un aspecto, la porción de unión a antígeno del CAR reconoce y se une a un antígeno dentro del dominio extracelular de la proteína FLT-3. En un aspecto, la proteína FLT-3 se expresa en una célula cancerosa.

El presente documento también proporciona inhibidores de FLT-3 y terapias de combinación. Los inhibidores de FLT-3 incluyen, de manera enunciativa mas no limitativa, moléculas pequeñas, proteínas recombinantes, células que expresan CAR anti-FLT-3, por ejemplo, TCAR, y anticuerpos anti-FLT-3 (por ejemplo, un anticuerpo monoespecífico o biespecífico anti-FLT-3) y fragmentos de los mismos. En algunas modalidades, los inhibidores

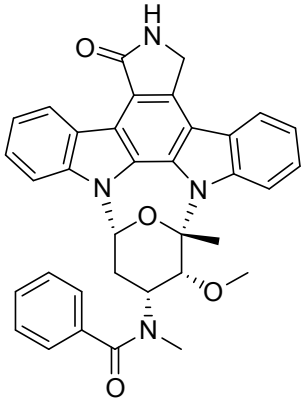
de anti-FLT-3 se pueden usar para tratar un tumor maligno de células B descrito en el presente documento. En una modalidad, el inhibidor de FLT-3 se administra en combinación con un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD19, por ejemplo, una célula que expresa un CAR descrita en el presente documento, por ejemplo, una célula que expresa un CAR que comprende un dominio de unión a anticuerpo que es murino, humano o humanizado.

En algunas modalidades, el inhibidor de FLT-3 comprende quizartinib (AC220; Ambit Biosciences) o una sal farmacéuticamente aceptable o derivado de la misma. Quizartinib es un inhibidor de tirosina quinasa receptora de moléculas pequeñas. La estructura del quizartinib (1-(5-(*tert*-butil)isoxazol-3-il)-3-(4-(7-(2-morfolinoetoxi)benzo[*d*]imidazo[2,1-b]tiazol-2-il)fenil)urea) se muestra a continuación.



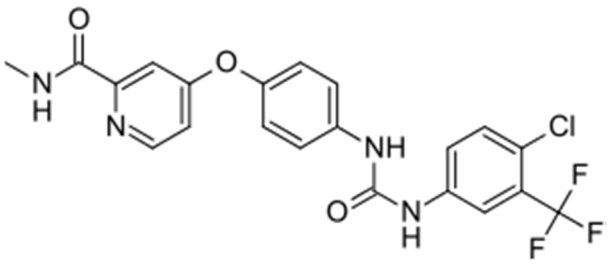
En algunas modalidades, el inhibidor de FLT-3 comprende midostaurina (PKC412; Technische Universität Dresden) o una sal farmacéuticamente aceptable o derivado del mismo**.** La midostaurina es un inhibidor de la proteína quinasa que es un derivado semisintético de la estaurosporina, un alcaloide de la bacteria Streptomyces staurosporeus.

La estructura de la midostaurina ((9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-hexahidro-10-etoxi-9-metil-11-(metilamino)-9,13-epoxi-1*H*,9*H*-diindol[1,2,3-gh:3',2',1'-lm]pirrol[3,4-j][1,7]benzodiamzonina-1-ona) se muestra a continuación



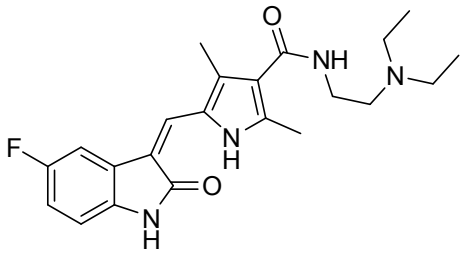
En algunas modalidades, la midostaurina se administra por vía oral, por ejemplo, en una dosis de aproximadamente 25-200 mg, por ejemplo, aproximadamente 25-50 mg, 50-100 mg, 100-150 mg o 150-200 mg. Por ejemplo, la midostaurina se administra, por ejemplo, por vía oral, en una dosis de aproximadamente 25-200 mg dos veces al día, por ejemplo, aproximadamente 25-50 mg, 50-100 mg, 100-150 mg o 150-200 mg dos veces al día. Véase, por ejemplo, el Identificador de Ensayo Clínico No. NCT01830361.

En una modalidad, el inhibidor de FLT-3 comprende sorafenib (Bayer y Onyx Pharmaceuticals) o una sal farmacéuticamente aceptable o derivado del mismo. El sorafenib es un inhibidor de moléculas pequeñas de múltiples proteínas tirosinas quinasas (por ejemplo, VEGFR y PDGFR), quinasas Raf (por ejemplo, C-Raf y B-Raf), y algunas serinas/teorinas quinasas intracelulares (por ejemplo, C-Raf, B-Raf de tipo silvestre y B-Raf mutante). Véase, por ejemplo, labeling.bayerhealthcare.com/html/products/pi/ Nexavar_PI.pdf. La estructura del sorafenib (4-[4-[[4-cloro-3-(trifluorometil)fenil]carbamoilamino]fenoxi]-*N*-metil-piridina-2-carboxamida) se muestra a continuación.

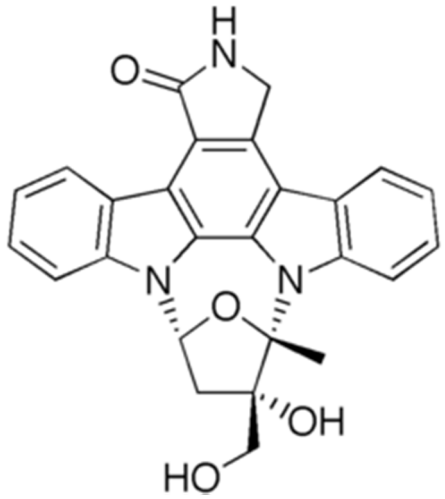


En algunas modalidades, el inhibidor de FLT-3 comprende sunitinib (anteriormente conocido como SU11248; Pfizer) o una sal farmacéuticamente aceptable o derivado del mismo. El sunitinib es un fármaco oral de moléculas pequeñas que inhibe múltiples tirosina quinasas receptoras, incluyendo FLT3. El sunitinib ha sido aprobado por la Administración de Alimentos

y Medicamentos (FDA) para el tratamiento del carcinoma de células renales (CCR) y el tumor del estroma gastrointestinal resistente a imatinib (GIST). La estructura del sunitinib (*N*-(2-dietilaminoetil)-5-[(*Z*)-(5-fluoro-2-oxo-1H-indol-3-iliden)metil]-2,4-dimetil-1*H*-pirrol-3-carboxamida) se muestra a continuación.



En algunas modalidades, el inhibidor de FLT-3 comprende lestaurtinib (CEP-701; Cephalon) o una sal farmacéuticamente aceptable o derivado del mismo. El lestaurtinib es un inhibidor de la tirosina quinasa que está estructuralmente relacionado con la estaurosporina. La estructura de lestaurtinib ((9*S*,10*S*,12*R*)-2,3,9,10,11,12-hexahidro-10-hidroxi-10-(hidroximetil)-9-metil-9,12-epoxi-1*H*-diindol[1,2,3-*fg*:3',2',1'-*kl*]pirrol[3,4-*i*][1,6]benzodiazocin-1-ona) se muestra a continuación.



En algunas modalidades, lestaurtinib se administra por vía oral, por ejemplo, en una dosis de aproximadamente 40-100 mg dos veces al día, por ejemplo, aproximadamente 40-60 mg, 50-70 mg, 60-80 mg, 70-90 mg o 80-100 mg dos veces al día. Véase, por ejemplo, el Identificador de Ensayo Clínico No. No. NCT00079482; o NCT00030186.

En algunas modalidades, el inhibidor de FLT-3 se conjuga o se une de otra manera a

un agente terapéutico.

En algunas modalidades, un inhibidor de FLT-3 incluye una célula que expresa un CAR anti-FLT-3, por ejemplo, TCAR, por ejemplo, una célula que expresa un constructo de CAR anti-FLT-3 o codificada por un CAR de unión a FLT-3 que comprende un scFv, CDR, o cadenas VH y VL. Por ejemplo, una célula que expresa un CAR anti-FLT-3, por ejemplo, TCAR, es una célula generada a través de la adaptación de un CAR de FLT-3 (que comprende un dominio de unión a FLT-3) en una célula (por ejemplo, una célula T o célula NK), por ejemplo, para la administración en combinación con una célula que expresa un CAR descrita en el presente documento. El presente documento también proporciona métodos de uso de las células que expresan CAR descritas en el presente documento para la terapia adoptiva.

En otro aspecto, el presente documento proporciona una población de células que expresan CAR, por ejemplo, células TCAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de FLT-3. Por ejemplo, en una modalidad, la población de células TCAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de FLT-3.

En una modalidad, el CAR de dominio de unión a antígeno (por ejemplo, un dominio de unión a antígeno de CD19, ROR1, CD20, CD22, CD123, CD10, CD34 o FLT-3) comprende una porción de scFv, por ejemplo, una porción de scFv humano. El scFv puede estar precedido por una secuencia líder opcional tal como la proporcionada en la SEQ ID NO.: 13, y seguido por una secuencia de bisagra opcional tal como la proporcionada en la SEQ ID NO.: 14 o SEQ ID NO.: 45 o SEQ ID NO.: 47 o SEQ ID NO.: 49, una región transmembrana tal como la proporcionada en SEQ ID NO.: 15, un dominio de señalización intracelular que incluye SEQ ID NO.: 16 o SEQ ID NO.: 51 y una secuencia de CD3 zeta que incluye SEQ ID NO.: 17 o SEQ ID NO.: 43, por ejemplo, donde los dominios son contiguos y están en el mismo marco de lectura para formar una proteína de fusión única.

En algunas modalidades, la presente divulgación incluye un ácido nucleico recombinante que comprende una molécula de ácido nucleico que codifica un CAR (por ejemplo, un CAR de CD19, un CAR de ROR1, un CAR de CD20, un CAR de CD22, un CAR de CD123, un CAR de CD10, un CAR de CD34 o un CAR de FLT-3), donde la molécula de ácido nucleico comprende la secuencia de ácido nucleico que codifica un dominio de unión a antígeno, por ejemplo, tal como el descrito en el presente documento, por ejemplo, que es

contiguo y está en el mismo marco de lectura que la secuencia de ácido nucleico que codifica un dominio de señalización intracelular. Un ejemplo de dominio de señalización intracelular que se puede usar en el CAR incluye, de manera enunciativa mas no limitativa, uno o más dominios de señalización intracelular, por ejemplo, CD3 zeta, CD28, 4-1BB y similares. En algunos casos, el CAR puede comprender cualquier combinación de CD3 zeta, CD28, 4-1BB y similares.

En una modalidad, el dominio de unión a antígeno (por ejemplo, CD19, ROR1, CD20, CD22, CD123, CD10, CD34 o FLT-3 dominio de unión a antígeno) se caracteriza por características o propiedades funcionales particulares de un anticuerpo o fragmento de anticuerpo. Por ejemplo, en una modalidad, la porción de una composición de CAR de la invención que comprende un dominio de unión a antígeno une específicamente un antígeno de células B humano (por ejemplo, CD19, ROR1, CD20, CD22, CD123, CD10, CD34 o FLT-3) o un fragmento del mismo. En ciertas modalidades, el scFv es contiguo y está en el mismo marco de lectura que una secuencia líder. En un aspecto, la secuencia líder es la secuencia del polipéptido proporcionada como SEQ ID NO.: 13.

En una modalidad, el dominio de unión a antígeno es un fragmento, por ejemplo, un fragmento variable de cadena única (scFv). En una modalidad, el dominio de unión a antígeno es un Fv, un Fab, un (Fab')2 o un anticuerpo híbrido bi-funcional (por ejemplo, bi-específico) (por ejemplo, Lanzavecchia et al., Eur. J. Immunol. 17, 105 (1987)). En un aspecto, los anticuerpos y fragmentos de los mismos de la invención se unen a una proteína de células B o a un fragmento de la misma con afinidad tipo silvestre o mejorada. En algunos casos, un scFv humano se puede derivar de una biblioteca de expresión.

En una modalidad, el dominio de unión a antígeno, por ejemplo, scFv, comprende al menos una mutación tal que el scFv mutado confiere una mayor estabilidad al constructo de CAR. En otra modalidad, el dominio de unión a antígeno, por ejemplo, scFv, comprende al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 mutaciones como resultado de, por ejemplo, el proceso de humanización, tales que el scFv mutado confiere una mayor estabilidad al constructo de CAR.

En una modalidad, la población de células que expresan CAR incluye, por ejemplo, una primera célula que expresa un CAR (por ejemplo, un CAR de CD19, un CAR de ROR1, un CAR de CD20, un CAR de CD22, un CAR de CD123, un CAR de CD10, un CAR de CD34 o un CAR de FLT-3), que incluye un dominio primario de señalización intracelular, y una segunda célula que expresa un CAR (por ejemplo, un CAR de CD19, un CAR de ROR1, un CAR de

CD20, un CAR de CD22, un CAR de CD123, un CAR de CD10, un CAR de CD34 o un CAR de FLT-3)), que incluye un dominio secundario de señalización.

Inhibidores de CD79b

Tal como se usa en el presente documento, el término "CD79b" se refiere a un determinante antigénico que se conoce por ser detectable en algunas células cancerosas hematológicas malignas, por ejemplo, células de leucemia. Las secuencias de aminoácidos y de ácido nucleico humanas y de ratón se pueden encontrar en bases de datos públicas, tales como GenBank, UniProt y Swiss-Prot. Por ejemplo, las secuencias de aminoácidos de CD79b humana se pueden encontrar en los No. de Acceso Nos. NP_000617.1 (isoforma precursora 1), NP_067613.1 (isoforma precursora 2) o NP_001035022.1 (isoforma precursora 3), y las secuencias de ARNm que las codifican se pueden encontrar en los No. de Acceso NM_000626.2 (variante de transcripción 1), NM_021602.2 (variante de transcripción 2) o NM_001039933.1 (variante de transcripción 3). Como se usa en el presente documento, "CD79b" incluye proteínas que comprenden mutaciones, por ejemplo, mutaciones puntuales, fragmentos, inserciones, deleciones y variantes de corte de CD79b de tipo silvestre de extensión completa. En un aspecto, la porción de unión a antígeno del CAR reconoce y se une a un antígeno dentro del dominio extracelular de la proteína CD79b. En un aspecto, la proteína CD79b se expresa en una célula cancerosa. En algunas modalidades, la proteína CD79b es una proteína CD79b de tipo silvestre; en otras modalidades, la proteína CD79b es una proteína CD79b mutante.

CD79b también se conoce como inmunoglobulina beta asociada, que es un componente del complejo multimérico del receptor de antígeno de linfocitos B. CD79b forma un heterodímero con otra proteína accesoria llamado CD79a (inmunoglobulina alfa), y el heterodímero se compleja con inmunoglobulinas de superficie en células B. CD79b es importante para el montaje y la expresión de superficie del receptor de antígeno de linfocitos B. CD79b y CD79a son importantes para el desarrollo de células pre-B y células B. La mutación y la expresión de CD79b aberrante se produce en muchas células de LLC B y pueden estar correlacionadas con la pérdida de la expresión de superficie y/o la señalización defectuosa del receptor de antígeno de linfocitos B en LLC B. Véase, por ejemplo, Thompson et al. Blood 90.4 (1997): 1387-94. En algunos casos, la sobreexpresión de una forma mutante o variante de corte y empalme de CD79b se ha correlacionado con la disminución del receptor de antígeno de

linfocitos B en LLC B y otros tumores malignos linfoides. Véase, por ejemplo, Cragg et al. Blood 100.9 (2002): 3068-76.

El presente documento proporciona inhibidores de CD79b y terapias de combinación. Los inhibidores de CD79b incluyen, de manera enunciativa mas no limitativa, moléculas pequeñas, proteínas recombinantes, células que expresan CAR anti-CD79b, por ejemplo, TCAR, y anticuerpos anti-CD79b (por ejemplo, un anticuerpo monoespecífico o biespecífico anti-CD79b) y fragmentos de los mismos. En algunas modalidades, los inhibidores de anti-CD79b se pueden usar para tratar un tumor maligno de células B descrito en el presente documento. En una modalidad, el inhibidor de CD79b se administra en combinación con un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD19, por ejemplo, una célula que expresa un CAR descrita en el presente documento, por ejemplo, una célula que expresa un CAR que comprende un dominio de unión a anticuerpo que es murino, humano o humanizado.

En una modalidad, el inhibidor de CD79b es un anticuerpo anti-CD79b o fragmento del mismo. En una modalidad, el anticuerpo anti-CD79b o fragmento del mismo comprende un anticuerpo monoclonal, por ejemplo, un anticuerpo monoespecífico o biespecífico o fragmento del mismo. Por ejemplo, el anticuerpo anti-CD79b o fragmento del mismo comprende un conjugado-fármaco de anticuerpo anti-CD79b tal como polatuzumab vedotin (Roche). En algunas modalidades, polatuzumab vedotin se usa para tratar un cáncer, por ejemplo, LNH, por ejemplo, linfoma folicular o DLBCL, por ejemplo, linfoma folicular DLBCL recidivante o refractario. Véase, por ejemplo, NCT02257567. En formas algunas modalidades, el anticuerpo anti-CD79b o fragmento del mismo es un anticuerpo biespecífico que comprende los componentes que se unen a CD32b y D79B, tales como MGD010 (MacroGenics). Véase, por ejemplo, NCT02376036.

En algunas modalidades, el inhibidor de CD79b se conjuga o se une de otra manera a un agente terapéutico.

En algunas modalidades, un inhibidor de CD79b incluye una célula que expresa un CAR anti-CD79b, por ejemplo, TCAR, por ejemplo, una célula que expresa un constructo de CAR anti-CD79b o codificada por un CAR de unión a CD79b que comprende un scFv, CDR o cadenas VH y VL. Por ejemplo, una célula que expresa un CAR anti-CD79b, por ejemplo, TCAR, es una célula generada a través de la adaptación de un CAR de CD79b (que comprende un dominio de unión a CD79b) en una célula (por ejemplo, una célula T o célula NK), por

ejemplo, para la administración en combinación con una célula que expresa un CAR descrita en el presente documento. El presente documento también proporciona métodos de uso de las células que expresan CAR descritas en el presente documento para la terapia adoptiva.

en otro aspecto, el presente documento proporciona una población de células que expresan CAR, por ejemplo, células TCAR o células NK que expresan CAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD79b. Por ejemplo, en una modalidad, la población de células que expresan CAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de CD79b.

Inhibidores de C179b

Tal como se usa en el presente documento, el término "CD179b" se refiere a un determinante antigénico que se conoce por ser detectable en algunas células cancerosas hematológicas malignas, por ejemplo, células de leucemia. Las secuencias de aminoácidos y de ácido nucleico humanas y de ratón se pueden encontrar en bases de datos públicas, tales como GenBank, UniProt y Swiss-Prot. Por ejemplo, las secuencias de aminoácidos de CD179b humana se pueden encontrar en los No. de Acceso Nos. NP_064455.1 (isoforma precursora a) o NP_690594.1 (isoforma precursora b), y las secuencias de ARNm que las codifican se pueden encontrar en los No. de Acceso NM_020070.3 (variante de transcripción 1) o NM_152855.2 (variante de transcripción 2). Como se usa en el presente documento, "CD179b" incluye proteínas que comprenden mutaciones, por ejemplo, mutaciones puntuales, fragmentos, inserciones, deleciones y variantes de corte de CD179b de tipo silvestre de extensión completa. En un aspecto, la porción de unión a antígeno del CAR reconoce y se une a un antígeno dentro del dominio extracelular de la proteína CD179b. En un aspecto, la proteína CD179b se expresa en una célula cancerosa. En algunas modalidades, la proteína CD179b es una proteína CD179b de tipo silvestre; en otras modalidades, la proteína CD179b es una proteína CD179b mutante.

CD179b también se llama polipéptido de tipo inmunoglobulina lambda 1 (IGLL1). CD179b es una subunidad de una cadena ligera heterodimérica que forma complejos con una cadena pesada mu de unión a membrana de IgG. Juntas, la cadena ligera y la cadena pesada forman el receptor de células preB. Las mutaciones en CD179b se han correlacionado con

deficiencia de células B y agammaglobulinemia. CD179b se expresa en algunas células cancerosas, por ejemplo, células de linfoma linfoblásticas células B precursoras.

El presente documento proporciona inhibidores de CD179b y terapias de combinación. Los inhibidores de CD179b incluyen, de manera enunciativa mas no limitativa, moléculas pequeñas, proteínas recombinantes, células que expresan CAR anti-CD179b, por ejemplo, TCAR, y anticuerpos anti-CD179b (por ejemplo, un anticuerpo monoespecífico o biespecífico anti-CD179b) y fragmentos de los mismos. En algunas modalidades, los inhibidores de anti-CD179b se pueden usar para tratar un tumor maligno de células B descrito en el presente documento. En una modalidad, el inhibidor de CD179b se administra en combinación con un inhibidor de CD20, por ejemplo, una célula que expresa un CAR de CD19, por ejemplo, una célula que expresa un CAR descrita en el presente documento, por ejemplo, una célula que expresa un CAR que comprende un dominio de unión a anticuerpo que es murino, humano o humanizado.

En una modalidad, el inhibidor de CD179b es un anticuerpo anti-CD179b o fragmento del mismo. En una modalidad, el anticuerpo anti-CD179b o fragmento del mismo comprende un anticuerpo monoclonal, por ejemplo, un anticuerpo monoespecífico o biespecífico o fragmento del mismo.

En algunas modalidades, el inhibidor de CD179b se conjuga o se une de otra manera a un agente terapéutico.

En algunas modalidades, un inhibidor de CD179b incluye una célula que expresa un CAR anti-CD179b, por ejemplo, TCAR, por ejemplo, una célula que expresa un constructo de CAR anti-CD179b o codificada por un CAR de unión a CD179b que comprende un scFv, CDR o cadenas VH y VL. Por ejemplo, una célula que expresa un CAR anti-CD179b, por ejemplo, TCAR, es una célula generada a través de la adaptación de un CAR de CD179b (que comprende un dominio de unión a CD179b) en una célula (por ejemplo, una célula T o célula NK), por ejemplo, para la administración en combinación con una célula que expresa un CAR descrita en el presente documento. El presente documento también proporciona métodos de uso de las células que expresan CAR descritas en el presente documento para la terapia adoptiva.

en otro aspecto, el presente documento proporciona una población de células que expresan CAR, por ejemplo, células TCAR o células NK que expresan CAR, que comprende

una mezcla de células que expresan CAR de CD19 y CAR de CD179b. Por ejemplo, en una modalidad, la población de células que expresan CAR puede incluir una primera célula que expresa un CAR de CD19 y una segunda célula que expresa un CAR de CD179b.

Inhibidores de CD79a

Tal como se usa en el presente documento, el término "CD79a" se refiere a un determinante antigénico que se conoce por ser detectable en algunas células cancerosas hematológicas malignas, por ejemplo, células de leucemia. Las secuencias de aminoácidos y de ácido nucleico humanas y de ratón se pueden encontrar en bases de datos públicas, tales como GenBank, UniProt y Swiss-Prot. Por ejemplo, las secuencias de aminoácidos de CD79a humana se pueden encontrar en los No. de Acceso Nos. NP_001774.1 (isoforma precursora 1) o NP_067612.1 (isoforma precursora 2), y las secuencias de ARNm que las codifican se pueden encontrar en los No. de Acceso NM_001783.3 (variante de transcripción 1) o NM_021601.3 (variante de transcripción 2). Como se usa en el presente documento, "CD79a" incluye proteínas que comprenden mutaciones, por ejemplo, mutaciones puntuales, fragmentos, inserciones, deleciones y variantes de corte de CD79a de tipo silvestre de extensión completa. En un aspecto, la porción de unión a antígeno del CAR reconoce y se une a un antígeno dentro del dominio extracelular de la proteína CD79a. En un aspecto, la proteína CD79a se expresa en una célula cancerosa. En algunas modalidades, la proteína CD79a es una proteína CD79a de tipo silvestre; en otras modalidades, la proteína CD79a es una proteína CD79a mutante.

CD79a también se llama alfa asociada a inmunoglobulina. CD79a se heterodimeriza con CD79b para formar un componente del complejo multimérico del receptor de antígeno de linfocitos B. CD79a se expresa en muchos cánceres hematológicos, por ejemplo, leucemias agudas (por ejemplo, LAM), linfomas de células B y mielomas.

El presente documento proporciona inhibidores de CD79a y terapias de combinación. Los inhibidores de CD79a incluyen, de manera enunciativa mas no limitativa, moléculas pequeñas, proteínas recombinantes, células que expresan CAR anti-CD79a, por ejemplo, TCAR, y anticuerpos anti-CD79a (por ejemplo, un anticuerpo monoespecífico o biespecífico anti-CD79a) y fragmentos de los mismos. En algunas modalidades, los inhibidores de anti-CD79a se pueden usar para tratar un tumor maligno de células B descrito en el presente documento. En una

modalidad, el inhibidor de CD79a se administra en combinación con un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD19, por ejemplo, una célula que expresa un CAR descrita en el presente documento, por ejemplo, una célula que expresa un CAR que comprende un dominio de unión a anticuerpo que es murino, humano o humanizado.

En una modalidad, el inhibidor de CD79a es un anticuerpo anti-CD79a o fragmento del mismo. En una modalidad, el anticuerpo anti-CD79a o fragmento del mismo comprende un anticuerpo monoclonal, por ejemplo, un anticuerpo monoespecífico o biespecífico o fragmento del mismo. Por ejemplo, el anticuerpo anti-CD79a o un fragmento del mismo comprende un anticuerpo anti-CD79a o un fragmento del mismo (por ejemplo, regiones variables o CDR) descrito en Polson et al. Blood 110.2(2007): 616-23, que se incluye en el presente documento a manera de referencia. Por ejemplo, el anticuerpo anti-CD79a o un fragmento del mismo comprende el anticuerpo 7H7, 15E4 o 16C11, o un fragmento del mismo (por ejemplo, regiones variables o CDR), descrito en Polson et al. Véase Id.

En algunas modalidades, el inhibidor de CD79a se conjuga o se une de otra manera a un agente terapéutico.

En algunas modalidades, un inhibidor de CD79a incluye una célula que expresa un CAR anti-CD79a, por ejemplo, TCAR, por ejemplo, una célula que expresa un constructo de CAR anti-CD79a o codificada por un CAR de unión a CD79a que comprende un scFv, CDR o cadenas VH y VL. Por ejemplo, una célula que expresa un CAR anti-CD79a, por ejemplo, TCAR, es una célula generada a través de la adaptación de un CAR de CD79a (que comprende un dominio de unión a CD79a) en una célula (por ejemplo, una célula T o célula NK), por ejemplo, para la administración en combinación con una célula que expresa un CAR descrita en el presente documento. El presente documento también proporciona métodos de uso de las células que expresan CAR descritas en el presente documento para la terapia adoptiva.

en otro aspecto, el presente documento proporciona una población de células que expresan CAR, por ejemplo, células TCAR o células NK que expresan CAR, que comprende una mezcla de células que expresan CAR de CD19 y CAR de CD79a. Por ejemplo, en una modalidad, la población de células que expresan CAR puede incluir una primera célula que expresa un CAR de CD20 y una segunda célula que expresa un CAR de CD79a.

Terapias CAR

Los inhibidores del presente documento, por ejemplo, células que expresan CAR dirigidos a CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a, pueden comprender una o más de las coposiciones descritas en el presente documento, por ejemplo, un dominio trasmembrana, un dominio de señalización intracelular, un dominio coestimulador, una secuencia líder o una bisagra.

En un aspecto, la presente invención abarca un constructo de ácido nucleico recombinante que comprende un transgen que codifica un CAR. En algunas modalidades, la molécula de ácido nucleíco comprende una secuencia de ácido nucléico que codifica un dominio de unión anti-CD19 seleccionado a partir de una o más se las SEQ ID NOS: 61-72, en donde la secuencia es contigua con y está en el mismo marco de lectura de la secuencia de ácido nucleíco que codifica un dominio de señalización intracelular. Un dominio de señalización intracelular que puede ser utilizado en el CAR incluye, pero no está limitado a uno o más dominios de señalización intracelular de, por ejemplo, CD3-zeta, CD28, 4-1BB y similares. En algunos casos, el CAR puede comprender cualquier combinación de CD3-zeta, CD28, 4-1BB y similares.

En un aspecto, la presente invención contempla modificaciones de la secuencia de aminoácidos de partida del anticuerpo o fragmento (por ejemplo, scFv) que generan moléculas funcionalmente equivalentes. Por ejemplo, VH o VL de un dominio de unión a antígeno, por ejemplo, scFv, comprendido en el CAR, se puede modificar para retener al menos aproximadamente 70 %, 71 %, 72 %, 73 %, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %,81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 % de identidad de la región marco VH o VL de partida del dominio de unión a antígeno, por ejemplo, scFv. La presente invención contempla modificaciones en todo el constructo de CAR, por ejemplo, modificaciones en una o más secuencias de aminoácidos de los diversos dominios del constructo de CAR con el fin de generar moléculas funcionalmente equivalentes. El constructo de CAR se puede modificar para retener al menos aproximadamente 70 %, 71 %, 72 %, 73 %, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 % de identidad del constructo de CAR de partida. La presente invención también contempla modificaciones de CDR, por ejemplo, modificaciones en una o más secuencias de aminoácidos de una o más CDR de un constructo de CAR con el fin de generar moléculas funcionalmente

equivalentes. Por ejemplo, la CDR puede tener, por ejemplo, hasta e incluyendo 1, 2, 3, 4, 5 o 6 alteraciones (por ejemplo, sustituciones) con respecto a una secuencia de CDR proporcionada en el presente documento.

Las secuencias de ácidos nucleicos que codifican para las moléculas deseadas se pueden obtener usando métodos recombinantes conocidos en la técnica, tales como, por ejemplo, realizando un paneo de células que expresan el gen, derivando el gen a partir de un vector conocido para incluir el mismo o mediante aislamiento directo a partir de células y tejidos que contienen el mismo, usando técnicas estándar. Alternativamente, el ácido nucleico de interés se puede producir de manera sintética, en lugar de clonarse.

La presente invención incluye, entre otras cosas, constructos de vectores retrovirales y lentivirales que expresan un CAR que se pueden transducir directamente a una célula.

La presente invención también incluye un constructo de ARN que se puede transfectar directamente a una célula. Un método de generación de ARNm para uso en la transfección implica la transcripción in vitro (IVT) de una plantilla con cebadores especialmente diseñados, seguida de la adición de poliA, para producir un constructo que contiene una secuencia no traducida 3' y 5' ("UTR"), un cap 5' y/o un sitio interno de entrada al ribosoma (IRES), el ácido nucleico a ser expresado y una cola poliA, típicamente con una longitud de 50-2000 bases (SEQ ID NO.: 118). El ARN así producido puede transfectar eficientemente diferentes tipos de células. En una modalidad, la plantilla incluye secuencias para el CAR. En una modalidad, un vector de ARN del CAR se transduce a una célula T mediante electroporación.

Dominio de unión a antígeno

En un aspecto, el CAR de la invención comprende un elemento de unión a un blanco específico denominado también un dominio de unión a antígeno. La elección de la fracción depende del tipo y el número de ligandos que definen la superficie de una célula blanco. Por ejemplo, el dominio de unión a antígeno puede ser escogido para reconocer un ligando que actúa como un marcador de superficie celular en las células blanco asociadas con un estado de enfermedad particular. Por lo tanto, ejemplos de marcadores de superficie celular que pueden actuar como ligandos para el dominio de unión a antígeno en un CAR de la invención incluyen aquellos asociados con infecciones virales, bacterianas y parasitarias, enfermedades

autoinmunes y células cancerosas. El dominio de unión a antígeno puede unirse, por ejemplo, a uno o más de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a.

En un aspecto, la respuesta de las células T mediada por CAR puede ser dirigida a un antígeno de interés modificando un dominio de unión a antígeno que se une específicamente a un antígeno deseado en el CAR.

El dominio de unión a antígeno (por ejemplo, un dominio de unión a antígeno que se une a uno o más de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a) puede ser cualquier dominio que se une al antígeno, incluyendo, de manera enunciativa mas no limitativa, un anticuerpo monoclonal, un anticuerpo policlonal, un anticuerpo recombinante, un anticuerpo murino, un anticuerpo humano, un anticuerpo humanizado y un fragmento funcional de los mismos, incluyendo, de manera enunciativa mas no limitativa, un anticuerpo de dominio único tal como un dominio variable de cadena pesada (VH), un dominio variable de cadena ligera (VL) y un dominio variable (VHH) de nanocuerpo derivado de camélido, y una estructura alternativa de la cual se sabe en la técnica que funciona como dominio de unión a antígeno, tal como un dominio de fibronectina recombinante, y similares.

En algunos casos, es beneficioso para el dominio de unión a antígeno ser derivado de la misma especie en la que el CAR será usado. Por ejemplo, para uso en seres humanos, puede ser beneficioso para el dominio de unión a antígeno (por ejemplo, un dominio de unión a antígeno que se une a uno o más de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a) del CAR comprender residuos humanos o humanizados para el dominio de unión a antígeno de un anticuerpo o fragmento de anticuerpo.

Un anticuerpo humanizado se puede producir usando una variedad de técnicas conocidas en la técnica, incluyendo, de manera enunciativa mas no limitativa, injerto de CDR (véase, por ejemplo, la Patente Europea No. EP 239,400; la Publicación Internacional No. WO 91/09967; y las Patentes de Estados Unidos No. No. 5,225,539, 5,530,101 y 5,585,089, cada una de las cuales se incluye en el presente documento en su totalidad a manera de referencia), inactivación o remodelado de superficie (véase, por ejemplo, las Patentes Europeas No. EP 592106 y EP 519596;. Padlan, 1991, Molecular Immunology, 28 (4/5): 489-498; Studnicka et al., 1994, Protein Engineering, 7(6): 805-814; y Roguska et al., 1994, PNAS, 91: 969-973, cada una de las cuales se incluye en el presente documento en su totalidad a manera de referencia), intercambio

de cadenas (véase, por ejemplo, la Patente de Estados Unidos No. 5,565,332, que se incluye en el presente documento en su totalidad a manera de referencia), y técnicas descritas en, por ejemplo, la Publicación de Solicitud de Patente de Estados Unidos No. US2005/0042664, la Publicación de Solicitud de Patente de Estados Unidos No. US2005/0048617, la Patente de Estados Unidos No. 6,407,213, la Patente de Estados Unidos No. 5,766,886, la Publicación Internacional No. WO 9317105, Tan et al., J. Immunol., 169: 1119-25 (2002), Caldas et al., Protein Eng., 13(5): 353-60 (2000), Morea et al., Methods, 20(3): 267-79 (2000), Baca et al., J. Biol. Chem., 272(16): 10678-84 (1997), Roguska et al., Protein Eng., 9(10): 895-904 (1996), Couto et al., Cancer Res., 55 (23 Supp): 5973s-5977s (1995), Couto et al., Cancer Res., 55(8): 1717-22 (1995), Sandhu J S, Gene, 150(2): 409-10 (1994) y Pedersen et al., J. Mol. Biol., 235(3): 959-73 (1994), cada uno de los cuales se incluye en el presente documento en su totalidad a manera de referencia. A menudo, los restos de marco en las regiones marco serán sustituidos por el residuo correspondiente del anticuerpo donador de CDR para alterar, por ejemplo, mejorar, la unión a antígeno. Estas sustituciones en el marco se identifican mediante métodos bien conocidos en la técnica, por ejemplo, mediante modelado de las interacciones entre la CDR y los restos de marco para identificar restos de marco importantes para la unión a antígeno, y comparación de secuencias para identificar restos de marco inusuales en posiciones específicas. (Véase, por ejemplo, Queen et al., Patente de los Estados Unidos No. 5,585,089; y Riechmann et al., 1988, Nature, 332: 323, que se incluyen en el presente documento en su totalidad a manera de referencia).

Un anticuerpo o fragmento de anticuerpo humanizado conserva uno o más residuos de aminoácidos provenientes de una fuente no humana. Estos residuos de aminoácidos no humanos se denominan frecuentemente como residuos "importados", y por lo general se toman de un dominio variable "importado". Según se explica en el presente documento, los anticuerpos o fragmentos de anticuerpo humanizados comprenden una o más CDR de regiones marco y moléculas de inmunoglobulina no humana, donde los residuos de aminoácidos que comprenden el marco se derivan completamente o en su mayoría de la línea germinal humana. Múltiples técnicas para la humanización de anticuerpos o fragmentos de anticuerpos son bien conocidas en la técnica y se pueden llevar a cabo esencialmente siguiendo el método de Winter y colaboradores (Jones et al., Nature, 321: 522-525 (1986); Riechmann et al., Nature, 332: 323-327 (1988); Verhoeyen et al., Science, 239: 1534-1536 (1988)), mediante la sustitución de CDR o secuencias de CDR de roedores por las secuencias correspondientes de un anticuerpo humano,

es decir, injertos de CDR (EP 239 400; Publicación PCT No. WO 91/09967; y Patente de Estados Unidos Nos. 4,816,567; 6,331,415; 5,225,539; 5,530,101; 5,585,089; 6,548,640, cuyos contenidos se incluyen en su totalidad en el presente documento a manera de referencia). En dichos anticuerpos y fragmentos de anticuerpos humanizados, sustancialmente menos de un dominio variable humano intacto ha sido sustituido por la secuencia correspondiente de una especie no humana. Los anticuerpos humanizados a menudo son anticuerpos humanos en los que algunos residuos de CDR y posiblemente algunos restos de marco (FR) se sustituyen por residuos de sitios análogos en anticuerpos de roedores. La humanización de anticuerpos y fragmentos de anticuerpos también se puede lograr mediante inactivación o remodelado de superficie (EP 592,106; EP 519,596; Padlan, 1991, Molecular Immunology, 28(4/5): 489-498; Studnicka et al., Protein Engineering, 7(6): 805-814 (1994); y Roguska et al., PNAS, 91: 969-973 (1994)) o intercambio de cadenas (Patente de Estados Unidos No. 5,565,332), cuyos contenidos se incluyen en su totalidad en el presente documento a manera de referencia.

Los dominios variables humanos, tanto ligeros como pesados, usados para la fabricación de anticuerpos humanizados se eligen con el fin de reducir la antigenicidad. De acuerdo con el llamado método de "ajuste óptimo", la secuencia del dominio variable de un anticuerpo de roedor se analiza con relación a toda la biblioteca de secuencias de dominios variables humanos conocidos. La secuencia humana que esté más cercana a la del roedor se acepta entonces como el marco humano (FR) para el anticuerpo humanizado (Sims et al., J. Immunol, 151: 2296 (1993); Chothia et al., J. Mol. Biol., 196: 901 (1987), cuyos contenidos se incluyen en su totalidad en el presente documento a manera de referencia). Otro método usa un marco específico derivado de la secuencia consenso de todos los anticuerpos humanos de un subgrupo particular de cadenas ligeras o pesadas. El mismo marco se puede usar para varios anticuerpos humanizados diferentes (véase, por ejemplo, Nicholson et al. Mol. Immun. 34 (16-17): 1157-1165 (1997); TCARer et al., Proc. Natl. Acad. Sci. USA, 89: 4285 (1992); Presta et al., J. Immunol., 151: 2623 (1993), cuyo contenido se incluye en el presente documento en su totalidad a manera de referencia). En algunas modalidades, la región marco, por ejemplo, las cuatro regiones marco de la región variable de cadena pesada se derivan de una secuencia de línea germinal VH4_4-59. En una modalidad, la región marco puede comprender una, dos, tres, cuatro o cinco modificaciones, por ejemplo, sustituciones, por ejemplo, del aminoácido en la secuencia murina correspondiente (por ejemplo, de SEQ ID NO.: 59). En una modalidad, la región marco, por ejemplo, las cuatro regiones marco de la región variable de cadena ligera se derivan de una

secuencia de línea germinal VK3_1.25. En una modalidad, la región marco puede comprender una, dos, tres, cuatro o cinco modificaciones, por ejemplo, sustituciones, por ejemplo, del aminoácido en la secuencia murina correspondiente (por ejemplo, de SEQ ID NO.: 59).

En algunos aspectos, la porción de una composición de CAR de la invención que comprende un fragmento de anticuerpo es humanizada reteniendo la alta afinidad por el antígeno blanco y otras propiedades biológicas favorables. De acuerdo con un aspecto de la invención, los anticuerpos y fragmentos de anticuerpos humanizados se preparan a través de un proceso de análisis de las secuencias parentales y diversos productos humanizados conceptuales usando modelos tridimensionales de las secuencias parentales y humanizadas. Los modelos de inmunoglobulina tridimensionales están comúnmente disponibles y son conocidos por las personas versadas en la materia. Existen programas informáticos que ilustran y muestran probables estructuras conformacionales tridimensionales de secuencias de inmunoglobulina candidatas específicas. Un examen de estos resultados permite analizar el posible papel de los residuos en el funcionamiento de la secuencia de inmunoglobulina candidata, por ejemplo, analizar los residuos que influyen en la capacidad de la inmunoglobulina candidata para unirse al antígeno blanco. De esta manera, residuos de FR se pueden seleccionar y combinar a partir de las secuencias receptoras y de importación, lo que permite lograr la característica deseada del anticuerpo o fragmento de anticuerpo, tal como una mayor afinidad por el antígeno blanco. En general, los residuos de CDR tienen una influencia directa y más sustancial en la unión al antígeno.

Un anticuerpo o fragmento de anticuerpo humanizado puede retener una especificidad antigénica similar a la del anticuerpo original, por ejemplo, en la presente invención, la capacidad de unirse a CD19, CD20 o CD22 humana. En algunas modalidades, un anticuerpo o fragmento de anticuerpo humanizado puede haber aumentado la afinidad y/o especificidad de unión a CD19, CD20 o CD22 humana.

En un aspecto, el dominio de unión por ejemplo, un dominio de unión a antígeno que se une a uno o más de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a) es un fragmento, por ejemplo, un fragmento variable de cadena única (scFv). En un aspecto, el dominio de unión a anti-CD19 es un Fv, un Fab, un (Fab')2 o un anticuerpo híbrido bi-funcional (por ejemplo, bi-específico) (por ejemplo, Lanzavecchia et al., Eur. J. Immunol. 17, 105 (1987)). En un aspecto, los anticuerpos y fragmentos de los mismos de

la invención se unen a una proteína CD19, CD20 o CD22 o a un fragmento de la misma con afinidad natural o aumentada.

En algunos casos, los scFv se pueden preparar según el método conocido en la técnica (véase, por ejemplo, Bird et al., (1988) Science 242: 423-426 y Huston et al., (1988) Proc. Natl. Acad. Sci. USA 85: 5879-5883). Es posible producir moléculas de scFv enlazando las regiones VH y VL usando polipéptidos enlazadores flexibles. Las moléculas de scFv comprenden un enlazador (por ejemplo, un enlazador Ser-Gly) con una longitud y/o composición de aminoácidos optimizadas. La longitud del enlazador puede afectar en gran medida la forma en la que las regiones variables de un scFv se pliegan e interactúan. De hecho, el plegado entre cadenas se evita si se emplea un polipéptido enlazador corto (por ejemplo, entre 5-10 aminoácidos). El plegado entre cadenas también se requiere para unir las dos regiones variables con el fin de formar un sitio de unión al epítopo funcional. Para ver ejemplos de la orientación y el tamaño del enlazador véase, por ejemplo, Hollinger et al. 1993 Proc Natl Acad. Sci. USA 90: 6444 a 6448, Publicación de Solicitud de Patente de Estados Unidos No. 2005/0100543, 2005/0175606, 2007/0014794 y Publicación PCT No. WO2006/020258 y WO2007/024715, que se incluye en el presente documento a manera de referencia.

Un scFv puede comprender un enlazador de al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50 o más residuos de aminoácidos entre sus regiones VL y VH. La secuencia del enlazador puede comprender cualquier aminoácido de origen natural. En algunas modalidades, la secuencia del enlazador comprende los aminoácidos glicina y serina. En otra modalidad, la secuencia del enlazador comprende conjuntos de repeticiones de glicina y serina tales como $(Gly_4Ser)n$, donde n es un entero positivo igual o mayor que 1 (SEQ ID NO.: 18). En una modalidad, el enlazador puede ser $(Gly_4Ser)_4$ (SEQ ID NO.: 106) o $(Gly_4Ser)_3$(SEQ ID NO.:107). La variación en la longitud del enlazador puede mantener o aumentar la actividad, dando lugar a una eficacia superior en los estudios de actividad.

En algunas modalidades, se puede modificar la secuencia de aminoácidos del dominio de unión a antígeno (por ejemplo, un dominio de unión a antígeno que se une a uno o más de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a) u otras porciones o el CAR en su totalidad), por ejemplo, se puede modificar una secuencia de aminoácidos descrita en el presente documento, por ejemplo, mediante una sustitución

conservadora. La técnica ha definido familias de residuos de aminoácidos que tienen cadenas laterales similares, incluyendo cadenas laterales básicas (por ejemplo, lisina, arginina, histidina), cadenas laterales ácidas (por ejemplo, ácido aspártico, ácido glutámico), cadenas laterales polares sin carga (por ejemplo, glicina, asparagina, glutamina, serina, treonina, tirosina, cisteína), cadenas laterales no polares (por ejemplo, alanina, valina, leucina, isoleucina, prolina, fenilalanina, metionina, triptófano), cadenas laterales ramificadas en beta (por ejemplo, treonina, valina, isoleucina) y cadenas laterales aromáticas (por ejemplo, tirosina, fenilalanina, triptófano, histidina).

El porcentaje de identidad en el contexto de dos o más ácidos nucleicos o secuencias de polipéptidos se refiere a dos o más secuencias que son la misma. Dos secuencias son "sustancialmente idénticas" si dos secuencias tienen un porcentaje específico de residuos de aminoácidos o nucleótidos que son iguales (por ejemplo, 60 % de identidad, opcionalmente 70 %, 71 %. 72 %, 73 %, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 % de identidad frente una región específica, o, cuando no se especifica, frente a toda la secuencia), cuando se comparan y se alinean para correspondencia máxima frente a una ventana de comparación, o una región designada medida usando uno de los siguientes algoritmos de comparación de secuencias o mediante alineamiento manual e inspección visual. Opcionalmente, la identidad existe frente a una región con una longitud de al menos aproximadamente 50 nucleótidos (o 10 aminoácidos), o frente a una región con una longitud de 100 a 500 o 1000 o más nucleótidos (o 20, 50, 200 o más aminoácidos).

Para la comparación de secuencias, típicamente una secuencia actúa como secuencia de referencia, contra la que se comparan las secuencias de prueba. Al usar un algoritmo de comparación de secuencias, las secuencias de prueba y de referencia se introducen en un ordenador, se designan coordenadas de subsecuencias, si es necesario, y se designan los parámetros de programa de algoritmo de secuencia. Pueden usarse los parámetros por defecto del programa, o pueden designarse parámetros alternativos. Luego, el algoritmo de comparación de secuencias calcula el porcentaje de identidad de secuencia para las secuencias de prueba relativas a la secuencia de referencia, basándose en los parámetros del programa. Los métodos de alineación de secuencias para comparación son bien conocidos en la técnica. El alineamiento óptimo de las secuencias para comparación se puede llevar a cabo, por ejemplo, mediante el

algoritmo de homología local de Smith y Waterman, (1970) Adv. Appl. Math. 2: 482c, mediante el algoritmo de alineamiento de homología de Needleman y Wunsch, (1970) J. Mol. Biol. 48: 443, mediante el método de búsqueda de similitud de Pearson y Lipman, (1988) Proc. Natl. Acad. Sci. USA 85: 2444, mediante implementaciones computarizadas de estos algoritmos (GAP, BESTFIT, FASTA y TFASTA en Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), o mediante alineamiento manual e inspección visual (véase, por ejemplo, Brent et al., (2003) Current Protocols in Molecular Biology).

Dos ejemplos de algoritmos que son adecuados para determinar el porcentaje de identidad de secuencia y la similitud de secuencia son los algoritmos BLAST y BLAST 2.0., los cuales se describen en Altschul et al., (1977) Nuc. Acids Res. 25:3389-3402; y Altschul et al., (1990) J. Mol. Biol. 215: 403-410, respectivamente. El software para realizar análisis BLAST está disponible públicamente a través del Centro Nacional de Información Biotecnológica.

El porcentaje de identidad entre dos secuencias de aminoácidos también se puede determinar usando el algoritmo de E. Meyers y W. Miller, (1988) Comput. Appl. Biosci. 4: 11-17) que se ha incorporado en el programa ALIGN (versión 2.0), usando una tabla de residuos de peso PAM120, una penalización por longitud de gap de 12 y una penalización por gap de 4. Además, el porcentaje de identidad entre dos secuencias de aminoácidos se puede determinar usando el algoritmo de Needleman y Wunsch (1970) J. Mol. Biol. 48: 444-453), el cual ha sido incorporado en el programa GAP en el paquete de software GCG (disponible en www.gcg.com), usando ya sea una matriz Blossom 62 o una matriz PAM250, y un peso de gap de 16, 14, 12, 10, 8, 6 o 4 y un peso de longitud de 1, 2, 3, 4, 5 o 6.

En un aspecto, la presente invención contempla modificaciones de la secuencia de aminoácidos de partida del anticuerpo o fragmento (por ejemplo, scFv) que generan moléculas funcionalmente equivalentes. Por ejemplo, VH o VL de un dominio de unión por ejemplo, un dominio de unión a antígeno que se une a uno o más de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a), por ejemplo, scFv, comprendido en el CAR, se puede modificar para retener al menos aproximadamente 70 %, 71 %, 72%, 73 %, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %,81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 % de identidad de la región marco VH o VL de partida del dominio de unión anti-CD19, por ejemplo, scFv. De manera más general, VH o VL de un dominio de unión a antígeno de células B, a CD10, CD20, CD22,

CD34, CD123, FLT-3 o ROR1, por ejemplo, scFv, comprendida en el CAR, se puede modificar para retener al menos aproximadamente 70 %, 71 %, 72%, 73 %, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %,81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 % de identidad de la región marco VH o VL de partida del dominio de unión a antígeno, por ejemplo, scFv. La presente invención contempla modificaciones en todo el constructo de CAR, por ejemplo, modificaciones en una o más secuencias de aminoácidos de los diversos dominios del constructo de CAR con el fin de generar moléculas funcionalmente equivalentes. El constructo de CAR se puede modificar para retener al menos aproximadamente 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% de identidad del constructo de CAR de partida.

CARs BIESPECÍFICOS

En una modalidad, una molécula de anticuerpo multiespecífica es una molécula de anticuerpo biespecífica. Un anticuerpo biespecífico tiene especificidad para no más de dos antígenos. Una molécula de anticuerpo biespecífica se caracteriza por una primera secuencia de dominio variable de inmunoglobulina que tiene especificidad de unión para un primer epítopo y una segunda secuencia de dominio variable de inmunoglobulina que tiene especificidad de unión para un segundo epítopo. En una modalidad, el primer y el segundo epítopos están en el mismo antígeno, por ejemplo, la misma proteína (o subunidad de una proteína multimérica). En una modalidad, el primer y el segundo epítopos se superponen. En una modalidad, el primer y el segundo epítopos no se superponen. En una modalidad, el primer y el segundo epítopos están en antígenos diferentes, por ejemplo, en proteínas diferentes (o diferentes subunidades de una proteína multimérica). En una modalidad, una molécula de anticuerpo biespecífica comprende una secuencia de dominio variable de cadena pesada y una secuencia de dominio variable de cadena ligera que tienen especificidad de unión para un primer epítopo y una secuencia de dominio variable de cadena pesada y una secuencia de dominio variable de cadena ligera que tienen especificidad de unión para un segundo epítopo. En una modalidad, una molécula de anticuerpo biespecífica comprende un medio anticuerpo que tiene especificidad de unión para un primer epítopo y un medio anticuerpo que tiene especificidad de unión para un segundo epítopo. En una modalidad, una molécula de anticuerpo biespecífica comprende un medio anticuerpo, o

un fragmento del mismo, que tiene especificidad de unión para un primer epítopo y un medio anticuerpo, o un fragmento del mismo, que tiene especificidad de unión para un segundo epítopo. En una modalidad, una molécula de anticuerpo biespecífica comprende un scFv, o un fragmento del mismo, que tiene especificidad de unión para un primer epítopo y un scFv, o un fragmento del mismo, que tiene especificidad de unión para un segundo epítopo. En una modalidad, el primer epítopo está ubicado en CD19 y el segundo epítopo está ubicado en CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1.

En ciertas modalidades, la molécula de anticuerpo es una molécula de anticuerpo multi-específica (*por ejemplo*, una molécula de anticuerpo biespecífica o triespecífica). Los protocolos para la generación de moléculas de anticuerpos biespecíficas o heterodiméricas se conocen en la técnica, incluyendo, de manera enunciativa mas no limitativa, *por ejemplo*, el enfoque "botón en ojal" descrito en, *por ejemplo*, US 5731168; el emparejamiento de Fc mediante orientación por interacción electrostática, tal como se describe en, *por ejemplo*, WO 09/089004, WO 06/106905 y WO 2010/129304; formación de heterodímeros mediante Dominios Modificados Genéticamente por Intercambio de Cadenas (SEED), tal como se describe en, *por ejemplo*, WO 07/110205; intercambio de brazos Fab, tal como se describe en, *por ejemplo*, WO 08/119353, WO 2011/131746 y WO 2013/060867; conjugado de anticuerpo doble, *por ejemplo*, mediante entrecruzamiento de anticuerpos para generar una estructura bi-específica usando un reactivo heterobifuncional que tiene un grupo amino-reactivo y un grupo reactivo sulfhidrilo, tal como se describe en, *por ejemplo*, US 4433059; determinantes de anticuerpos biespecíficos generados recombinando medios anticuerpos (Fab o pares de cadena pesada-ligera) de diferentes anticuerpos a través de ciclo de reducción y oxidación de uniones de disulfuro entre las dos cadenas pesadas, tal como se describe en, *por ejemplo*, US 4444878; anticuerpos trifuncionales, *por ejemplo*, tres fragmentos Fab' entrecruzados a través de grupos reactivos sulfhidrilo, tal como se describe en, *por ejemplo*, US5273743; proteínas de unión biosintéticas, *por ejemplo*, par de scFv entrecruzados a través de extremos C-terminal, preferiblemente a través de entrecruzamiento químico de reactivos disulfuro o amino-reactivos, tal como se describe en, *por ejemplo*, US5534254; anticuerpos bifuncionales, *por ejemplo*, fragmentos Fab con diferentes especificidades de unión dimerizados a través de cremalleras de leuquina (*por ejemplo*, c-fos y c-jun) que tienen el dominio constante reemplazado, tal como se describe en, *por ejemplo*, US5582996; receptores oligoespecíficos mono y oligovalentes, *por ejemplo*, regiones VH-CH1 de dos anticuerpos (dos fragmentos Fab) enlazadas mediante un enlazador polipéptido entre la

región CH1 de un anticuerpo y la región VH del otro anticuerpo típicamente con cadenas ligeras asociadas, tal como se describe en, *por ejemplo*, US5591828; conjugados anticuerpo-ADN biespecíficos, *por ejemplo*, entrecruzamiento de anticuerpos o fragmentos Fab a través de una pieza de doble cadena de ADN, tal como se describe en, *por ejemplo*, US5635602; proteínas de fusión biespecíficas, *por ejemplo*, un constructo de expresión que contiene dos scFv con un enlazador péptido helicoidal hidrófilo entre ellos y una región constante completa, tal como se describe en, *por ejemplo*, US5637481; proteínas de unión multivalentes y multiespecíficas, *por ejemplo*, dímeros de polipéptidos con un primer dominio con región de unión de región variable de cadena pesada de Ig, un segundo dominio con región de unión de región variable de cadena ligera de Ig, generalmente conocidos como diacuerpos (las estructuras de orden superior también se incluyen y crean moléculas biespecíficas, triespecíficas o tetraespecíficas, tal como se describe en, *por ejemplo*, US5837242; constructos de minicuerpos con cadenas VL y VH enlazadas, conectadas además con espaciadores péptidos a una región bisagra de anticuerpo y región CH3, que pueden ser dimerizados para formar moléculas biespecíficas/multivalentes, tal como se describe en, por ejemplo, US5837821; dominios VH y VL enlazados mediante un enlazador péptido corto (por ejemplo, 5 o 10 aminoácidos) o sin ningún enlazador en ninguna de las orientaciones, que pueden formar dímeros para formar diacuerpos biespecíficos; trimeros y tetrámeros, tal como se describe en, por ejemplo, US5844094; cadena de dominios VH (o dominios VL en miembros de familias) conectada mediante enlaces péptidos con grupos entrecruzables en el C-terminal, asociada además dominós VL para formar una serie de FV (o scFv), tal como se describe en, por ejemplo, US5864019; y polipéptidos de unión de cadena única con un dominio VH y un dominio VL enlazados a través de un enlazador polipéptido se combinan en estructuras multivalentes mediante entrecruzamiento no covalente o químico para formar, por ejemplo, estructuras homobivalentes, heterobivalentes, trivalentes y tetravalentes usando formatos de tipo scFV o diacuerpos, tal como se describe en, por ejemplo, US5869620. Ejemplos adicionales de moléculas multiespecíficas y biespecíficas y métodos para producirlas se encuentran, por ejemplo, en US5910573, US5932448, US5959083, US5989830, US6005079, US6239259, US6294353, US6333396, US6476198, US6511663, US6670453, US6743896, US6809185, US6833441, US7129330, US7183076, US7521056, US7527787, US7534866, US7612181, US2002004587A1, US2002076406A1, US2002103345A1, US2003207346A1, US2003211078A1, US2004219643A1, US2004220388A1, US2004242847A1, US2005003403A1, US2005004352A1, US2005069552A1, US2005079170A1,

US2005100543A1, US2005136049A1, US2005136051A1, US2005163782A1, US2005266425A1, US2006083747A1, US2006120960A1, US2006204493A1, US2006263367A1, US2007004909A1, US2007087381A1, US2007128150A1, US2007141049A1, US2007154901A1, US2007274985A1, US2008050370A1, US2008069820A1, US2008152645A1, US2008171855A1, US2008241884A1, US2008254512A1, US2008260738A1, US2009130106A1, US2009148905A1, US2009155275A1, US2009162359A1, US2009162360A1, US2009175851A1, US2009175867A1, US2009232811A1, US2009234105A1, US2009263392A1, US2009274649A1, EP346087A2, WO0006605A2, WO02072635A2, WO04081051A1, WO06020258A2, WO2007044887A2, WO2007095338A2, WO2007137760A2, WO2008119353A1, WO2009021754A2, WO2009068630A1, WO9103493A1, WO9323537A1, WO9409131A1, WO9412625A2, WO9509917A1, WO9637621A2, WO9964460A1. El contenido de las solicitudes listadas anteriormente se incluye en el presente documento a manera de referencia.

Dentro de cada anticuerpo o fragmento de anticuerpo (por ejemplo, scFv) de una molécula de anticuerpo biespecífica, la VH puede estar hacia arriba o hacia abajo de la VL. En algunas modalidades, el anticuerpo o fragmento de anticuerpo hacia arriba (por ejemplo, scFv) está dispuesto con su VH (VH_1) hacia arriba de su VL (VL_1) el anticuerpo o fragmento de anticuerpo hacia abajo (por ejemplo, scFv) está dispuesto con su VL (VL_2) hacia abajo de su VH (VH_2), de manera tal que la molécula de anticuerpo biespecífica general está dispuesta como VH_1-VL_1-VL_2-VH_2. En otras modalidades, el anticuerpo o fragmento de anticuerpo hacia arriba (por ejemplo, scFv) está dispuesto con su VL (VL_1) hacia arriba de su VH (VH_1) el anticuerpo o fragmento de anticuerpo hacia abajo (por ejemplo, scFv) está dispuesto con su VH (VH_2) hacia abajo de su VL (VL_2), de manera tal que la molécula de anticuerpo biespecífica general está dispuesta como VL_1-VH_1-VH_2-VL_2. Opcionalmente, un enlazador está dispuesto entre los dos anticuerpos o fragmentos de anticuerpos (por ejemplo, scFv), por ejemplo, entre VL_1 y VL_2 si el constructo está dispuesto como VH_1-VL_1-VL_2-VH_2, o entre VH_1 y VH_2 si el constructo está dispuesto como VL_1-VH_1-VH_2-VL_2. El enlazador puede ser un enlazador tal se describe en el presente documento, por ejemplo, un enlazador (Gly_4-Ser)n, donde n es 1, 2, 3, 4, 5 o 6, por ejemplo, 4 (SEQ ID NO.: 53). En general, el enlazador entre los dos scFv debe ser lo suficientemente largo para evitar el emparejamiento inadecuado entre los dominios de los dos scFv. Opcionalmente, un enlazador está dispuesto entre la VL y la VH del primer scFv.

Opcionalmente, un enlazador está dispuesto entre la VL y la VH del segundo scFv. En constructos que tienen varios enlazadores, cualquiera de dos o más de los enlazadores pueden ser iguales o diferentes. Por consiguiente, en algunas modalidades, un CAR biespecífico comprende VLS, VHS y, opcionalmente uno o más enlazadores en una disposición tal como se describe en el presente documento.

En ciertas modalidades, la molécula de anticuerpo es una molécula de anticuerpo biespecífica que tiene una primera especificidad de unión para un primer epítopo de células B y una segunda especificidad de unión para otro antígeno de células B. Por ejemplo, en algunas modalidades, la molécula de anticuerpo biespecífica tiene una primera especificidad de unión para CD19 y una segunda especificidad de unión para una o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a. En algunas modalidades, la molécula de anticuerpo biespecífica tiene una primera especificidad de unión para CD19 y una segunda especificidad de unión para CD22.

TCR quimérico

En un aspecto, los anticuerpos y fragmentos de anticuerpos descritos en el presente documento (por ejemplo, aquellos dirigidos contra CD10, CD19, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a) se pueden injertar en uno o más dominios constantes de una cadena de receptores de células T ("TCR"), por ejemplo, una cadena de TCR alfa o TCR beta, para crear un TRC quimérico que se une específicamente a un antígeno asociado con cáncer. Al margen de las limitaciones que impone la teoría, se cree que los TCR quiméricos enviarán señales a través del complejo de TCR una vez ocurre la unión al antígeno. Por ejemplo, un scFv como tal como se describe en el presente documento, puede ser injertado en el dominio constante, por ejemplo, al menos una parte del dominio constante extracelular, el dominio transmembrana y el dominio citoplásmico, de una cadena de TCR, por ejemplo, la cadena de TCR alfa y/o la cadena de TCR beta. Como otro ejemplo, un fragmento de anticuerpo, por ejemplo un dominio VL descrito en el presente documento, puede ser injertado en el dominio constante de una cadena de TRC alfa, y un fragmento de anticuerpo, por ejemplo un dominio VH descrito en el presente documento, puede ser injertado en el dominio constante de una cadena de TCR beta (o alternativamente, un dominio VL puede ser injertado en el dominio constante de la cadena de TCR beta y un dominio VH puede ser injertado en una cadena de TCR

alfa). Como otro ejemplo, las CDR de un anticuerpo o fragmento de anticuerpo, por ejemplo, las CDR de un anticuerpo o fragmento de anticuerpo tal como se describe en cualquiera de las Tablas del presente documento, pueden ser injertadas en una cadena de TCR alfa y/o beta para crear un TCR quimérico que se une específicamente a un antígeno asociado con el cáncer. Por ejemplo, las LC CDR divulgadas en el presente documento pueden ser injertadas en el dominio variable de una cadena de TRC alfa y las HC CDR divulgadas en el presente documento pueden ser injertadas en al dominio variable de una cadena de TRC beta, o viceversa. Estos TCR quiméricos pueden ser producidos a través de cualquier método apropiado (por ejemplo, Willemsen RA et al, Gene Therapy 2000; 7: 1369–1377; Zhang T et al, Cancer Gene Ther 2004; 11: 487–496; Aggen et al, Gene Ther. 2012 Apr;19(4): 365-74).

Estructuras que no son anticuerpos

En algunas modalidades, el dominio de unión a antígeno comprende una estructura no anticuerpo, por ejemplo, una fibronectina, anquirina, anticuerpo de dominio, lipocalina, inmuno-fármaco modular pequeño, maxicuerpo, proteína A o afilina. La estructura no anticuerpo tiene la capacidad dirigirse a un antígeno en una célula. En algunas modalidades, el dominio de unión a antígeno es un polipéptido o fragmento del mismo de una proteína de origen natural que se expresa en una célula. En algunas modalidades, el dominio de unión a antígeno comprende una estructura no anticuerpo. Es posible usar una amplia variedad de estructuras no anticuerpo siempre y cuando el polipéptido resultante incluya al menos una región de unión que se una específicamente al antígeno blanco en una célula blanco.

Las estructuras no anticuerpo incluyen: fibronectina (Novartis, MA), anquirina (Molecular Partners AG, Zúrich, Suiza), anticuerpos de dominio (Domantis, Ltd., Cambridge, MA, y Ablynx nv, Zwijnaarde, Bélgica), lipocalina (Pieris Proteolab AG , Freising, Alemania), inmuno-fármacos modulares pequeños (Trubion Pharmaceuticals Inc., Seattle, WA), maxicuerpos (Avidia, Inc., Mountain View, CA), proteína A (Affibody AG, Suecia) y afilina (gamma-cristalina o ubiquitina) (Scil Proteins GmbH, Halle, Alemania).

Las estructuras de fibronectina pueden estar basadas en un dominio de fibronectina III (por ejemplo, el décimo módulo de la fibronectina tipo III (dominio Fn3 ^{10}). El dominio de fibronectina tipo III tiene 7 u 8 hebras beta que están distribuidas entre dos láminas beta, que a su vez se empaquetan una contra la otra para formar el núcleo de la proteína, y también contiene bucles (análogos a las CDR) que conectan las hebras beta entre sí y están expuestos a disolvente.

Hay al menos tres de estos bucles en cada borde del sándwich de láminas beta, donde el borde es la frontera de la proteína perpendicular a la dirección de las hebras beta (véase US 6,818,418). Debido a esta estructura, esta estructura no anticuerpo imita las propiedades de unión de antígenos que son similares en naturaleza y afinidad a dichos anticuerpos. Estas estructuras se pueden usar en una estrategia de aleatorización y mezcla de bucles in vitro que es similar al proceso de maduración de afinidad de anticuerpos in vivo.

La tecnología anquirina se basa en el uso de proteínas con módulos de repetición derivados de anquirina como estructuras para contener regiones variables que pueden ser usadas para la unión a diferentes blancos. El módulo de repetición de anquirina es un polipéptido de 33 aminoácidos que consta de dos hélices alfa paralelas y un giro beta. La unión de las regiones variables se optimiza principalmente usando la expresión en ribosomas.

Los avímeros se derivan de proteínas naturales que contienen dominio A, tales como HER3. Estos dominios son usados por la naturaleza para interacciones proteína-proteína, y en el ser humano más de 250 proteínas están basadas estructuralmente en dominios A. Los avímeros consisten en una serie de diferentes monómeros de "domino A" (2-10), enlazados a través de enlazadores de aminoácidos. Los avímeros se pueden crear de manera tal que se puedan unir al antígeno blanco usando la metodología descrita en, por ejemplo, las Solicitudes de Patente de Estados Unidos No. 20040175756; 20050053973; 20050048512; y 20060008844.

Los ligandos de afinidad por aficuerpos son proteínas pequeñas y simples compuestas de un paquete de tres hélices basado en la estructura de uno de los dominios de unió a IgG de la Proteína A. La Proteína A es una proteína superficial de la bacteria Staphylococcus aureus. Este dominio de estructura consta de 58 aminoácidos, 13 de los cuales se aleatorizan para generar bibliotecas de aficuerpos con un gran número de variantes de ligando (véase, por ejemplo, US 5,831,012). Las moléculas de aficuerpo imitan anticuerpos, tienen un peso molecular de 6 kDa, en comparación con el peso molecular de los anticuerpos, que es 150 kDa. A pesar de su pequeño tamaño, el sitio de unión de las moléculas de aficuerpo es similar al de un anticuerpo.

Las proteínas miméticas del epítopo (PEM) son moléculas de tamaño mediano, cíclica y de tipo peptídico (MW 1-2kDa) que imitan las estructuras secundarias horquilla beta de las proteínas, la principal estructura secundaria involucrada en las interacciones proteína-proteína. Los dominios de unión a antígeno, por ejemplo, aquellos que comprenden scFv, anticuerpos de dominio único o anticuerpos de camélidos, se pueden dirigir a cualquier receptor/ligando blanco descrito en el presente documento, por ejemplo, receptores de PD1, PD-L1 o PD-L2.

En una modalidad, el dominio de unión a antígeno comprende el dominio extracelular, o un fragmento de unión contra-ligando del mismo, de molécula que une un contra-ligando en la superficie de una célula blanco.

Un dominio de unión a antígeno puede comprender el dominio extracelular de un receptor inhibidor. El apareamiento con un contra-ligando de la molécula co-inhibidora se redirige a una optimización de la respuesta efectora inmune.

Un dominio de unión a antígeno puede comprender el dominio extracelular de una molécula coestimuladora, conocido como un dominio ECD coestimulador. El apareamiento de un contra-ligando de la molécula coestimulador produce la optimización de la respuesta efectora inmune.

Dominio transmembrana

Con respecto al dominio transmembrana, en diversas modalidades, un CAR puede estar diseñado para comprender un dominio transmembrana que está fijado al dominio extracelular del CAR. Un dominio transmembrana puede incluir uno o más aminoácidos adicionales adyacentes a la región transmembrana, por ejemplo, uno o más aminoácidos asociados a la región extracelular de la proteína de la que se derivó la transmembrana (por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 hasta 15 aminoácidos de la región extracelular) y/o uno o más aminoácidos adicionales asociados a la región intracelular de la proteína de la que se derivó la transmembrana (por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 hasta 15 aminoácidos de la región intracelular). En un aspecto, el dominio transmembrana es uno que está asociado a uno de los otros dominios del CAR, por ejemplo, en una modalidad, el dominio transmembrana puede ser de la misma proteína de la que se deriva el dominio de señalización, el dominio coestimulador o el dominio bisagra. En otro aspecto, el dominio transmembrana no se deriva de la misma proteína de la que se deriva cualquier otro domino del CAR. En algunos casos, el dominio transmembrana puede ser seleccionado o modificado mediante sustitución de aminoácidos para evitar la unión de dichos dominios a los dominios transmembrana de las mismas proteínas o de proteínas diferentes de la membrana superficial, por ejemplo, para minimizar las interacciones con otros miembros del complejo de receptor. En un aspecto, el dominio transmembrana tiene la capacidad de realizar homodimerización con otro CAR en la superficie celular de la célula que expresa CAR. En un aspecto diferente, la secuencia de aminoácidos del dominio transmembrana

puede ser modificada o sustituida con el fin de minimizar las interacciones con los dominios de la pareja de unión inalterada presente en la misma célula que expresa CAR.

El dominio transmembrana se puede derivar bien sea de una fuente natural o de una fuente recombinante. Cuando la fuente es natural, el dominio se puede derivar de cualquier proteína unida a membrana o transmembrana. En un aspecto, el dominio transmembrana tiene la capacidad de señalizar al o los dominios intracelulares siempre que el CAR se ha unido a un blanco. Un dominio transmembrana de uso particular en esta invención puede incluir al menos la(s) región(es) transmembrana de, por ejemplo, la cadena alfa, beta o zeta del receptor de células T, CD28, CD3 épsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, CD154. En algunas modalidades, un dominio transmembrana puede incluir al menos la(s) región(es) transmembrana de, por ejemplo, KIRDS2, OX40, CD2, CD27, LFA-1 (CD11a, CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD40, BAFFR, HVEM (LIGHTR), SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD160, CD19, IL2R beta, IL2R gamma, IL7R α, ITGA1, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, TNFR2, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (táctil), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, PAG/Cbp, NKG2D, NKG2C o CD19.

En algunos casos, el dominio transmembrana puede estar fijado a la región extracelular del CAR, por ejemplo, el dominio de unión a antígeno del CAR, a través de una bisagra, por ejemplo, una bisagra de una proteína humana. Por ejemplo, en una modalidad, la bisagra puede ser una bisagra de Ig (inmunoglobulina) humana, por ejemplo, una bisagra de IgG4, una bisagra de IgD, un enlazador de GS (por ejemplo, un enlazador de GS descrito en el presente documento), una bisagra de KIR2DS2 o una bisagra de CD8a. En una modalidad, la bisagra o espaciador comprende (por ejemplo, consta de) una secuencia de aminoácidos de SEQ ID NO.: 14. En un aspecto, el dominio transmembrana comprende (por ejemplo, consta de) un dominio transmembrana de SEQ ID NO: 15.

En un aspecto, la bisagra o espaciador comprende una bisagra de IgG4. Por ejemplo, en una modalidad, la bisagra o espaciador comprende una bisagra de la secuencia de aminoácidos

ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI
SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKM (SEQ
ID NO.: 45). En algunas modalidades, la bisagra o espaciador comprende una bisagra codificada por una secuencia de nucleótidos de
GAGAGCAAGTACGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCGAGTTCCTGGGCGGA
CCCAGCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCCGGACC
CCCGAGGTGACCTGTGTGGTGGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTT
CAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCCCGGGAG
GAGCAGTTCAATAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGA
CTGGCTGAACGGCAAGGAATACAAGTGTAAGGTGTCCAACAAGGGCCTGCCCAGCA
GCATCGAGAAAACCATCAGCAAGGCCAAGGGCCAGCCTCGGGAGCCCCAGGTGTA
CACCCTGCCCCCTAGCCAAGAGGAGATGACCAAGAACCAGGTGTCCCTGACCTGCC
TGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAG
CCCGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACAGCGACGGCAGCTTCTT
CCTGTACAGCCGGCTGACCGTGGACAAGAGCCGGTGGCAGGAGGGCAACGTCTTTA
GCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAGC
CTGTCCCTGGGCAAGATG (SEQ ID NO.: 46).

En un aspecto, la bisagra o espaciador comprende una bisagra de IgD. Por ejemplo, en una modalidad, la bisagra o espaciador comprende una bisagra de la secuencia de aminoácidos
RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKEKEKEEQEERET
KTPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVVGSDLKDAHLTWEVAGKVPTG
GVEEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCTLNHPSLPPQRLMALREPAAQAP
VKLSLNLLASSDPPEAASWLLCEVSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGST
TFWAWSVLRVPAPPSPQPATYTCVVSHEDSRTLLNASRSLEVSYVTDH (SEQ ID NO.:
47). En algunas modalidades, la bisagra o espaciador comprende una bisagra codificada por una secuencia de nucleótidos de
AGGTGGCCCGAAAGTCCCAAGGCCCAGGCATCTAGTGTTCCTACTGCACAGCCCCA
GGCAGAAGGCAGCCTAGCCAAAGCTACTACTGCACCTGCCACTACGCGCAATACTG
GCCGTGGCGGGGAGGAGAAGAAAAAGGAGAAAGAGAAAGAAGAACAGGAAGAGA
GGGAGACCAAGACCCCTGAATGTCCATCCCATACCCAGCCGCTGGGCGTCTATCTCT

TGACTCCCGCAGTACAGGACTTGTGGCTTAGAGATAAGGCCACCTTTACATGTTTCG
TCGTGGGCTCTGACCTGAAGGATGCCCATTTGACTTGGGAGGTTGCCGGAAAGGTA
CCCACAGGGGGGGTTGAGGAAGGGTTGCTGGAGCGCCATTCCAATGGCTCTCAGAG
CCAGCACTCAAGACTCACCCTTCCGAGATCCCTGTGGAACGCCGGGACCTCTGTCAC
ATGTACTCTAAATCATCCTAGCCTGCCCCCACAGCGTCTGATGGCCCTTAGAGAGCC
AGCCGCCCAGGCACCAGTTAAGCTTAGCCTGAATCTGCTCGCCAGTAGTGATCCCCC
AGAGGCCGCCAGCTGGCTCTTATGCGAAGTGTCCGGCTTTAGCCCGCCCAACATCTT
GCTCATGTGGCTGGAGGACCAGCGAGAAGTGAACACCAGCGGCTTCGCTCCAGCCC
GGCCCCCACCCCAGCCGGGTTCTACCACATTCTGGGCCTGGAGTGTCTTAAGGGTCC
CAGCACCACCTAGCCCCCAGCCAGCCACATACACCTGTGTTGTGTCCCATGAAGAT
AGCAGGACCCTGCTAAATGCTTCTAGGAGTCTGGAGGTTTCCTACGTGACTGACCAT
T (SEQ ID NO.: 48).

En un aspecto, el dominio transmembrana puede ser recombinante, en cuyo caso comprenderá residuos predominantemente hidrófobos tales como leucina y valina. En un aspecto, se puede encontrar un triplete de fenilalanina, triptófano y valina en cada extremo de un dominio transmembrana recombinante.

Opcionalmente, un oligo- o polipéptido enlazador corto, con una longitud entre 2 y 10 aminoácidos, puede formar el enlace entre el dominio transmembrana y la región citoplasmática del CAR. Un doblete glicina-serina ofrece un enlazador particularmente adecuado. Por ejemplo, en un aspecto, el enlazador comprende la secuencia de aminoácidos de GGGGSGGGGS (SEQ ID NO.: 49). En algunas modalidades, el enlazador está codificado por una secuencia de nucleótidos de GGTGGCGGAGGTTCTGGAGGTGGAGGTTCC (SEQ ID NO.: 50).

En un aspecto, la bisagra o el espaciador comprende una bisagra KIR2DS2.

Dominio citoplasmático

El dominio citoplasmático o la región citoplasmática del CAR incluye un dominio de señalización intracelular. Un dominio de señalización intracelular es generalmente responsable de activar al menos una de las funciones efectoras normales de la célula inmunitaria en la que se introdujo el CAR.

Ejemplos de dominios de señalización intracelular para uso en el CAR de la invención

incluyen las secuencias citoplasmáticas del receptor de células T (TCR) y los co-receptores que actúan conjuntamente para iniciar la transducción de señales después del apareamiento del receptor de antígeno, así como cualquier derivado o variante de estas secuencias y cualquier secuencia recombinante que tenga la misma capacidad funcional.

Se sabe que las señales generadas solamente a través del TCR son insuficientes para la plena activación de la célula T y que también se requiere una señal secundaria y/o coestimuladora. Por lo tanto, se puede decir que la activación de la célula T está mediada por dos clases distintas de secuencias de señalización citoplasmáticas: aquellas que inician la activación primaria dependiente de antígeno a través del TCR (dominios primarios de señalización intercelular) y aquellas que actúan de una manera independiente del antígeno para proporcionar una señal secundaria o coestimuladora (dominio citoplasmático secundario, por ejemplo, un dominio coestimulador).

Un dominio primario de señalización regula la activación primaria del complejo TCR ya sea de manera estimuladora o de manera inhibidora. Los dominios primarios de señalización intercelular que actúan de una manera estimuladora pueden contener motivos de señalización que se conocen como motivo de activación del inmunorreceptor basado en tirosina o ITAM.

Algunos ejemplos de ITAM que contienen dominios primarios de señalización intercelular que son de uso particular en la invención incluyen aquellos de CD3 zeta, FcR gama (FCER1G) común, Fc gama RIIa, FcR beta (Fc épsilon R1b), CD3 gama, CD3 delta, CD3 épsilon, CD79a, CD79b, CD278 (también conocida como “ICOS”), FcεRI, DAP10, DAP12 y CD66d. En una modalidad, un CAR de la invención comprende un dominio de señalización intracelular, por ejemplo, un dominio primario de señalización de CD3 zeta.

En una modalidad, un dominio primario de señalización comprende un dominio de ITAM modificado, por ejemplo, un dominio de ITAM mutado con actividad alterada (por ejemplo, aumentada o disminuida) en comparación con el dominio de ITAM inalterado. En una modalidad, un dominio primario de señalización comprende un dominio primario de señalización intracelular que contiene ITAM modificado, por ejemplo, un dominio primario de señalización intracelular que contiene ITAM optimizado y/o truncado. En una modalidad, un dominio primario de señalización comprende uno, dos, tres, cuatro o más motivos ITAM.

Otros ejemplos de moléculas que contienen un dominio primario de señalización

intracelular que son de uso particular en la invención incluyen las moléculas de DAP10, DAP12 y CD32.

Dominio de señalización coestimulatorio

El dominio de señalización intracelular del CAR puede comprender el dominio de señalización CD3 zeta por sí solo o puede estar combinado con cualquier otro u otros dominios de señalización intracelular deseados útiles en el contexto de un CAR de la invención. Por ejemplo, el dominio de señalización intracelular del CAR puede comprender la porción de la cadena CD3 zeta y un dominio coestimulador de señalización. El dominio coestimulador de señalización se refiere a una porción del CAR que comprende el dominio intracelular de una molécula coestimuladora. En una modalidad, el dominio intracelular esta diseñado para comprender el dominio de señalización de CD3-zeta y el dominio de señalización de CD28. En un aspecto, el dominio intracelular está diseñado para comprender el dominio de señalización de CD3-zeta y el dominio de señalización de ICOS.

Una molécula coestimuladora puede ser una molécula de superficie celular diferente a un receptor de antígeno o sus ligandos que se requiere para una respuesta eficaz de los linfocitos a un antígeno. Ejemplos de dichas moléculas incluyen CD27, CD28, 4-1BB (CD137), OX40, CD30, CD40, PD1, ICOS, antígeno-1 asociado a la función linfocitaria (LFA-1), CD2, CD7, LIGHT, NKG2C, B7-H3 y un ligando que se une específicamente con CD83, y similares. Por ejemplo, se ha demostrado que la coestimulación de CD27 mejora la expansión, la función efectora y la supervivencia de las células TCAR humanas in vitro y aumenta la persistencia de las células T humanas y la actividad antitumoral in vivo (Song et al. Blood. 2012; 119(3): 696-706). Ejemplos adicionales de dichas moléculas coestimuladoras incluyen la molécula CMH clase I, proteínas receptoras de TNF, proteínas similares a inmunoglobulina, receptores de citoquina, integrinas, moléculas de activación de señalización de linfocitos (proteínas SLAM), receptores activadores de células NK, BTLA, receptor de ligandos Toll, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alfa, CD8beta, IL2R beta, IL2R gamma, IL7Ralfa, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2,

TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (táctil), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, y un ligando que se une específicamente a CD83.

Las secuencias de señalización intracelular dentro de la porción citoplasmática del CAR de la invención pueden estar enlazadas entre sí en un orden aleatorio o especificado. Opcionalmente, un oligo- o polipéptido enlazador corto, con una longitud entre 2 y 10 aminoácidos (por ejemplo, 2, 3, 4, 5, 6, 7, 8, 9 o 10 aminoácidos) puede formar el enlace entre las secuencias de señalización intracelular. En una modalidad, un doblete glicina-serina se puede usar como un enlazador adecuado. En una modalidad, un solo aminoácido, por ejemplo, una alanina, una glicina, se puede usar como un enlazador adecuado.

En un aspecto, el dominio de señalización intracelular está diseñado para comprender dos o más, por ejemplo, 2, 3, 4, 5 o más, dominios coestimuladores de señalización. En una modalidad, los dos o más, por ejemplo, 2, 3, 4, 5 o más, dominios coestimuladores de señalización están separados por una molécula enlazadora, por ejemplo, una molécula enlazadora descrita en el presente documento. En una modalidad, el dominio de señalización intracelular comprende dos dominios coestimuladores de señalización. En algunas modalidades, la molécula enlazadora es un residuo de glicina. En algunas modalidades, el enlazador es un residuo de alanina.

En un aspecto, el dominio de señalización intracelular está diseñado para comprender el dominio de señalización de CD3 zeta y el dominio de señalización de CD28. En un aspecto, el dominio de señalización intracelular está diseñado para comprender el dominio de señalización de CD3 zeta y el dominio de señalización de 4-1BB. En un aspecto, el dominio de señalización de 4-1BB es un dominio de señalización de SEQ ID NO.: 16. En un aspecto, el dominio de señalización de CD1 zeta es un dominio de señalización de SEQ ID NO.: 17.

En un aspecto, el dominio de señalización intracelular está diseñado para comprender el dominio de señalización de CD3 zeta y el dominio de señalización de CD27. En un aspecto, el dominio de señalización de CD27 comprende una secuencia de aminoácidos de QRRKYRSNKGESPVEPAEPCRYSCPREEEGSTIPIQEDYRKPEPACSP (SEQ ID NO.: 51). En un aspecto, el dominio de señalización de CD27 está codificado por una secuencia de ácido

nucleico de AGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTACATGAACATGACTCCCCGCCG CCCCGGGCCCACCCGCAAGCATTACCAGCCCTATGCCCCACCACGCGACTTCGCAG CCTATCGCTCC (SEQ ID NO.: 52).

CARs de receptores de células asesinas naturales (NKR)

En una modalidad, una molécula de CAR descrita en el presente documento comprende uno o más componentes de un receptor de células asesinas naturales (NKR), formando de este modo un CAR de NKR (NKR-CAR). El componente NKR puede ser un dominio transmembrana, un dominio bisagra o un dominio citoplásmico de cualquiera de los siguientes receptores de células asesinas naturales: receptor de células asesinas de tipo inmunoglobulina (KIR), por ejemplo, KIR2DL1, KIR2DL2/L3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, DIR2DS5, KIR3DL1/S1, KIR3DL2, KIR3DL3, KIR2DP1 t KIR3DP1; receptor de citotoxicidad natural(NCR), por ejemplo, NKp30, NKp44, NKp46; familia de moléculas de activación de señalización de linfocitos (SLAM) de receptores de células inmunitarias, por ejemplo, CD48, CD229, 2B4, CD84, NTB-A, CRACC, BLAME CD2F-10; receptor Fc (FcR), por ejemplo, CD16, y CD64; y receptores de Ly49, por ejemplo, Ly49A, Ly49C. Las moléculas NKR-CAR descritas en el presente documento pueden interactuar con una molécula adaptadora o dominio de señalización intracelular, por ejemplo, DAP12. Ejemplos de configuraciones y secuencias de moléculas de CAR que comprenden componentes NKR se describen en la Publicación Internacional No. WO2014/145252, cuyo contenido se incluye en el presente documento a manera de referencia.

Estrategias para la regulación de receptores quiméricos de antígeno

En algunas modalidades, se desea un CAR regulable (RCAR), en el que sea posible controlar la actividad de CAR, para optimizar la seguridad y la eficacia de una terapia con CAR. Existen muchas maneras en las que se pueden regular las actividades de CAR. Por ejemplo, la inducción de apoptosis usando, por ejemplo, una caspasa fusionada a un dominio de dimerización (véase, por ejemplo, Di et al., N Engl. J. Med. 2011 nov. 3; 365(18): 1673-1683), se puede utilizar como un interruptor de seguridad en la terapia con CAR de la presente invención.

En una modalidad, las células (por ejemplo, células T o células NK) que expresan un

CAR de la presente invención comprenden además un interruptor inducible de apoptosis, en donde una caspasa humana (por ejemplo, Caspasa 9) o una versión modificada se fusiona a una modificación de la proteína humana FKB que permite la dimerización condicional. En presencia de una molécula pequeña, tal como un rapalogo (por ejemplo, AP 1903, AP20187) la Caspasa inducible (por ejemplo, la Caspasa 9) es activada y ocasiona una rápida apoptosis y muerte de las células (por ejemplo, células T o células NK) que expresan un CAR de la presente invención. Ejemplos de interruptores inducibles de apoptosis basados en Caspasa (o uno o más aspectos de tales interruptores) han sido descritos en, por ejemplo, US2004040047; US20110286980; US20140255360; WO1997031899; WO2014151960; WO2014164348; WO2014197638; WO2014197638, todas las cuales se incorporan en su totalidad en la presente como referencia.

En otro ejemplo, células que expresan CAR también pueden expresar una molécula de Caspasa-9 (iCaspasa-9) inducible que, tras la administración de un fármaco dimerizador (por ejemplo, rimiducid (también llamado AP1903 (Bellicum Pharmaceuticals) o AP20187 (Ariad)), conduce a la activación de la Caspasa-9 y la apoptosis de las células. La molécula iCaspasa-9 contiene un dominio de unión de un inductor químico de dimerización (CID), el cual media la dimerización en presencia de un CID. Esto se traduce en el agotamiento inducible y selectivo de las células que expresan CAR. En algunos casos, la molécula iCaspasa-9 está codificada por una molécula de ácido nucleico diferente del o los vectores que codifican el CAR. En algunos casos, la molécula iCaspasa-9 está codificada por la misma molécula de ácido nucleico del vector que codifica el CAR. La molécula iCaspasa-9 puede proporcionar un interruptor de seguridad para evitar cualquier toxicidad de las células que expresan CAR. Véase, por ejemplo, Song et al. Cancer Gene Ther. 2008; 15(10):667-75; Id. de Ensayo Clínico No. NCT02107963; y Di Stasi et al. N. Engl. J. Med. 2011; 365: 1673-83.

Estrategias alternativas para la regulación de la terapia con CAR de la presente invención incluyen el uso de moléculas pequeñas o anticuerpos que desactiven o desactiven la actividad de CAR, por ejemplo, mediante la eliminación de las células que expresan CAR, por ejemplo, mediante la inducción de citotoxicidad mediada por células dependiente de anticuerpos (ADCC). Por ejemplo, las células que expresan CAR descritas en el presente documento también pueden expresar un antígeno que es reconocido por moléculas capaces de inducir destrucción celular, por ejemplo, ADCC o destrucción celular inducida por complementos. Por ejemplo, las células que expresan CAR descritas en el presente documento también pueden expresar un receptor

capaz de ser identificado como blanco por un anticuerpo o fragmento de anticuerpo. Ejemplos de dichos receptores incluyen EpCAM, VEGFR, integrinas (por ejemplo, integrinas αvβ3, α4, αI¾β3, α4β7, α5β1, αvβ3, αv), miembros de la superfamilia de receptores de TNF (por ejemplo, TRAIL-R1 , TRAIL-R2), receptor de PDGF, receptor de interferón, receptor de folato, GPNMB, ICAM-1, HLA-DR, CEA, CA-125, MUC1, TAG-72, receptor de IL-6, 5T4, GD2, GD3, CD2, CD3, CD4, CD5, CD11 , CD11a/LFA-1, CD15, CD18/ITGB2, CD19, CD20, CD22, receptor de CD23/lgE, CD25, CD28, CD30, CD33, CD38, CD40, CD41 , CD44, CD51 , CD52, CD62L, CD74, CD80, CD125, CD147/basigin, CD152/CTLA-4, CD154/CD40L, CD195/CCR5, CD319/SLAMF7, y EGFR, y versiones truncadas de los mismos (por ejemplo, versiones que preservan uno o más epítopos extracelulares pero que carecen de una o más regiones dentro del dominio citoplasmático).

Por ejemplo, una célula que expresa un CAR descrita en el presente documento también puede expresar un receptor del factor de crecimiento epidérmico truncado (EGFR), que carece de la capacidad de señalización, pero conserva el epítopo que es reconocido por moléculas capaces de inducir ADCC, por ejemplo, cetuximab (Erbitux ®), de manera que la administración de cetuximab induce ADCC y la consiguiente reducción de células que expresan CAR (véase, por ejemplo, WO2011/056894, y Jonnalagadda et al., Gene Ther. 2013; 20(8)853-860). Otra estrategia incluye expresar un gen suicida/marcador altamente compacto que combina epítopos blanco de antígenos CD32 y CD20 en las células que expresan CAR descritas en el presente documento, que unen rituximab, produciendo la reducción selectiva de las células que expresan CAR, por ejemplo, mediante ADCC (véase, por ejemplo, Philip et al., Blood 2014; 124(8)1277-1287). Otros métodos para agotar células que expresan CAR descritos en el presente documento incluyen la administración de CAMPATH, un anticuerpo anti-CD52 monoclonal que se dirige y une selectivamente linfocitos maduros, por ejemplo, células que expresan CAR, para la destrucción, por ejemplo, mediante la inducción de ADCC. En otras modalidades, la célula que expresa un CAR puede ser identificada como blanco selectivamente usando un ligando de CAR, por ejemplo, un anticuerpo anti-idiotípico. En algunas modalidades, el anticuerpo anti-idiotípico puede generar actividad de células efectoras, por ejemplo, ADCC o ADC, reduciendo así el número de células que expresan CAR. En otras modalidades, el ligando de CAR, por ejemplo, el anticuerpo anti-idiotípico, se puede acoplar a un agente que induce la muerte celular, por ejemplo, una toxina, lo que reduce el número de células que expresan CAR. Alternativamente, las moléculas de CAR mismas pueden ser configuradas de manera tal que se regule la actividad,

por ejemplo, se active y se desactive, tal como se describe a continuación.

En otras modalidades, una célula que expresa un CAR descrita en el presente documento también puede expresar una proteína blanco reconocida por el agente reductor de células T. En una modalidad, la proteína blanco es CD20 y el agente reductor de células T es un anticuerpo anti-CD20, por ejemplo, rituximab. En esta modalidad, el agente reductor de células T se administra cuando es deseable reducir o eliminar la célula que expresa CAR, por ejemplo, para mitigar la toxicidad inducida por CAR. En otras modalidades, el agente reductor de células T es un anticuerpo anti-CD52, por ejemplo, alemtuzumab.

En un aspecto, un RCAR comprende un conjunto de polipéptidos, típicamente dos en las modalidades más simples, donde los componentes de un CAR estándar descritos en el presente documento, por ejemplo, un dominio de unión a antígeno y un dominio de señalización intracelular, se reparten en polipéptidos o miembros diferentes. En algunas modalidades, el conjunto de polipéptidos incluye un interruptor de dimerización que, ante la presencia de una molécula de dimerización, puede acoplar los polipéptidos entre sí, por ejemplo, puede acoplar un dominio de unión a antígeno a un dominio de señalización intracelular. En una realización, un CAR de la presente invención usa un interruptor de dimerización tal como los descritos en, por ejemplo, WO2014127261, cuyo contenido se incluye en el presente documento a manera de referencia. Descripción y ejemplos adicionales de configuraciones de dichos CAR se proporcionan en el presente documento y en la Publicación Internacional No. WO 2015/090229, cuyo contenido se incluye en su totalidad en el presente documento a manera de referencia.

En algunas modalidades, un RCAR involucra un dominio interruptor, por ejemplo, un interruptor FKBP, como se muestra en la SEQ ID NO: 122, o comprender un fragmento de FKBP que tiene la capacidad de unirse con FRB, como s emuetsra en la SEQ ID NO.: 123. EN algunas modalidades, el RCAR involucra un dominio interruptor que comprende una secuencia FRB, por ejemplo, como s emuestra en la SEQ ID NO: 124, o una secuencia FRB mutante que, por ejemplo, como se estableceen cualquiera de las SEQ ID Nos: 125 – 130.

D V P D Y A S L G G P S S P K K K R K V S R G V Q V E T I S P G D G R T F P K R G Q T C V V H Y T G M L E D G K K F D S S R D R N K P F K F M L G K Q E V I R G W E E G V A Q M S V G Q R A K L T I S P D Y A Y G A T G H P G I I P P H A T L V F D V E L L K L E T S Y (SEQ ID NO: 122)

V Q V E T I S P G D G R T F P K R G Q T C V V H Y T G M L E D G K K F D S S R D R N K P F K F M L G K Q E V I R G W E E G V A Q M S V G Q R A K L T I S P D Y A Y G A T G H P G I I P P H A T L V F D V E L L K L E T S (SEQ ID NO.: 123)

ILWHEMWHEG LEEASRLYFG ERNVKGMFEV LEPLHAMMER GPQTLKETSF NQAYGRDLME AQEWCRKYMK SGNVKDLTQA WDLYYHVFRR ISK (SEQ ID NO: 124)

Tabla 1. Ejemplos de FRB mutante que tienen una mayor afinidad a una molécula de dimerización.

FRB mutante	**Secuencia de Aminoácidos**	**SEQ ID NO.:**
E2032I mutante	ILWHEMWHEGLIEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRISKTS	125
E2032L mutante	ILWHEMWHEGLLEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAQEWCRKYMKSGNVKDLTQAWDLYYHVFRRISKTS	126
T2098L mutante	ILWHEMWHEGLEEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAQEWCRKYMKSGNVKDLLQAWDLYYHVFRRISKTS	127
E2032, T2098 mutante	ILWHEMWHEGL**X**EASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAQEWCRKYMKSGNVKDL**X**QAWDLYYHVFRRISKTS	128
E2032I, T2098L mutante	ILWHEMWHEGLIEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAQEWCRKYMKSGNVKDLLQAWDLYYHVFRRISKTS	129
E2032L, T2098L mutante	ILWHEMWHEGLLEASRLYFGERNVKGMFEVLEPLHAMMERGPQTLKETSFNQAYGRDLMEAQEWCRKYMKSGNVKDLLQAWDLYYHVFRRISKTS	130

CAR segmentado

En algunas modalidades, la célula que expresa un CAR usa un CAR segmentado. El enfoque de CAR segmentado se describe con más detalle en las publicaciones WO2014/055442 y WO2014/055657. En pocas palabras, un sistema de CAR segmentado comprende una célula que expresa un primer CAR que tiene un primer dominio de unión a antígeno y un dominio coestimulador (por ejemplo, 41BB), y la célula también expresa un segundo CAR que tiene un

segundo dominio de unión a antígeno y un dominio de señalización intracelular (por ejemplo, CD3 zeta). Cuando la célula se encuentra con el primer antígeno, el dominio coestimulador se activa, y la célula prolifera. Cuando la célula se encuentra con el segundo antígeno, el dominio de señalización intracelular se activa, y comienza la actividad que destruye las células. Por lo tanto, la célula que expresa un CAR solo se activa completamente en presencia de ambos antígenos.

Transfección de ARN

El presente documento describe métodos para la producción de un ARN de CAR transcrito in vitro. La presente invención también incluye (entre otras cosas) un constructo de ARN que codifica a CAR que se puede transfectar directamente a una célula. Un método de generación de ARNm para uso en la transfección puede implicar la transcripción in vitro (IVT) de una plantilla con cebadores especialmente diseñados, seguida de la adición de poliA, para producir un constructo que contiene una secuencia no traducida 3' y 5' ("UTR"), un cap 5' y/o un sitio interno de entrada al ribosoma (IRES), el ácido nucleico a ser expresado y una cola poliA, típicamente con una longitud de 50-2000 bases (SEQ ID NO.: 118). El ARN así producido puede transfectar eficientemente diferentes tipos de células. En un aspecto, la plantilla incluye secuencias para el CAR.

En un aspecto, el CAR está codificado por un ARN mensajero (ARNm). En un aspecto, el ARNm que codifica el CAR se introduce en una célula efectora inmune, por ejemplo, una célula T o una célula NK, para la producción de una célula que expresa CAR, por ejemplo, una célula TCAR o una célula NK de CAR.

En una modalidad, el ARN del CAR transcrito in vitro puede ser introducido en una célula como una forma de transfección transitoria. El ARN se produce mediante transcripción in vitro usando una plantilla generada por reacción en cadena de la polimerasa (PCR). El ADN de interés de cualquier fuente se puede convertir directamente por PCR en una plantilla para síntesis de ARNm in vitro usando cebadores apropiados y ARN polimerasa. La fuente de ADN puede ser, por ejemplo, ADN genómico, ADN de plásmido, ADN de fago, ADNc, secuencia de ADN sintético o cualquier otra fuente apropiada de ADN. Una plantilla deseada para la transcripción in vitro es un CAR de la presente invención. Por ejemplo, la plantilla para el ARN

del CAR comprende una región extracelular que comprende un dominio variable de cadena única de un anticuerpo antitumoral; una región bisagra, un dominio transmembrana (por ejemplo, un dominio transmembrana de CD8a); y una región citoplasmática que incluye un dominio de señalización intracelular, por ejemplo, que comprende el dominio de señalización de CD3-zeta y el dominio de señalización de 4-1BB.

En una modalidad, el ADN a ser usado para PCR contiene un marco abierto de lectura. El ADN puede ser de una secuencia de ADN de origen natural del genoma de un organismo. En una modalidad, el ácido nucleico puede incluir algunas o todas de las regiones no traducidas (UTR) 5' y/o 3'. El ácido nucleico puede incluir exones e intrones. En una modalidad, el ADN que será usado para PCR es una secuencia de ácido nucleico humano. En otra modalidad, el ADN que será usado para PCR es una secuencia de ácido nucleico humano, incluyendo las UTR 5 'y 3'. Alternativamente, el ADN puede ser una secuencia de ADN artificial que no se expresa normalmente en un organismo de origen natural. Un ejemplo de secuencia de ADN artificial es una secuencia que contiene porciones de genes que están ligados entre sí para formar un marco abierto de lectura que codifica una proteína de fusión. Las porciones de ADN que están ligadas pueden ser de un solo organismo o de más de un organismo.

La PCR se usa para generar una plantilla para la transcripción in vitro de ARNm, que se utiliza para la transfección. Los métodos para realizar la PCR son bien conocidos en la técnica. Los cebadores usados en la PCR están diseñados para tener regiones que son sustancialmente complementarias a las regiones del ADN que serán usadas como una plantilla para la PCR. "Sustancialmente complementaria", tal como se usa en el presente documento, se refiere a secuencias de nucleótidos donde una mayoría o la totalidad de las bases en la secuencia del cebador son complementarias, o una o más bases no son complementarias, o no están apareadas adecuadamente. Las secuencias sustancialmente complementarias tienen la capacidad de aparearse o hibridarse con el ADN blanco bajo condiciones de apareamiento usadas para PCR. Los cebadores se pueden diseñar para ser sustancialmente complementarios a cualquier parte de la plantilla de ADN. Por ejemplo, los cebadores se pueden diseñar para amplificar la porción de un ácido nucleico que normalmente se transcribe en células (el marco abierto de lectura), incluyendo UTR 5 'y 3'. Los cebadores también se pueden diseñar para amplificar una porción de un ácido nucleico que codifica un dominio particular de interés. En una modalidad, los cebadores están diseñados para amplificar la región de codificación de un ADNc humano,

incluyendo la totalidad o porciones de UTR 5 'y 3'. Los cebadores útiles para PCR se pueden generar mediante métodos sintéticos que son bien conocidos en la técnica. Los "cebadores directos" son cebadores que contienen una región de nucleótidos que son sustancialmente complementarios a los nucleótidos en la plantilla de ADN que están hacia arriba de la secuencia de ADN que será amplificada. "Hacia arriba" se usa en el presente documento para referirse a una posición 5' en la secuencia de ADN que será amplificada en relación con la cadena transcrita. Los "cebadores inversos" son cebadores que contienen una región de nucleótidos que son sustancialmente complementarios a los nucleótidos una plantilla de ADN de doble cadena que están hacia abajo de la secuencia de ADN que va a ser amplificada. "Hacia abajo" se usa en el presente documento para referirse a una posición 3' en la secuencia de ADN que será amplificada en relación con la cadena transcrita.

Cualquier ADN polimerasa útil para PCR se puede usar en los métodos descritos en el presente documento. Los reactivos y de la polimerasa se pueden obtener comercialmente de diversas fuentes.

También es posible usar estructuras químicas con capacidad de promover la estabilidad y/o la eficacia de traducción. En algunas modalidades, el ARN tiene 5 'y 3' UTR. En una modalidad, 5'-UTR tiene una longitud de entre uno y 3000 nucleótidos. La longitud de las secuencias 5' y 3' UTR que serán añadidas a la región de codificación puede ser alterada mediante diferentes métodos, incluyendo, de manera enunciativa mas no limitativa, el diseño de cebadores para PCR que se aparejen a diferentes regiones de los UTR. Usando este enfoque, un experto en la materia puede modificar las longitudes de 5 'y 3' UTR necesarias para lograr la eficacia de traducción optima después de la transfección del ARN transcrito.

Los 5 'y 3' UTR pueden ser los 5 'y 3' UTR de origen natural y endógenos del ácido nucleico de interés. Alternativamente, las secuencias UTR que no son endógenas del ácido nucleico de interés se pueden añadir incorporando las secuencias UTR en los cebadores directo e inverso o mediante cualquier otra modificación de la plantilla. El uso de secuencias UTR que no son endógenas del ácido nucleico de interés puede ser útil para modificar la estabilidad y/o la eficacia de traducción del ARN. Por ejemplo, se sabe que elementos ricos en AU en secuencias 3'-UTR pueden disminuir la estabilidad del ARNm. Por lo tanto, se pueden seleccionar o diseñar un 3'-UTR para aumentar la estabilidad del ARN transcrito con base en propiedades de los UTR que son ampliamente conocidas en la técnica.

En una modalidad, el 5'-UTR puede contener la secuencia de Kozak del ácido nucleico endógenos. Alternativamente, cuando un 5'-UTR que no es endógenos al ácido nucleico de interés se está agregando por PCR tal como se describió anteriormente, se puede rediseñar una secuencia de consenso Kozak añadiendo la secuencia 5'-UTR. Las secuencias Kosaz pueden aumentar la eficiencia de la traducción de algunas transcripciones de ARN, pero no parece ser que todos los ARN lo requieran para una traducción eficiente. El requisito de secuencias Kozak para muchos ARNm se conoce en la técnica. En otras modalidades, el 5'-UTR puede ser el 5'-UTR de un virus de ARN, cuyo genoma de ARN es estable en células. En otras modalidades, se pueden usar diferentes análogos de nucleótidos en el 3 'o 5' UTR para impedir la degradación de la exonucleasa del ARNm.

Para permitir la síntesis de ARN a partir de una plantilla de ADN sin necesidad de clonación de genes, un promotor de transcripción debe estar fijado a la plantilla de ADN hacia arriba de la secuencia que va a ser transcrita. Cuando una secuencia que funciona como un promotor para una ARN polimerasa se añade al extremo 5' del cebador directo, el promotor de ARN polimerasa se incorpora en el producto de PCR hacia arriba del marco abierto de lectura que va a ser transcrito. En una modalidad, el promotor es un promotor de polimerasa T7, tal como se describe en el presente documento. Otros promotores útiles incluyen, de manera enunciativa mas no limitativa, promotores T3 y de ARN polimerasa SP6. Secuencias de nucleótidos de consenso para promotores T7, T3 y SP6 se conocen en la técnica.

En una modalidad, el ARNm tiene un cap en el extremo 5 'y una cola poli(A) en el extremo 3', los cuales determinan la unión al ribosoma, la iniciación de la traducción y la estabilidad del ARNm en la célula. En una plantilla de ADN circular, por ejemplo, un ADN plásmido, la ARN polimerasa produce un producto concatemérico largo que no es adecuado para la expresión en células eucariotas. La transcripción de ADN plásmido linealizado en el extremo de la 3'-UTR produce ARNm de tamaño normal, el cual no es eficaz en la transfección eucariota, incluso si es poliadenilado después de la transcripción.

En una plantilla de ADN lineal, la ARN polimerasa del fago T7 puede extender el extremo 3' de la transcripción más allá de la última base de la plantilla (Schenborn y Mierendorf, Nuc Acids Res., 13: 6223-36 (1985); Nacheva y Berzal-Herranz, Eur. J. Biochem., 270: 1485-65 (2003).

El método convencional para integrar segmentos de poliA/T a una plantilla de ADN es la

clonación molecular. Sin embargo, la secuencia poliA/T integrada al ADN plásmido puede causar inestabilidad en el plásmido, y por esta razón las plantillas de ADN plásmido obtenidas a partir de células bacterianas a menudo están contaminadas con deleciones y otras aberraciones. En consecuencia, los procedimientos de clonación no solo son complicados y toman mucho tiempo, sino que además con frecuencia son poco confiables. Es por esto que un método que permita la construcción de plantillas de ADN con segmentos de poliA/T 3' sin necesidad de clonación es altamente deseable.

El segmento de poliA/T de la plantilla de ADN transcripccional se puede producir durante PCR usando un cebador inverso que contiene una cola de poliT, tal como una cola 100T (SEQ ID NO: 29) (el tamaño puede estar entre 50 y 5000 T (SEQ ID NO: 30)), o después de PCR usando cualquier otro método, incluyendo, de manera enunciativa más no limitativa, ligadura de ADN o recombinación in vitro. Las colas poli(A) también proporcionan estabilidad al ARN y reducen su degradación. Generalmente, la longitud de una cola poli(A) se correlaciona positivamente con la estabilidad del ARN transcrito. En una modalidad, la cola poli(A) tiene entre 100 y 5000 adenosinas (SEQ ID NO: 57).

Las colas poli(A) de ARN se pueden extender aún más después de la transcripción in vitro usando una polimerasa poli(A), tal como polimerasa poliA de E. coli (E-PAP) En una modalidad, el aumento de la longitud de una cola poli(A) de 100 nucleótidos a entre 300 y 400 nucleótidos (SEQ ID NO: 104) produce un aumento de dos veces en la eficiencia de traducción del ARN. Además, fijar diferentes grupos químicos al extremo 3' puede aumentar la estabilidad del ARNm. Esta fijación puede contener nucleótidos modificados/artificiales, aptámeros y otros compuestos. Por ejemplo, se pueden incorporar análogos de ATP a la cola poli(A) usando polimerasa poli(A). Los análogos de ATP pueden aumentar aún más la estabilidad del ARN.

Los cap en el extremo 5' también proporcionar estabilidad a las moléculas de ARN. En una modalidad, los ARN producidos mediante los métodos descritos en el presente documento incluyen un cap 5'. El cap 5' se proporciona usando técnicas conocidas en la técnica y se describe en el presente documento (Cougot, et al., Trends in Biochem. Sci., 29: 436-444 (2001); Stepinski, et al., RNA, 7:1468-95 (2001); Elango, et al., Biochim. Biophys. Res. Commun., 330: 958-966 (2005)).

Los ARN producidos a través de los métodos descritos en el presente documento también pueden contener una secuencia de un sitio interno de entrada al ribosoma (IRES). La

secuencia IRES puede ser cualquier secuencia viral, cromosómica o diseñada artificialmente que inicie la unión del ribosoma dependiente de cap al ARNm y facilite la iniciación de la traducción. Esto incluye cualquier soluto adecuado para la electroporación de células, que contenga factores que facilitan la permeabilidad y la viabilidad celular, tales como azúcares, péptidos, lípidos, proteínas, antioxidantes y agentes tensioactivos.

El ARN puede ser introducido en células blanco usando un número cualquiera de diversos métodos, por ejemplo, métodos disponibles comercialmente, incluyendo, de manera enunciativa mas no limitativa, electroporación (Amaxa Nucleofector-II (Amaxa Biosystems, Cologne, Germany)), (ECM 830 (BTX) (Harvard Instruments, Boston, Mass.) o Gene Pulser II (BioRad, Denver, Colo.), Multiporator (Eppendort, Hamburg, Alemania), transfección mediada por liposomas catiónicos usando lipofección, encapsulación de polímeros, transfección mediada por péptidos o sistemas biolísticos de descarga de partículas tales como "gene guns" (véase, por ejemplo, Nishikawa, et al. Hum Gene Ther., 12(8):861-70 (2001).

Métodos de administración no virales

En algunos aspectos, se pueden usar métodos no virales para entregar un ácido nucleico que codifica un CAR describo en el presente documento a una célula o tejido o un sujeto.

En algunas modalidades, el método no viral incluye el uso de un transposón (también llamado un elemento transponible). En algunas modalidades, un transposón es un trozo de ADN que se puede insertar a sí mismo en un lugar específico de un genoma, por ejemplo, un trozo de ADN que es capaz de auto-replicarse e insertar su copia en un genoma, o un trozo de ADN que se puede remover de un ácido nucleico más largo e insertar en otro lugar en un genoma. Por ejemplo, un transposón comprende una secuencia de ADN compuesta de repeticiones invertidas que flanquean genes para transposición.

Ejemplos de método para entregar ácido nucleico usando un transposón incluyen un sistema de transposones Sleeping Beauty (SBTS) y un sistema de transposones piggyBac (PB). Véase, por ejemplo, Aronovich et al. Hum. Mol. Genet. 20.R1(2011): R14-20; Singh et al. Cancer Res. 15 (2008): 2961–2971; Huang et al. Mol. Ther. 16 (2008): 580–589; Grabundzija et al. Mol. Ther. 18 (2010): 1200–1209; Kebriaei et al. Blood. 122.21 (2013): 166; Williams. Molecular Therapy 16.9 (2008): 1515–16; Bell et al. Nat. Protoc. 2.12 (2007): 3153-65; y Ding

et al. Cell. 122.3 (2005): 473-83, los cuales se incluyen en el presente documento a manera de referencia.

El SBTS incluye dos componentes: 1) un transposón que contiene un transgén y 2) una enzima transposasa. La transposasa puede transponer el transposón de un plásmido portador (u otro ADN donante) a un ADN blanco, tal como un cromosoma/genoma de la célula hospedera. Por ejemplo, la transposasa se une al plásmido portador/ADN donante, corta el transposón (incluyendo el transgén o transgenes) del plásmido y lo inserta en el genoma de la célula hospedera. Véase, por ejemplo, Aronovich et al.

Ejemplos de transposones incluyen un transposón basado en pT2. Véase, por ejemplo, Grabundzija et al. Nucleic Acids Res. 41.3(2013): 1829-47; y Singh et al. Cancer Res. 68.8 (2008): 2961–2971, los cuales se incluyen en el presente documento a manera de referencia. Ejemplos de transposasas incluyen una transposasa de tipo Tc1/mariner, por ejemplo, la transposasa SB10 o la transposasa SB11 (una transposasa hiperactiva que puede expresarse, por ejemplo, de un promotor de citomegalovirus). Véase, por ejemplo, Aronovich et al.; Kebriaei et al.; y Grabundzija et al., los cuales se incluyen en el presente documento a manera de referencia.

El uso del SBTS permite la integración y expresión eficientes de un transgén, por ejemplo, un ácido nucleico que codifica una CAR descrito en el presente documento. El presente documento proporciona métodos para generar una célula, por ejemplo, célula T o célula NK, que expresa de manera estable un CAR descrito en el presente documento, por ejemplo, usando un sistema de transposones tal como SBTS.

De acuerdo con los métodos descritos en el presente documento, en algunas modalidades, uno o más ácidos nucleicos, por ejemplo, plásmidos, que contienen los componentes del SBTS son entregados a una célula (por ejemplo, célula T o NK). Por ejemplo, el o los ácidos nucleicos son entregados a través de métodos estándar de entrega de ácidos nucleicos (por ejemplo, ADN de plásmido) de entrega, por ejemplo, los métodos descritos en el presente documento, por ejemplo, electroporación, transfección o lipofección. En algunas modalidades, el ácido nucleico contiene un transposón que comprende un transgén, por ejemplo, un ácido nucleico que codifica una CAR descrito en el presente documento. En algunas modalidades, el ácido nucleico contiene un transposón que comprende un transgén (por ejemplo, un ácido nucleico que codifica una CAR descrito en el presente documento), así como una secuencia de ácido nucleico que codifica una enzima transposasa. En otras modalidades, se

proporciona un sistema con dos ácidos nucleicos, por ejemplo, un sistema de doble plásmido, por ejemplo, donde un primer plásmido contiene un transposón que comprende un transgén, y un segundo plásmido contiene una secuencia de ácido nucleico que codifica una enzima transposasa. Por ejemplo, el primer y el segundo ácidos nucleicos son co-entregados a una célula hospedera.

En algunas modalidades, las células, por ejemplo, las células T o NK, se generan de tal manera que expresan un CAR descrito en el presente documento mediante el uso de una combinación de inserción de genes usando el SBTS y edición genética utilizando una nucleasa (por ejemplo, nucleasas de dedo de zinc (ZFN), una nucleasa efectora de tipo activador de transcripción (TALEN), el sistema CRISPR/Cas, o meganucleasa modificada, endonucleasas de detección rediseñadas).

En algunas modalidades, el uso de un método no viral de entrega permite la reprogramación de las células, por ejemplo, células T o NK, y la infusión directa de las células en un sujeto. Las ventajas de los vectores no virales incluyen, de manera enunciativa más no limitativa, la facilidad y costo relativamente bajo de producir las cantidades suficientes requeridas para satisfacer una población de pacientes, la estabilidad durante el almacenamiento y la falta de inmunogenicidad.

Constructos de ácido nucleico que codifican un CAR, por ejemplo, un CAR de CD19 CAR de CD20 o un CAR de CD22.

La presente invención también proporciona moléculas de ácido nucleico que codifican uno o más constructos de CAR descritos en el presente documento, por ejemplo, un CAR de CD19, un CAR de CD20 o un CAR de CD22. En un aspecto, la molécula de ácido nucleico se proporciona como un transcrito de ARN mensajero. En un aspecto, la molécula de ácido nucleico se proporciona como un constructo de ADN.

Por consiguiente, en un aspecto, la invención se refiere a una molécula de ácido nucleico aislada que codifica un receptor quimérico de antígeno (CAR), donde el CAR comprende un dominio de unión anti-CD19 (por ejemplo, que se una a CD19, CD20 o CD22), un dominio transmembrana y un dominio de señalización intracelular que comprende un dominio estimulador, por ejemplo, un dominio coestimulador de señalización y/o un dominio primario de

señalización, por ejemplo, cadena zeta.

En una modalidad, el dominio de unión es un dominio de unión anti-CD19 descrito en el presente documento, por ejemplo, un dominio de unión anti-CD19 que comprende una secuencia seleccionada de un grupo que consiste en SEQ ID NO.: 1, SEQ ID NO.: 2, SEQ ID NO.: 3, SEQ ID NO.: 4, SEQ ID NO.: 5, SEQ ID NO.: 6, SEQ ID NO.: 7, SEQ ID NO.: 8, SEQ ID NO.: 9, SEQ ID NO.: 10, SEQ ID NO.: 11, SEQ ID NO.: 12 y SEQ ID NO.: 59, o una secuencia con 95-99 % de identidad frente a las mismas.

En una modalidad, el ácido nucleico comprende unácido nuclpeico que codifica CD22 como se muestra en la **Tabla 6** o una secuencia con un 95-99% de identidad con las mismas. En una modalidad, el ácido nucléico es un ácido nucleíco que codifica una secuencia de aminoácidos mostrada en cualquiera de las **Tablas 6A –10B**, o una secuencia con 95-99% de identidad con las mismas.

En una modalidad, el ácido nucleico comprende unácido nuclpeico que codifica CD20 como se muestra en la **Tabla 11A** o una secuencia con un 95-99% de identidad con las mismas. En una modalidad, el ácido nucléico es un ácido nucleíco que codifica una secuencia de aminoácidos mostrada en cualquiera de las **Tablas 11A –15B**, o una secuencia con 95-99% de identidad con las mismas.

En una modalidad, el dominio transmembrana es un dominio transmembrana de una proteína seleccionada del grupo que consiste en la cadena alfa, beta o zeta del receptor de células T, CD28, CD3 épsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 y CD154. En una modalidad, el dominio transmembrana comprende una secuencia de SEQ ID NO.: 15, o una secuencia con 95-99% de identidad frente a la misma.

En una modalidad, el dominio de unión a CD19 está conectado al dominio transmembrana mediante una región bisagra, por ejemplo, una bisagra descrita en el presente documento. En una modalidad, la región bisagra comprende SEQ ID NO.: 14 o SEQ ID NO.: 45 o SEQ ID NO.: 47 o SEQ ID NO.: 5, o una secuencia con 95-99 % de identidad frente a las mismas.

En una modalidad, la molécula de ácido nucleico aislada comprende además una secuencia que codifica un dominio coestimulador. En una modalidad, el dominio coestimulador

comprende un dominio de señalización funcional de una proteína seleccionada del grupo que consiste en OX40, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18), ICOS (CD278) y 4-1BB (CD137). En una modalidad, el dominio coestimulador es un dominio de señalización funcional de una proteína seleccionada del grupo que consiste en una molécula CMH clase I, proteínas receptoras de TNF, proteínas similares a inmunoglobulina, receptores de citoquina, integrinas, moléculas de activación de señalización de linfocitos (proteínas SLAM), receptores activadores de células NK, BTLA, receptor de ligandos Toll, OX40, CD2, CD7, CD27, CD28, CD30, CD40, CDS, ICAM-1, LFA-1 (CD11a/CD18), 4-1BB (CD137), B7-H3, CDS, ICAM-1, ICOS (CD278), GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD4, CD8alfa, CD8beta, IL2Rbeta, IL2Rgamma, IL7Ralfa, ITGA4, VLA1, CD49a, ITGA4, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (táctil), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, y un ligando que se une específicamente a CD83. En una modalidad, el dominio coestimulador comprende una secuencia de SEQ ID NO.: 16, o una secuencia con 95-99 % de identidad frente a la misma.

En una modalidad, el dominio de señalización intracelular comprende un dominio de señalización funcional de 4-1BB y un dominio de señalización funcional de CD3 zeta. En una modalidad, el dominio de señalización intracelular comprende la secuencia de SEQ ID NO.: 16 o SEQ ID NO.: 51, o una secuencia con 95-99 % de identidad frente a la misma, y la secuencia de SEQ ID NO.: 17 o SEQ ID NO.: 43, o una secuencia con 95-99 % de identidad frente a la misma, donde las secuencias que comprenden el dominio de señalización intracelular se expresan en el mismo marco y como una única cadena de polipéptido.

En otro aspecto, la invención se refiere a una molécula de ácido nucleico aislada que codifica un constructo de CAR que comprende una secuencia líder de SEQ ID NO.: 13, un dominio scFv que tiene una secuencia seleccionada del grupo que consiste en SEQ ID NO.: 1, SEQ ID NO.: 2, SEQ ID NO.: 3, SEQ ID NO.: 4, SEQ ID NO.: 5, SEQ ID NO.: 6, SEQ ID NO.: 7, SEQ ID NO.: 8, SEQ ID NO.: 9, SEQ ID NO.: 10, SEQ ID NO.: 11, SEQ ID NO.: 12, y SEQ

ID NO.: 59 (o una secuencia con 95-99 % de identidad frente a la misma), una región bisagra de SEQ ID NO.: 14 o SEQ ID NO.: 45 o SEQ ID NO.: 47 o SEQ ID NO.: 49 (o una secuencia con 95-99 % de identidad frente a la misma), un dominio transmembrana que tiene una secuencia de SEQ ID NO.: 15 (o una secuencia con 95-99% de identidad frente a la misma), un dominio coestimulador de 4-1BB que tiene una secuencia de SEQ ID NO.: 16 o un dominio coestimulador de CD27 que tiene una secuencia de SEQ ID NO.: 51 (o una secuencia con 95- 99 % de identidad frente a la misma), y un dominio estimulador CD3 zeta que tiene una secuencia de SEQ ID NO.: 17 o SEQ ID NO.: 43 (o una secuencia con 95-99 % de identidad frente a la misma).

En otro aspecto, la invención se refiere a una molécula de polipéptido aislada codificada por la molécula de ácido nucleico. En una modalidad, la molécula de polipéptido aislada comprende una secuencia seleccionada de un grupo que consiste en SEQ ID NO.: 31, SEQ ID NO.: 32, SEQ ID NO.: 33, SEQ ID NO.: 34, SEQ ID NO.: 35, SEQ ID NO.: 36, SEQ ID NO.: 37, SEQ ID NO.: 38, SEQ ID NO.: 39, SEQ ID NO.: 40, SEQ ID NO.: 41, SEQ ID NO.: 42, SEQ ID NO.: 59, o una secuencia con 95-99 % de identidad frente a las mismas.

En otro aspecto, la invención se refiere a una molécula de ácido nucleico que codifica un receptor quimérico de antígeno (CAR) que comprende un dominio de unión anti-CD19, un dominio transmembrana y un dominio de señalización intracelular que comprende un dominio estimulador, y donde dicho dominio de unión a anticuerpo anti-CD19 comprende una secuencia seleccionada del grupo que consiste en SEQ ID NO.: 1, SEQ ID NO.: 2, SEQ ID NO.: 3, SEQ ID NO.: 4, SEQ ID NO.: 5, SEQ ID NO.: 6, SEQ ID NO : 7, SEQ ID NO.: 8, SEQ ID NO.: 9, SEQ ID NO.: 10, SEQ ID NO.: 11, SEQ ID NO.: 12 y SEQ ID NO.: 59, o una secuencia con 95-99 % de identidad frente a las mismas.

En una modalidad, la molécula de CAR codificada (por ejemplo, CAR CD19, CAR CD20 o CAR CD22) comprende además una secuencia que codifica un dominio coestimulador. En una modalidad, el dominio coestimulador comprende un dominio de señalización funcional de una proteína seleccionada del grupo que consiste en OX40, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a/CD18) y 4-1BB (CD137). En una modalidad, el dominio coestimulador comprende una secuencia de SEQ ID NO.: 16. En una modalidad, el dominio transmembrana es un dominio transmembrana de una proteína seleccionada del grupo que consiste en la cadena alfa, beta o zeta del receptor de células T, CD28, CD3 épsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 y CD154. En una modalidad, el dominio

transmembrana comprende una secuencia de SEQ ID NO.: 15. En una modalidad, el dominio de señalización intracelular comprende un dominio de señalización funcional de 4-1BB y un dominio de señalización funcional de zeta. En una modalidad, el dominio de señalización intracelular comprende la secuencia de SEQ ID NO.: 16 y la secuencia de SEQ ID NO.: 17, donde las secuencias que comprenden el dominio de señalización intracelular se expresan en el mismo marco y como una única cadena de polipéptido. En una modalidad, el dominio de unión anti-CD19 está conectado al dominio transmembrana mediante una región bisagra. En una modalidad, la región bisagra comprende SEQ ID NO.: 14. En una modalidad, la región bisagra comprende SEQ ID NO.: 45 o SEQ ID NO.: 47 o SEQ ID NO.: 49.

En otro aspecto, la invención se refiere a una molécula de CAR codificada que comprende una secuencia líder de SEQ ID NO.: 13, un dominio scFv que tiene una secuencia seleccionada del grupo que consiste en SEQ ID NO.: 1, SEQ ID NO.: 2, SEQ ID NO.: 3, SEQ ID NO.: 4, SEQ ID NO.: 5, SEQ ID NO.: 6, SEQ ID NO.: 7, SEQ ID NO.: 8, SEQ ID NO.: 9, SEQ ID NO.: 10, SEQ ID NO.: 11, SEQ ID NO.: 12, y SEQ ID NO.: 59, o una secuencia con 95-99 % de identidad frente a la misma, una región bisagra de SEQ ID NO.: 14 o SEQ ID NO.: 45 o SEQ ID NO.: 47 o SEQ ID NO.: 49, un dominio transmembrana que tiene una secuencia de SEQ ID NO.: 15, un dominio coestimulador de 4-1BB que tiene una secuencia de SEQ ID NO.:16 o un dominio coestimulador de CD27 que tiene una secuencia de SEQ ID NO.: 51 y un dominio estimulador CD3 zeta que tiene una secuencia de SEQ ID NO.: 17 o SEQ ID NO.: 43. En una modalidad, la molécula de CAR codificada comprende una secuencia seleccionada de un grupo que consiste en SEQ ID NO.: 31, SEQ ID NO.: 32, SEQ ID NO.: 33, SEQ ID NO.: 34, SEQ ID NO.: 35, SEQ ID NO.: 36, SEQ ID NO.: 37, SEQ ID NO.: 38, SEQ ID NO.: 39, SEQ ID NO.: 40, SEQ ID NO.: 41, SEQ ID NO.: 42 y SEQ ID NO.: 59, o una secuencia con 95-99 % de identidad frente a la misma.

Las secuencias de ácidos nucleicos que codifican para las moléculas deseadas se pueden obtener usando métodos recombinantes conocidos en la técnica, tales como, por ejemplo, realizando un paneo de células que expresan el gen, derivando el gen a partir de un vector conocido para incluir el mismo o mediante aislamiento directo a partir de células y tejidos que contienen el mismo, usando técnicas estándar. Alternativamente, el gen interés se puede producir de manera sintética, en lugar de clonarse.

La presente invención también proporciona vectores en los que se inserta el ADN de la

presente inversión. Los vectores derivados de retrovirus tales como el lentivirus son herramientas adecuadas para lograr la transferencia de genes a largo plazo, ya que permiten una integración estable y a largo plazo de un transgén y su propagación en células hijas. Los vectores lentivirales tienen la ventaja adicional en comparación con los vectores derivados de onco-retrovirus, como los virus de leucemia de ratón, de poder transducir células no proliferantes, tales como los hepatocitos. Además, tienen la ventaja de una baja inmunogenicidad. Un vector retroviral también puede ser, por ejemplo, un vector gammaretroviral. Un vector gammaretroviral puede incluir, por ejemplo, un promotor, una señal de empaquetamiento (ψ), un sitio de unión del cebador (PBS), una o más (por ejemplo, dos) repeticiones terminales largas (LTR) y un transgén de interés, por ejemplo, un gen que codifica un CAR. Un vector gammaretroviral puede carecer de genes estructurales virales tales como gag, pol y env. Ejemplos de vectores gammaretrovirales incluyen el virus de la leucemia murina (MLV), el virus productor de focos esplénicos (SFFV) y el virus del sarcoma mieloproliferativo (MPSV), y vectores derivados de los mismos. Otros vectores gammaretrovirales se describen, por ejemplo, en Tobias Maetzig et al., "Gammaretroviral Vectors: Biology, Technology and Application" Viruses. 2011 Jun; 3(6): 677–713.

En otra modalidad, el vector que comprende el ácido nucleico que codifica el CAR deseado de la invención es un vector adenoviral (A5/35). En otra modalidad, la expresión de ácidos nucleicos que codifican CAR se puede realizar usando de transposones como sleeping beauty, crispr, CAS9 y nucleasas de dedo de zinc. Véase más adelante June et al. 2009*Nature Reviews Immunology* 9.10: 704-716, que se incluye en el presente documento a manera de referencia.

Unvector también puede incluir, por ejemplo, una secuencia señal para facilitar la secreción, una señal de poliadenilación y un terminador de la transcripción (por ejemlo, a partir del gen de la hormona de crecimiento bovino (BGH)), un elemento que permite la replicación episomal y la replicación en procariotas (por ejemplo, origen SV40 y ColE1 u otros conocidos en la técnica) t/o elementos para permitir la selección (por ejemplo, gen de resistencia a la ampicilina y/o marcador de Zeocina).

Para resumir brevemente, la expresión de ácidos nucleicos naturales o sintéticos que codifican CAR se logra típicamente enlazando operativamente un ácido nucleico que codifica el polipéptido de CAR o porciones del mismo a un promotor, e incorporando el constructo a un

vector de expresión. Los vectores pueden ser adecuados para eucariotas de replicación e integración. Los vectores de clonación típicos contienen terminadores de transcripción y traducción, secuencias de iniciación y promotores útiles para la regulación de la expresión de la secuencia de ácido nucleico deseada.

En algunos aspectos, los constructos de expresión de la presente invención también se pueden usar para la inmunización de ácidos nucleicos y la terapia génica, usando protocolos estándar de entrega de genes. Los métodos para la entrega de genes son conocidos en la técnica. Véase, por ejemplo, las Patentes de Estados Unidos No. 5,399,346, 5,580,859, 5,589,466, que se incluyen en el presente documento en su totalidad a manera de referencia. En otra modalidad, la invención proporciona un vector de terapia génica.

El ácido nucleico puede ser clonado en diversos tipos de vectores. Por ejemplo, el ácido nucleico puede clonarse en un vector, incluyendo, de manera enunciativa más no limitativa, un plásmido, un fagémido, un derivado de fago, un virus animal y un cósmido. Los vectores de interés particular incluyen vectores de expresión, vectores de replicación, vectores de generación de sondas y vectores de secuenciación.

Además, el vector de expresión se puede proporcionar a una célula en la forma de un vector viral. La tecnología de vectores virales es bien conocida en la técnica y se describe, por ejemplo, en Sambrook et al., 2012, MOLECULAR CLONING: A LABORATORY MANUAL, volúmenes 1 -4, Cold Spring Harbor Press, NY), y en otros manuales de virología y biología molecular. Los virus, que son útiles como vectores, incluyen, entre otros, retrovirus, adenovirus, virus adeno-asociados, virus del herpes y lentivirus. En general, un vector adecuado contiene un origen de replicación funcional en al menos un organismo, una secuencia de promotor, sitios convenientes de endonucleasas de restricción y uno o más marcadores seleccionables, (por ejemplo, WO 01/96584; WO 01/29058; y Patente de Estados Unidos No. 6,326,193).

Una variedad de sistemas basados en virus se ha desarrollado para la transferencia génica en células de mamífero. Por ejemplo, los retrovirus proporcionan una plataforma conveniente para sistemas de entrega de genes. Un gen seleccionado se puede insertar en un vector y empacar en partículas retrovirales usando técnicas conocidas en la técnica. El virus recombinante puede entonces ser aislado y entregado a células del sujeto ya sea in vivo o ex vivo. Varios sistemas retrovirales son conocidos en la técnica. En algunas modalidades, se usan vectores adenovirales. Varios vectores adenovirales son conocidos en la técnica. En una modalidad, se usan vectores

lentivirales.

Los elementos promotores adicionales, por ejemplo, potenciadores, regulan la frecuencia de iniciación transcripcional. Típicamente, estos se encuentran en la región de 30-110 pares de bases hacia arriba del sitio de inicio, aunque se ha demostrado que varios promotores contienen elementos funcionales también hacia abajo del sitio de inicio. El espaciamiento entre los elementos promotores es con frecuencia flexible, de modo que la función del promotor se conserva cuando los elementos se invierten o se mueven uno respecto del otro. En el promotor de la timidina quinasa (tk), el espaciamiento entre los elementos promotores se puede aumentar a 50 pares de bases antes de que la actividad comience a disminuir. Dependiendo del promotor, parece que algunos elementos individuales pueden funcionar ya sea cooperativamente o de manera independiente para activar la transcripción. Ejemplos de promotores incluyen el gen CMV IE, EF-1α, ubiquitina C o promotores de fosfoglicerato quinasa (PGK). En una modalidad, el promotor es un promotor PGK, por ejemplo, un promotor PGK truncado, como se describe en el presente documento.

Un ejemplo de un promotor que es capaz de expresar un transgén de CAR en una célula T de mamífero es el promotor EF1a. El promotor EF1a inalterado conduce la expresión de la subunidad alfa del complejo del factor de elongación 1, que es responsable de la entrega enzimática de aminoacil-ARNt al ribosoma. El promotor EF1a se ha usado ampliamente en los plásmidos de expresión de mamíferos y ha demostrado ser eficaz en la conducción de la expresión de CAR de transgenes clonados a un vector lentiviral. Véase, por ejemplo, Milone et al., Mol. Ther. 17(8): 1453–1464 (2009). En un aspecto, el promotor EF1a comprende la secuencia proporcionada en SEQ ID NO.: 100.

Otro ejemplo de un promotor es la secuencia del promotor inmediato temprano de citomegalovirus (CMV). Esta secuencia de promotor es una secuencia de promotor constitutivo fuerte, capaz de conducir altos niveles de expresión de cualquier secuencia de polinucleótidos enlazada operativamente a la misma. Sin embargo, también se pueden usar otras secuencias de promotor constitutivo, incluyendo, de manera enunciativa más no limitativa, virus de simio 40 (SV40), promotor temprano, virus de tumor mamario de ratón (MMTV), virus de la inmunodeficiencia humana (VIH), promotor de repetición terminal larga (LTR), promotor de MoMuLV, promotor de virus de la leucemia aviar, promotor inmediato temprano del virus de Epstein-Barr, promotor del virus del sarcoma de Rous, así como promotores de genes humanos

tales como, entre muchos otros, promotor de la actina, promotor de la miosina, promotor del factor de elongación 1, promotor de la hemoglobina y promotor de la creatina quinasa. Además, la invención no debe limitarse al uso de promotores constitutivos. Los promotores inducibles también se contemplan como parte de la invención. El uso de un promotor inducible proporciona un interruptor molecular capaz de activar la expresión de la secuencia de polinucleótidos a la que está enlazado operativamente cuando se desea tal expresión, o de inactivar la expresión cuando no se desea la expresión. Algunos ejemplos de promotores inducibles incluyen, de manera enunciativa más no limitativa, promotor de la metalotionina, promotor de glucocorticoides, promotor de la progesterona y promotor de la tetraciclina.

Otro ejemplo de un promotor es el promotor de la fosfoglicerato quinasa (PGK). En algunas modalidades, es deseable usar un promotor de PGK truncado (por ejemplo, un promotor de PGK con una o más, por ejemplo, 1, 2, 5, 10, 100, 200, 300 o 400, deleciones de nucleótidos en comparación con la secuencia del promotor de PGK de tipo silvestre). Las secuencias de nucleótidos de los ejemplos de promotores de PGK se proporcionan a continuación.

Promotor PGK WT:

ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACG
CGAGGCCTCCGAACGTCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGAT
GGCGGGGTGTGGGGCGGAGGGCGTGGCGGGGAAGGGCCGGCGACGAGAGCCGCGC
GGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCGCCAGCCGCGCGACGGTAAC
GAGGGACCGCGACAGGCAGACGCTCCCATGATCACTCTGCACGCCGAAGGCAAATA
GTGCAGGCCGTGCGGCGCTTGGCGTTCCTTGGAAGGGCTGAATCCCCGCCTCGTCCT
TCGCAGCGGCCCCCCGGGTGTTCCCATCGCCGCTTCTAGGCCCACTGCGACGCTTGC
CTGCACTTCTTACACGCTCTGGGTCCCAGCCGCGGCGACGCAAAGGGCCTTGGTGC
GGGTCTCGTCGGCGCAGGGACGCGTTTGGGTCCCGACGGAACCTTTTCCGCGTTGG
GGTTGGGGCACCATAAGCT (SEQ ID NO.: 1323)

Ejemplos de promotores PGK truncados:

PGK100:

ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACG
CGAGGCCTCCGAACGTCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGAT
GGCGGGGTG (SEQ ID NO.: 1324)

PGK200:

ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACG CGAGGCCTCCGAACGTCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGAT GGCGGGGTGTGGGGCGGAGGGCGTGGCGGGGAAGGGCCGGCGACGAGAGCCGCGC GGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCGCCAGCCGCGCGACGGTAAC G (SEQ ID NO.: 1325)

PGK300:

ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACG CGAGGCCTCCGAACGTCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGAT GGCGGGGTGTGGGGCGGAGGGCGTGGCGGGGAAGGGCCGGCGACGAGAGCCGCGC GGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCGCCAGCCGCGCGACGGTAAC GAGGGACCGCGACAGGCAGACGCTCCCATGATCACTCTGCACGCCGAAGGCAAATA GTGCAGGCCGTGCGGCGCTTGGCGTTCCTTGGAAGGGCTGAATCCCCG (SEQ ID NO.: 1326)

PGK400:

ACCCCTCTCTCCAGCCACTAAGCCAGTTGCTCCCTCGGCTGACGGCTGCACG CGAGGCCTCCGAACGTCTTACGCCTTGTGGCGCGCCCGTCCTTGTCCCGGGTGTGAT GGCGGGGTGTGGGGCGGAGGGCGTGGCGGGGAAGGGCCGGCGACGAGAGCCGCGC GGGACGACTCGTCGGCGATAACCGGTGTCGGGTAGCGCCAGCCGCGCGACGGTAAC GAGGGACCGCGACAGGCAGACGCTCCCATGATCACTCTGCACGCCGAAGGCAAATA GTGCAGGCCGTGCGGCGCTTGGCGTTCCTTGGAAGGGCTGAATCCCCGCCTCGTCCT TCGCAGCGGCCCCCCGGGTGTTCCCATCGCCGCTTCTAGGCCCACTGCGACGCTTGC CTGCACTTCTTACACGCTCTGGGTCCCAGCCG (SEQ ID NO.: 1327)

Un vector también puede incluir, por ejemplo, una secuencia de señal para facilitar la secreción, una señal de poliadenilación y un terminador de transcripción (por ejemplo, gen de la hormona de crecimiento bovino (BGH)), un elemento que permite la replicación episomal y la replicación en procariotas (por ejemplo, origen SV40 y ColE1 u otros conocidos en la técnica) y/o elementos que permiten la selección (por ejemplo, gen de resistencia a ampicilina y/o marcador de zeocina).

Para evaluar la expresión de un polipéptido de CAR o porciones del mismo, el vector de

expresión que se introducirá en una célula también puede contener un gen marcador seleccionable, o un gen reportero, o ambos, para facilitar la identificación y selección de células que expresan a partir de la población de células que se busca transfectar o infectar a través de vectores virales. En otros aspectos, el marcador seleccionable se puede colocar en una porción separada de ADN y usarse en un procedimiento de co-transfección. Tanto los marcadores seleccionables como los genes reporteros pueden ser flanqueados con secuencias reguladoras apropiadas para permitir la expresión en las células huésped. Algunos marcadores seleccionables útiles incluyen, por ejemplo, genes de resistencia a antibióticos, tales como neo y similares.

Los genes reporteros se usan para identificar células potencialmente transfectadas y para evaluar la funcionalidad de las secuencias reguladoras. En general, un gen reportero es un gen que no está presente en o expresado por el organismo o tejido receptor y que codifica un polipéptido cuya expresión se manifiesta mediante alguna propiedad fácilmente detectable, por ejemplo, la actividad enzimática. La expresión del gen reportero se somete a ensayo en un momento adecuado después de que el ADN se ha introducido en las células receptoras. Algunos genes reporteros adecuados pueden incluir genes que codifican la luciferasa, beta-galactosidasa, cloranfenicol acetil transferasa, fosfatasa alcalina segregada, o el gen de la proteína verde fluorescente (por ejemplo, Ui-Tei et al., 2000 FEBS Letters 479.: 79-82). 79-82). Algunos sistemas de expresión adecuados son bien conocidos y se pueden preparar usando técnicas conocidas u obtenerse comercialmente. En general, el constructo con la menor región flanqueante 5' que muestre el nivel de expresión más alto del gen reportero se identifica como el promotor. Tales regiones promotoras pueden ser enlazadas a un gen reportero y usarse para evaluar agentes por su capacidad para modular la transcripción activada por promotor.

En algunas modalidades, el vector puede comprender dos o más secuencias de ácido nucleico que codifican un CAR, por ejemplo, un primer CAR que se une a CD19 y un segundo CAR, por ejemplo, un CAR inhibidor o un CAR que se une específicamente a un segundo antígeno, por ejemplo, CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a. En dichas modalidades, las dos o más secuencias de ácido nucleico que codifican el CAR están codificadas por una sola molécula nucleica en el mismo marco y como una única cadena de polipéptido. En este aspecto, las dos o más CAR, pueden, por ejemplo, estar separados por uno o más sitios de escisión de péptidos. (por ejemplo, un sitio de auto-escisión o un sustrato para una proteasa intracelular). Ejemplos de sitios de escisión de péptidos incluyen

los siguientes, donde los residuos GSG son opcionales:

T2A: (GSG)EGRGSLLTCGDVEENPGP (SEQ ID NO.: 1328)

P2A: (GSG)ATNFSLLKQAGDVEENPGP (SEQ ID NO.: 1329)

E2A: (GSG)QCTNYALLKLAGDVESNPGP (SEQ ID NO.: 1330)

F2A: (GSG)VKQTLNFDLLKLAGDVESNPGP (SEQ ID NO.: 1331)

Métodos para introducir y expresar genes en una célula se conocen en la técnica. En el contexto de un vector de expresión, el vector puede introducirse fácilmente en una célula hospedera, por ejemplo, de mamífero, bacteriana, levadura o de insecto, mediante cualquier método de la técnica. Por ejemplo, el vector de expresión se puede transferir a una célula hospedera mediante medios físicos, químicos o biológicos.

Los métodos físicos para la introducción de un polinucleótido en una célula hospedera incluyen precipitación con fosfato de calcio, lipofección, bombardeo de partículas, micro-inyección, electroporación, y similares. Los métodos para producir células que comprenden vectores y/o ácidos nucleicos exógenos son bien conocidos en la técnica. Véase, por ejemplo, Sambrook et al., 2012, MOLECULAR CLONING: A LABORATORY MANUAL, volúmenes 1-4, Cold Spring Harbor Press, NY). Un método adecuado para la introducción de un polinucleótido en una célula hospedera es transfección con fosfato de calcio.

Los métodos biológicos para la introducción de un polinucleótido de interés en una célula hospedera incluyen el uso de vectores de ADN y ARN. Los vectores virales, y especialmente los vectores retrovirales, se han convertido en el método más comúnmente usado para la inserción de genes en células de mamífero, por ejemplo, células humanas. Otros vectores virales pueden ser derivados de lentivirus, poxvirus, virus herpes simplex I, adenovirus y virus adeno-asociados, y similares. Véase, por ejemplo, Patentes de los Estados Unidos No. 5,350,674 y 5,585,362.

Los medios químicos para la introducción de un polinucleótido en una célula hospedera incluyen sistemas de dispersión coloidal, tales como complejos de macromoléculas, nanocápsulas, microesferas, esferas y sistemas basados en lípidos, incluyendo emulsiones de aceite en agua, micelas, micelas mixtas y liposomas. Un ejemplo de un sistema coloidal usado como un vehículo de entrega in vitro e in vivo es un liposoma (por ejemplo, una vesícula de membrana artificial). Otros métodos de vanguardia para la entrega dirigida de ácidos nucleicos

están disponibles, tales como la entrega de polinucleótidos con nanopartículas dirigidas u otro sistema de entrega de tamaño sub-micra adecuado.

En el caso en que se usa un sistema de administración no viral, un ejemplo de vehículo de entrega es un liposoma. El uso de formulaciones lipídicas se contempla para la introducción de los ácidos nucleicos en una célula hospedera (in vitro, ex vivo o in vivo). En otro aspecto, el ácido nucleico puede estar asociado a un lípido. El ácido nucleico asociado a un lípido puede estar encapsulado en el interior acuoso de un liposoma, entremezclado dentro de la bicapa lipídica de un liposoma, fijado a un liposoma mediante una molécula enlazadora que está asociada al liposoma y al oligonucleótido, atrapado en un liposoma, complejado con un liposoma, dispersado en una solución que contiene un lípido, mezclado con un lípido, combinado con un lípido, contenido como una suspensión en un lípido, contenido o complejado con una micela o asociado de alguna otra manera a un lípido. Las composiciones asociadas a vectores lípidos, lípidos/ADN, lípidos/de expresión no se limitan a ninguna estructura particular en solución. Por ejemplo, pueden estar presentes en una estructura bicapa, como micelas, o con una estructura de "colapsada". También pueden simplemente estar entremezcladas en una solución, posiblemente formando agregados que no son uniformes en tamaño o forma. Los lípidos son sustancias grasas que pueden ser de origen natural o lípidos sintéticos. Por ejemplo, los lípidos incluyen gotitas grasas que se producen naturalmente en el citoplasma, así como la clase de compuestos que contienen hidrocarburos alifáticos de cadena larga y sus derivados, tales como ácidos grasos, alcoholes, aminas, amino alcoholes y aldehídos.

Lípidos adecuados para uso se pueden obtener de fuentes comerciales. Por ejemplo, la dimiristil fosfatidilcolina ("DMPC") se puede obtener en Sigma, St. Louis, MO; el fosfato de dicetilo ("DCP") se puede obtener en K & K Laboratories (Plainview, NY); el colesterol ("Choi") se puede obtener en Calbiochem-Behring; el dimiristilo fosfatidilglicerol ("DMPG") y otros lípidos se pueden obtener en Avanti Polar Lipids, Inc. (Birmingham, AL.). Las soluciones madre de lípidos en cloroformo o cloroformo/metanol se pueden almacenar a aproximadamente -20ºC. El cloroformo se usa como el único disolvente ya que se evapora más fácilmente que el metanol. "Liposoma" es un término genérico que abarca una variedad de vehículos unilamelares y multilamelares de lípidos formados por la generación de bicapas o agregados lipídicos cerrados. Los liposomas se pueden caracterizar por tener estructuras vesiculares con una membrana bicapa de fosfolípidos y un medio acuoso interno. Los liposomas multilamelares

tienen múltiples capas lipídicas separadas por medio acuoso. Se forman espontáneamente cuando se suspenden fosfolípidos en un exceso de solución acuosa. Los componentes lipídicos se auto-reorganizan antes de la formación de estructuras cerradas y atrapan agua y solutos disueltos entre las bicapas lipídicas (Ghosh et al., 1991 Glycobiology 5: 505-10). Sin embargo, también se contemplan las composiciones que tienen estructuras en solución diferentes de la estructura vesicular normal. Por ejemplo, los lípidos pueden asumir una estructura micelar o simplemente existir como agregados no uniformes de moléculas lipídicas. También se contemplan complejos de lipofectamina-ácido nucleico.

Independientemente del método usado para introducir ácidos nucleicos exógenos en una célula hospedera o exponer una célula al inhibidor de la presente invención de otra manera, con el fin de confirmar la presencia de la secuencia de ADN recombinante en la célula hospedera, se pueden realizar diversos ensayos. Dichos ensayos incluyen, por ejemplo, ensayos "biológicos moleculares" bien conocidos por los expertos en la técnica, tal como Southern y Northern blotting, RT-PCR y PCR; ensayos "bioquímicos", tales como detección de la presencia o ausencia de un péptido específico, por ejemplo, a través de medios inmunológicos (ELISA y Western blots) o a través ensayos descritos en el presente documento para identificar agentes que están dentro del alcance de la invención.

La presente invención proporciona además un vector que comprende una molécula de ácido nucleico que codifica un CAR. En un aspecto, un vector de CAR se puede transducir directamente en una célula, *por ejemplo,* una célula T. En un aspecto, el vector es un vector de clonación o de expresión, *por ejemplo,* un vector que incluye, de manera enunciativa mas no limitativa, uno o más plásmidos (*por ejemplo*, plásmidos de expresión, vectores de clonación, minicírculos, minivectores, minicromosomas), constructos de vectores retrovirales y lentivirales. En un aspecto, el vector tiene la capacidad de expresar el constructo de CAR en células T de mamíferos. En un aspecto, la célula T de mamífero es una célula T humana.

Células inmunes efectoras que expresan un CAR

En otro aspecto, la presente invención proporciona una población de células que expresan un CAR. En algunas modalidades la población de células que expresan CAR comprende una célula que expresa uno o más CARs descritos en el presente documento. En algunas modalidades, la población de células que expresan un CAR comprende una mezcla de células que expresan diferentes CARs.

Por ejemplo, en una realización, la población de células TCAR puede incluir una primera célula que expresa un CAR que tiene un dominio de unión a antígeno a un antígeno tumoral que se describe en el presente documento, por ejemplo, CD19, y una segunda célula que expresa un CAR que tiene un dominio de unión a un antígeno diferente, por ejemplo, un dominio de unión a antígeno a un antígeno tumoral diferente se describe en el presente documento, por ejemplo, un dominio de unión a un antígeno tumoral se describe en el presente documento que difiere del antígeno tumoral vinculado por el dominio de unión a antígeno del CAR expresado por la primera célula, por ejemplo, antígeno CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a.

Como otro ejemplo, la población de células que expresa CAR puede incluir una primera célula que expresa un CAR que incluye un dominio de unión a un antígeno tumoral, antígeno que se describe en el presente documento, y una segunda célula que expresa un CAR que incluye un dominio de unión a un blanco que no sea antígeno un antígeno tumoral tal como se describe en el presente documento. En una realización, la población de células que expresan CAR incluye, por ejemplo, una primera célula que expresa un CAR que incluye un dominio primario de señalización intracelular, y una segunda célula que expresa un CAR que incluye un dominio secundario de señalización. Cualquiera de los dos o ambos de las células que expresan CAR puede tener un promotor PGK truncado, por ejemplo, como se describe en el presente documento, unido operativamente al ácido nucleico que codifica el CAR.

En otro aspecto, la presente invención proporciona una población de células en la que al menos una célula en la población expresa un CAR que tiene dominio de unión a un antígeno de tumor, un antígeno que se describe en este documento, y una segunda célula que expresa otro agente, por ejemplo, un agente que mejora la actividad de una célula que expresa CAR. La células que expresan CAR de la población pueden tener un promotor PGK truncado, por ejemplo, como se describe en el presente documento, unido operativamente al ácido nucleico que codifica el CAR. En una realización, el agente puede ser un agente que inhibe una molécula inhibidora. Las moléculas inhibidoras, por ejemplo, PD-1, pueden, en algunas realizaciones, disminuir la capacidad de una célula que expresa CAR de montar una respuesta inmune efectora. Ejemplos de moléculas inhibidoras incluyen PD-1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (CEACAM-1, CEACAM-3, y/o CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160 , 2B4, CD80, CD86, CMH de clase I, B7-H4 (VTCN1), HVEM (TNFRSF14 o CD270), KIR, A2AR, CMH de

clase II, B7-H3 (CD276), GAL9, adenosina, y TGFR (por ejemplo, TGFRbeta). En una realización, el agente que inhibe una molécula inhibidora comprende un primer polipéptido, por ejemplo, una molécula de inhibidor, asociado con un segundo polipéptido que proporciona una señal positiva a la célula, por ejemplo, un dominio de señalización intracelular que se describe en el presente documento. En una realización, el agente comprende un primer polipéptido, por ejemplo, de una molécula inhibidora tal como PD1, PD-L1, CTLA4, TIM3, CEACAM (por ejemplo, CEACAM-1, CEACAM-3, y/o CEACAM-5), LAG3 , VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 o TGFR beta, o un fragmento de cualquiera de estos, y un segundo polipéptido que es un dominio de señalización intracelular que se describe en el presente documento (por ejemplo, que comprende un dominio coestimulador (por ejemplo, 41BB, CD27, OX40 o CD28, por ejemplo, como se describe en la presente memoria) y/o un dominio primario de señalización (por ejemplo, un dominio de señalización CD3-zeta que se describe en este documento). En una realización, el agente comprende un primer polipéptido de PD-1 o un fragmento del mismo, y un segundo polipéptido de un dominio de señalización intracelular descrito en este documento (por ejemplo, un dominio de señalización de CD28 descrito en este documento y o un dominio de señalización/CD3 zeta que se describe en este documento).

Co-expresión de CAR con otras moléculas o agentes

Co-expresión de un segundo CAR

En un aspecto, la célula que expresa CAR descrita en este documento puede comprender además un segundo CAR, por ejemplo, un segundo CAR que incluye un dominio diferente de unión a antígeno, por ejemplo, para el mismo objetivo (CD19) o un objetivo diferente (por ejemplo, CD10, CD20 , CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a). En una realización, el segundo CAR incluye un dominio de unión a un objetivo, antígeno expresado en células de leucemia mieloide aguda, tales como, por ejemplo, CD20, CD22, ROR1, CD10, CD33, CLL-1, CD34, CD123, FLT3, CD79b, CD179b y CD79a. En una realización, la célula que expresa CAR comprende un primer CAR que se dirige a un primer antígeno e incluye un dominio de señalización intracelular que tiene un dominio coestimulador, pero no un dominio de primaria señalización, y un segundo CAR que se dirige a un segundo antígeno, diferente, e incluye un dominio de señalización intracelular que tiene un dominio de señalización primaria, pero no es un dominio de señalización coestimulador. Si bien no se desea estar limitado por la teoría, la

colocación de un dominio de señalización coestimulador, por ejemplo, el 4-1BB, CD28, CD27 o OX-40, sobre el primer CAR, y el dominio primario de señalización, por ejemplo, CD3 zeta, en el segundo CAR pueden limitar la actividad CAR a las células en las que se expresan las dos blancos. En una realización, la célula que expresa CAR comprende un primer CAR CD19 que incluye un dominio de unión a CD19, un dominio transmembrana y un dominio coestimulador y un segundo CAR que se dirige a un antígeno distinto de CD19 (por ejemplo, un antígeno expresado en células de AML, por ejemplo, CD22, CD20, ROR1, CD10, CD33, CLL-1, CD34, CD123, FLT3, CD79b, CD179b, o CD79a) e incluye un dominio de unión al antígeno, un dominio transmembrana y un dominio primario de señalización. En otra realización, la célula que expresa CAR comprende un primer CAR CD19 que incluye un dominio de unión de CD19, un dominio transmembrana y un dominio primario de señalización y un segundo CAR que se dirige a un antígeno distinto de CD19 (por ejemplo, un antígeno expresado en células de AML, por ejemplo, CD22, CD20, ROR1, CD10, CD33, CD123, CLL-1, CD34, FLT3, CD79b, CD179b, o CD79a) e incluye un dominio de unión al antígeno, un dominio transmembrana y un dominio de señalización coestimuladora.

En un aspecto, la célula que expresa CAR descrita en este documento puede comprender además un segundo CAR, por ejemplo, un segundo CAR que incluye un dominio diferente de unión a antígeno, por ejemplo, a la misma diana (por ejemplo, CD19) o un objetivo diferente (por ejemplo, una objetivo que no sea CD19, por ejemplo, CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a). En una realización, la célula que expresa CAR comprende un primer CAR que se dirige a un primer antígeno e incluye un dominio de señalización intracelular que tiene un dominio coestimulador, pero no un dominio primario de señalización, y un segundo CAR que se dirige a un segundo antígeno, diferente, e incluye un dominio de señalización intracelular que tiene un dominio primario de señalización, pero no es un dominio de señalización coestimulador. La colocación de un dominio de señalización coestimulador, por ejemplo, el 4-1BB, CD28, CD27, OX-40 o ICOS, sobre el primer CAR, y el dominio de señalización primaria, por ejemplo, CD3 zeta, en el segundo CAR puede limitar la actividad CAR a las células donde se expresan las dos dianas. En una realización, la célula que expresa CAR comprende un primer CAR que incluye un dominio de unión a antígeno, un dominio transmembrana y un dominio coestimulador y un segundo CAR que se dirige a otro antígeno e incluye un dominio de unión a antígeno, un dominio transmembrana y un dominio primario de señalización. En otra realización, la célula que expresa CAR comprende un primer CAR que incluye un dominio de unión al

antígeno, un dominio transmembrana y un dominio primario de señalización y un segundo CAR que se dirige a otro antígeno e incluye un dominio de unión al antígeno, un dominio transmembrana y un dominio de señalización coestimulador.

En una realización, la célula que expresa CAR comprende un XCAR se describe en este documento (por ejemplo, CAR CD19, CAR CD20, o CAR CD22) y un CAR inhibidor. En una realización, la célula que expresa CAR comprende un CAR CD19 descrito en este documento y un CAR inhibidor. En una realización, el CAR inhibidor comprende un dominio de unión a antígeno que se une un antígeno encontrado en las células normales, pero no en las células de cáncer, por ejemplo, células normales que también expresan CD19. En una realización, el CAR inhibidor comprende el dominio de unión al antígeno, un dominio transmembrana y un dominio intracelular de una molécula inhibidora. Por ejemplo, el dominio intracelular del CAR inhibidor puede ser un dominio intracelular de PD-1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (CEACAM-1, CEACAM-3, y / o CEACAM-5), LAG3 , VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), CMH de clase I, B7-H4 (VTCN1), HVEM (TNFRSF14 o CD270), KIR, A2AR, CMH de clase II, GAL9, adenosina, y TGFR (por ejemplo, TGFRbeta).
En una realización, cuando la célula que expresa CAR comprende dos o más CARs diferentes, los dominios de los CARs diferentes de unión a antígeno pueden ser tales, que los dominios de unión a antígeno no interactúan unos con otros. Por ejemplo, una célula que expresa un primer y un segundo CAR puede tener un dominio de unión al antígeno del primer CAR, por ejemplo, como un fragmento, por ejemplo, un scFv, que no forma una asociación con el dominio de unión al antígeno del segundo CAR, por ejemplo, el dominio de unión al antígeno del segundo CAR es un VHH.

Co-expresión de un agente que aumenta la actividad de CAR

En otro aspecto, la célula que expresa CAR descrita en este documento puede expresar además otro agente, por ejemplo, un agente que potencia la actividad o de la aptitud de una célula que expresa CAR.

Por ejemplo, en una realización, el agente puede ser un agente que inhibe una molécula que modula o regula, por ejemplo, inhibe, la función de las células T. En algunas realizaciones, la molécula que modula o regula la función de las células T es una molécula inhibidora. Las

moléculas inhibidoras, por ejemplo, PD1, pueden, en algunas realizaciones, disminuir la capacidad de una célula que expresa CAR de montar una respuesta inmune efectora. Ejemplos de moléculas inhibidoras incluyen PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (por ejemplo, CEACAM-1, CEACAM-3 y / o CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD160, 2B4, CD80, CD86, B7-H3 (CD276), CMH de clase I, B7-H4 (VTCN1), HVEM (TNFRSF14 o CD270), KIR, A2AR, CMH de clase II, GAL9, adenosina, y TGFR (por ejemplo, TGFR beta).

En una realización, un ácido nucleico inhibidor, por ejemplo, un ácido nucleico inhibidor, por ejemplo, un ARN de doble cadena, por ejemplo, un siARN o shARN, un clúster regularmente espaciado con repeticiones palindrómicas cortas (CRISPR), una transcripción activador como efector de nucleasa (TALEN), o una endonucleasa de dedo de zinc (ZFN), por ejemplo, como se describe en el presente documento, se puede utilizar para inhibir la expresión de una molécula que modula o regula, por ejemplo, inhibe, la función de las células T en la célula que expresa CAR. En una realización, el agente es un shARN, por ejemplo, un shARN que se describe en este documento. En una realización, el agente que modula o regula, por ejemplo, inhibe, la función de células T se inhibe dentro de una célula que expresa CAR. Por ejemplo, una molécula de dsARN que inhibe la expresión de una molécula que modula o regula, por ejemplo, inhibe, la función de las células T está relacionada con el ácido nucleico que codifica un componente, por ejemplo, todos los componentes, del CAR.

En una realización, el agente que inhibe una molécula inhibidora comprende un primer polipéptido, por ejemplo, una molécula de inhibidor, asociado con un segundo polipéptido que proporciona una señal positiva a la célula, por ejemplo, un dominio de señalización intracelular se describe en el presente documento. En una realización, el agente comprende un primer polipéptido, por ejemplo, de una molécula inhibidora tal como PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (por ejemplo, CEACAM-1, CEACAM-3 y / o CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 o CD270), KIR, A2AR, CMH clase I, CMH clase II, GAL9, adenosina, o TGFR (por ejemplo, beta TGFR), o un fragmento de cualquiera de éstos (por ejemplo, al menos una parte de un dominio extracelular de cualquiera de éstos), y un segundo polipéptido que es un dominio de señalización intracelular que se describe en el presente documento (por ejemplo, que comprende un dominio coestimulador (por ejemplo, 41BB, CD27 o CD28, por ejemplo, como se describe en la presente memoria) y/o un dominio primario de

señalización (por ejemplo, un dominio de señalización CD3 zeta que se describe en este documento). En una realización, el agente comprende un primer polipéptido de PD1 o un fragmento del mismo (por ejemplo, al menos una parte de un dominio extracelular de PD1), y un segundo polipéptido de un dominio de señalización intracelular que se describe en el presente documento (por ejemplo, un dominio de señalización de CD28 descritosen este documento y/o un un dominio de señalización CD3 zeta que se describe en este documento). PD1 es un miembro de inhibidor de la familia de los receptores CD28, que también incluye CD28, CTLA-4, ICOS, y BTLA. PD-1 se expresa en células B activadas, células T y células mieloides (Agata et al 1996 Int Immunol 8:.. 765-75). Se han demostrado dos ligandos para PD1, PD-L1 y PD-L2 para disminuir la activación de células T tras la unión a PD1 (Freeman et un 2000 J Exp Med 192: 1027-1034; Latchman et al 2001 Nat Immunol 2: 261-8; Carter et al 2002 Eur J Immunol 32: 634-43). PD-L1 es abundante en cánceres humanos (Dong et al 2003 J Mol Med. 81: 281-7; Blank et al 2005 Cancer Immunol Immunother 54: 307-314; Konishi et al 2004 Clin Cancer Res 10: 5094.) . La inmunosupresión puede revertirse mediante la inhibición de la interacción local de PD1 con PD-L1.

En una realización, el agente comprende el dominio extracelular (ECD) de una molécula de inhibidor, por ejemplo, muerte programada 1 (PD1), puede estar condensado a un dominio transmembrana y los dominios de señalización intracelulares tales como 41BB y CD3 zeta (también denominado en este documento un CAR PD1). En una realización, el CAR PD1, cuando se usa en combinaciones con un CAR CD19 descrito en este documento, mejora la persistencia de la célula T. En una realización, el CAR es un CAR PD1 que comprende el dominio extracelular de PD1 indica como se muestra en la SEQ ID NO: 121. En una realización, el CAR PD1 comprende la secuencia de aminoácidos de la SEQ ID NO: 121.

Malpvtalllplalllhaarppgwfldspdrpwnpptfspallvvtegdnatftcsfsntsesfvlnwyrmspsnqtdklaafpedrsqp gqdcrfrvtqlpngrdfhmsvvrarrndsgtylcgaislapkaqikeslraelrvterraevptahpspsprpagqfqtlvtttpaprpptp aptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpee eeggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkg errrgkghdglyqglstatkdtydalhmqalppr (SEQ ID NO: 121).

En una realización, el CAR PD1 comprende la secuencia de aminoácidos proporcionada a continuación (SEQ ID NO: 119).

pgwfldspdrpwnpptfspallvvtegdnatftcsfsntsesfvlnwyrmspsnqtdklaafpedrsqpgqdcrfrvtqlpngrdfhm svvrarrndsgtylcgaislapkaqikeslraelrvterraevptahpspsprpagqfqtlvtttpaprpptpaptiasqplslrpeacrpaag gavhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapay kqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglstatk dtydalhmqalppr (SEQ ID NO: 119).

En una realización, el agente comprende una secuencia de ácido nucleico que codifica el CAR PD1, por ejemplo, el CAR PD1 que se describe en este documento. En una realización, la secuencia de ácido nucleico para el CAR PD1 se muestra a continuación, con la PD1 ECD subrayado a continuación en la SEQ ID NO: 120

atggccctccctgtcactgccctgcttctccccctcgcactcctgctccacgccgctagaccacccggatggtttctggactctccggatcgc ccgtggaatcccccaaccttctcaccggcactcttggttgtgactgagggcgataatgcgaccttcacgtgctcgttctccaacacctccgaa tcattcgtgctgaactggtaccgcatgagcccgtcaaaccagaccgacaagctcgccgcgtttccggaagatcggtcgcaaccgggaca ggattgtcggttccgcgtgactcaactgccgaatggcagagacttccacatgagcgtggtccgcgctaggcgaaacgactccgggaccta cctgtgcggagccatctcgctggcgcctaaggcccaaatcaaagagagcttgagggccgaactgagagtgaccgagcgcagagctgag gtgccaactgcacatccatccccatcgcctcggcctgcggggcagtttcagaccctggtcacgaccactccggcgccgcgcccaccgac tccggccccaactatcgcgagccagcccctgtcgctgaggccggaagcatgccgccctgccgccggaggtgctgtgcatacccgggga ttggacttcgcatgcgacatctacatttgggctcctctcgccggaacttgtggcgtgctccttctgtccctggtcatcaccctgtactgcaagcg gggtcggaaaaagcttctgtacattttcaagcagcccttcatgaggcccgtgcaaaccacccaggaggaggacggttgctcctgccggttc cccgaagaggaagaaggaggttgcgagctgcgcgtgaagttctcccggagcgccgacgcccccgcctataagcagggccagaaccag ctgtacaacgaactgaacctgggacggcgggaagagtacgatgtgctggacaagcggcgcggccgggaccccgaaatgggcgggaa gcctagaagaaagaaccctcaggaaggcctgtataacgagctgcagaaggacaagatggccgaggcctactccgaaattgggatgaag ggagagcggcggaggggaaaggggcacgacggcctgtaccaaggactgtccaccgccaccaaggacacatacgatgccctgcacat gcaggcccttcccccctcgc (SEQ ID NO: 120).

En otro ejemplo, en una realización, el agente que mejora la actividad de una célula que expresa CAR puede ser una molécula coestimuladora o un ligando molécula coestimuladora. Ejemplos de moléculas coestimuladoras incluyen moléculas CMH de clase I, BTLA y un receptor de ligando Toll, así como OX40, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a / CD18), ICOS (CD278), y el 4-1BB (CD137). Otros ejemplos de tales moléculas coestimuladoras incluyen CDS, ICAM-1, GITR, BAFFR, HVEM (LightR), SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD160, CD19, CD4, CD8alpha, CD8beta, beta IL2R, gamma IL2R , alfa IL7R, ITGA4, Vla1, CD49a,

ITGA4, IA4, CD49d, ITGA6, VLA-6, CD49f, ITGAD, CD11d, ITGAE, CD103, ITGAL, CD11a, LFA-1, ITGAM, CD11b, ITGAX, CD11c, ITGB1, CD29, ITGB2, CD18, LFA-1, ITGB7, NKG2D, NKG2C, TNFR2, TRANCE / RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (tactile), CEACAM1, CRTAM, Ly9 (CD229), CD160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Ly108), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/CBP, CD19a, y un ligando que se une específicamente con CD83, por ejemplo, como se describe en el presente documento. Ejemplos de ligandos de moléculas coestimuladoras incluyen CD80, CD86, CD40L, ICOSL, CD70, OX40L, 4-1BBL, GITRL, y LIGHT. En formas de realización, el ligando de molécula coestimuladora es un ligando para una molécula coestimuladora diferente del dominio molécula coestimuladora del CAR. En formas de realización, el ligando de la molécula coestimuladora es un ligando para una molécula coestimuladora que es el mismo que el dominio coestimulador de la molécula de CAR. En una realización, el ligando de la molécula coestimuladora es 4-1BBL. En una realización, el ligando coestimulador es CD80 o CD86. En una realización, el ligando de la molécula coestimuladora es CD70. En algunas formas de realización, una célula efectora inmune que expresa CAR, descrita en este documento puede modificarse adicionalmente para expresar una o más moléculas coestimuladoras o ligandos de molécula coestimuladora.

Co-expresión de CAR con un receptor de quimioquinas

En formas de realización, la célula que expresa CAR descrita en este documento comprende además una molécula de receptor de quimioquinas. La expresión transgénica de los receptores de quimiocinas CCR2b o CXCR2 en células T aumenta el tráfico a tumores sólidos secretores de CCL2- o CXCL1, incluyendo melanoma y neuroblastoma (Craddock et al, J Immunother 2010 Oct; 33 (8): 780-8 y Kershaw et al, Hum Gene Ther. 2002 Nov 1; 13 (16): 1971-80). Así, sin desear estar ligado por la teoría, se cree que los receptores de quimioquinas expresados en células que expresan CAR que reconocen quimiocinas secretadas por los tumores, por ejemplo, tumores sólidos, puede mejorar la identificación de la célula que expresa CAR al tumor, facilitar la infiltración de la célula que expresa CAR al tumor, y mejorar la eficacia antitumoral de la célula que expresa CAR. La molécula de receptor de quimioquinas puede comprender un receptor de quimiocinas de origen natural o recombinante o un fragmento de unión a quimiocinas de la misma. Una molécula de receptor de quimioquinas adecuada para la expresión en una célula que expresa

CAR, descrito en este documento incluyen un receptor de quimioquinas CXC (por ejemplo, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, o CXCR7), un receptor de quimioquinas CC (por ejemplo, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CCR11 o), un receptor de quimioquinas CX3C (por ejemplo, CX3CR1), un receptor de quimioquinas XC (por ejemplo, XCR1), o un fragmento de unión a quimiocinas de la misma. En una realización, la molécula de receptor de quimioquinas se expresa con un CAR descrito en este documento se selecciona basándose en la(s) quimiocina (s) secretada por el tumor. En una realización, la célula que esxpresa CAR descrita en este documento comprende además, por ejemplo, expresa, un receptor CCR2b o un receptor CXCR2. En una realización, el CAR que se describe en este documento y la molécula de receptor de quimioquinas están en el mismo vector o están en dos vectores diferentes. En realizaciones en las que el CAR descrito en este documento y la molécula de receptor de quimioquinas están en el mismo vector, el CAR y la molécula de receptor de quimioquinas están cada uno bajo el control de dos promotores diferentes o están bajo el control del mismo promotor.

Expresión condicional de Potenciadores de la Respuesta Inmune

También se proporcionan en este documento composiciones y métodos para expresar condicionalmente un agente que potencia la respuesta inmune o actividad de una célula que expresa CAR descrita en este documento.

En un aspecto, la presente exposición presenta una célula efectora inmune que está diseñada para expresar constitutivamente un CAR, también se denomina en este documento como un CAR no condicional. En una realización, un CAR no condicional tal como se describe en el presente documento comprende un dominio de unión a antígeno que se une a un antígeno asociado a cáncer, por ejemplo, CD19, CD10, CD20, CD22, CD34, CD123, FLT-3, o ROR1. En formas de realización, el CAR no condicional que expresan las células inmunes efectoras comprende además un agente condicionalmente expresado que mejora la eficacia terapéutica, por ejemplo, la respuesta inmune, de la célula efectora inmune que expresa CAR. En tales realizaciones, la expresión del agente expresado condicionalmente se produce tras la activación de la célula efectora inmune que expresa CAR no condicional, por ejemplo, tras la unión de la molécula de CAR no condicional a su diana, por ejemplo, un antígeno de cáncer asociado, por ejemplo, CD19,

CD10, CD20, CD22, CD34, CD123, FLT-3, o ROR1.

Agentes potenciadores de la respuesta inmune como se describe aquí se puede caracterizar por una o más de las siguientes: 1) los blancos o se une a un antígeno de cáncer asociado diferente de al que se dirige el CAR no condicional; 2) inhibe la expresión o actividad de un puesto de control inmune o molécula inhibidora; y/o 3) activa la expresión y/o secreción de un componente que mejora la respuesta inmune o la activación de una célula inmune efectora. El agente potenciador de la respuesta inmune puede ser un polipéptido o un ácido nucleico, por ejemplo, un ácido nucleico que codifica un polipéptido que aumenta la respuesta inmune. Ejemplos de agentes expresados condicionalmente que mejoran la respuesta inmune incluyen, pero no se limitan a, un CAR adicional (denominado como CAR condicional); una molécula basada en el TCR (por ejemplo, un TCR-CAR); un inhibidor de un puesto de control inmunológico o una molécula inhibidora; y/o una citocina. En formas de realización, el CAR condicional se une a un antígeno asociado a cáncer diferente de aquel al que se dirige el CAR no condicional. En formas de realización, el inhibidor de un puesto de control inmune o molécula inhibidora descrita en este documento es un anticuerpo o fragmento de unión a antígeno del mismo, un ácido nucleico inhibitorio (por ejemplo, un siARN o shARN), o una molécula pequeña que inhibe o disminuye la actividad de un puesto de control inmunológico o molécula inhibidora seleccionado de PD1, PD-L1, CTLA4, TIM3, CEACAM (por ejemplo, CEACAM-1, CEACAM-3 y / o CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 o CD270), KIR, A2AR, CMH clase I, CMH clase II, GAL9, adenosina, o TGFR beta. En formas de realización, la citoquina comprende fragmentos funcionales o derivados de los mismos IL-2, IL-7, IL-15 o IL-21.

En formas de realización, la célula efectora inmune comprende un CAR no condicional y uno o más CARs condicionales, donde el CAR condicional se une a un antígeno de cáncer asociado diferente de la que se dirige el CAR no condicional. A modo de ejemplo, en una realización, una célula efectora inmune comprende un CAR no condicional que se une a CD19 y uno o más CARs condicionales que se unen a CD10, CD20, CD22, CD34, CD123, FLT-3, o ROR1, o una combinación de los mismos. En otra realización, una célula efectora inmune comprende un CAR no condicional que se une a CD10, CD20, CD22, CD34, CD123, FLT-3, o ROR1 y un CAR

condicional que se une a CD19.

La expresión condicional del agente que potencia la respuesta inmunitaria tras la activación de la célula efectora inmune que expresa CAR se logra uniendo operativamente una región de control de activación-condicional al agente que potencia la respuesta inmune (por ejemplo, a una secuencia de ácido nucleico que codifica tal agente). En una realización, la región de control condicional de activación comprende una secuencia promotora que inicia la expresión de, por ejemplo, la transcripción, de la respuesta inmune unida operativamente al agente potenciador de la activación de la célula inmune efectora. En una realización, la región de control de activación condicional comprende una o más secuencias reguladoras (por ejemplo, una secuencia o sitio de unión a factor de transcripción) que facilitan la iniciación de la expresión tras la activación de la célula efectora inmune. En formas de realización, la región de control de activación-condicional comprende una secuencia promotora y/o una o más secuencias de unión del factor de transcripción de un promotor o secuencia reguladora de un gen que se regula positivamente en uno o más de los siguientes: célula efectora inmune (por ejemplo, célula T) desarrollo de activación, la diferenciación de células T, la polarización de las células T, o células T colaboradoras. Ejemplos de tales genes incluyen, pero no se limitan a, NFAT (factor nuclear de células T activadas), ATF2 (factor activador de la transcripción 2), NFκB (factor nuclearκB), IL-2, receptor IL-2 (IL-2R), IL-3, GM-CSF, IL-4, IL-10 e IFN-γ.

En una realización, la región de control de activación-condicional comprende uno o más, por ejemplo, 1, 2, 3, 4, 5, 6, o más, secuencias de unión o sitios de NFAT. En formas de realización, la secuencia de unión NFATen el promotor comprende (5'-GGAAA-3 ') (SEQ ID NO: 1312), opcionalmente situado en una secuencia de consenso más larga de 5' (A / T)GGAAA(A / N)(A / T/C)N3' (SEQ ID NO: 1313). En formas de realización, la secuencia de unión a NFAT-es una secuencia kappa B similar a κB, tal como GGGACT (SEQ ID NO: 1314). (Véase, Gibson et al, The Journal of Immunology, 2007, 179:.. 3831 a 3840)

En una realización, la región de control de activación-condicional comprende además un promotor de IL-2 (o una IL-2 promotor mínimo), un promotor de IL-2R, un promotor ATF2, o un promotor NF-κB, o cualquier fragmento funcional o derivado de la misma. En una realización, la región de control de activación-condicional comprende una o más secuencias de unión de NFAT, por ejemplo, 3 o 6 secuencias de unión de NFAT y un promotor de IL-2, por ejemplo, un promotor

mínimo IL-2. En una realización, la región de control de activación-condicional comprende la secuencia de AGCTTGGATCCAAGAGGAAAATTTGTTTCATACAGAAGGCGTTAAGAGGAAAATTTGTTTCATACAGAAGGCGTTAAGAGGAAAATTTGTTTCATACAGAAGGCGTTCAAGCTTGTCGAC (SEQ ID NO: 1315).

Fuentes de células

Antes de la expansión y modificación genética, u otro tipo de modificación, se puede obtener una fuente de células, por ejemplo, células T o células asesinas naturales (NK), de un sujeto. Los ejemplos de sujetos incluyen humanos, monos, chimpancés, perros, gatos, ratones, ratas y especies transgénicas de los mismos. Las células T se pueden obtener de una variedad de fuentes, incluyendo células mononucleares de sangre periférica, médula ósea, tejido de ganglio linfático, sangre del cordón umbilical, tejido del timo, tejido de un sitio de infección, ascitis, derrame pleural, tejido esplénico y tumores.

En ciertos aspectos de la presente divulgación, las células efectoras inmunes, por ejemplo, las células T, se pueden obtener de una unidad de sangre extraída de un sujeto usando un número cualquiera de técnicas conocidas por los expertos en la técnica, tales como la separación Ficoll™. En un aspecto, células de la sangre circulante de un individuo se obtienen mediante aféresis. El producto de la aféresis usualmente contiene linfocitos, incluyendo células T, monocitos, granulocitos, células B, otros glóbulos blancos nucleados, glóbulos rojos y plaquetas. En un aspecto, las células obtenidas mediante aféresis pueden ser lavadas para eliminar la fracción de plasma y, opcionalmente, para colocar las células en un tampón o medio adecuado para posteriores etapas de procesamiento. En una modalidad, las células se lavan con tampón fosfato salino (PBS). En una modalidad alternativa, la solución de lavado carece de calcio y puede carecer de magnesio o puede carecer de muchos o todos los cationes divalentes.

Los pasos iniciales de activación en ausencia de calcio pueden producir una activación ampliada. Tal como un experto en la técnica puede observar fácilmente, un paso de lavado se puede llevar a cabo mediante métodos conocidos en la técnica, tales como usar una centrífuga de flujo continuo semi-automatizada (por ejemplo, procesador celular Cob 22291, Baxter CytoMate, o Haemonetics Cell Saver 5) de acuerdo con las instrucciones del fabricante. Después del lavado, las células pueden ser resuspendidas en una variedad de tampones biocompatibles,

tales como, por ejemplo, tampón fosfato salino (PBS) libre de Ca, libre de Mg, PlasmaLyte A u otra solución salina con o sin tampón. Alternativamente, se pueden retirar los componentes no deseados de la muestra de aféresis y las células se pueden resuspender directamente en medios de cultivo.

Se reconoce que los métodos de la solicitud pueden usar condiciones de medios de cultivo que comprenden 5 % o menos, por ejemplo 2 %, de suero AB humano, y emplean condiciones de medios de cultivo y composiciones conocidas, por ejemplo, aquellas descritas en Smith et al., "Ex vivo expansion of human T cells for adoptive immunotherapy using the novel Xeno-free CTS Immune Cell Serum Replacement" Clinical & Translational Immunology (2015) 4, e31; doi: 10.1038/cti.2014.31.

En un aspecto, las células T se aíslan de linfocitos de sangre periférica mediante lisis de glóbulos rojos y agotando los monocitos, por ejemplo, mediante centrifugación a través de un gradiente de PERCOLL o mediante elutriación centrífuga a contracorriente.

Los métodos descritos en el presente documento incluyen, por ejemplo, la selección de una subpoblación específica de células efectoras inmunes, por ejemplo, células T, que son una población con depleción de células T reguladoras, con depleción de células CD25+, usando, por ejemplo, una técnica de selección negativa, por ejemplo, tal como se describe en el presente documento. En algunas modalidades, la población con depleción de células T reguladoras contiene menos de 30 %, 25 %, 20 %, 15 %, 10 %, 5 %, 4 %, 3 %, 2 %, 1 % de células CD25+.

En una modalidad, las células T reguladoras, por ejemplo, las células T CD25+, se eliminan de la población que usa un anticuerpo anti-C25, o un fragmento del mismo, o un ligando de unión a CD25, IL-2. En una modalidad, el anticuerpo anti-CD25, o fragmento del mismo, o el ligando de unión a CD25, se conjuga con un sustrato, por ejemplo, una esfera, o se recubre de otra manera en un sustrato, por ejemplo, una esfera. En una modalidad, el anticuerpo anti-CD25, o fragmento del mismo, está conjugado a un sustrato tal como se describe en el presente documento.

En una modalidad, las células T reguladoras, por ejemplo, células T CD25+, se eliminan de la población usando un reactivo de agotamiento de CD25 de Miltenyi™. En una modalidad, la relación de células a reactivo de agotamiento de CD25 es de 1e7 células a 20 uL, o de 1e7 células a 15 uL, o de 1e7 células a 10 uL, o de 1e7 células a 5 uL, o de 1e7 células a 2,5 uL, o de

1e7 células a 1,25 ul. En una modalidad, por ejemplo, para células T reguladoras, por ejemplo, se usa el agotamiento de CD25+, mayor a 500 millones de células / ml. En un aspecto adicional, se usa una concentración de 600, 700, 800, o 900 millones de células/ml.

En una modalidad, la población de células efectoras inmunes que será agotada o reducida incluye aproximadamente 6 x 10^9 células T CD25+. En otros aspectos, la población de células efectoras inmunes que será agotada o reducida incluye aproximadamente entre 1 x 10^9 y 1x 10^{10} células T CD25+, y cualquier valor entero en este rango. En una modalidad, la población de células T reguladoras agotadas resultante tiene 2 x 10^9 células T reguladoras, por ejemplo, células CD25+, o menos (por ejemplo, 1 x 10^9, 5 x 10^8, 1 x 10^8, 5 x 10^7, 1 x 10^7, o menos células CD25+).

En una modalidad, las células T reguladoras, por ejemplo, células CD25 +, se eliminan de la población usando el sistema CliniMAC con un conjunto de tubos de agotamiento, tal como, por ejemplo, tubos 162-01. En una modalidad, el sistema CliniMAC se usa bajo condiciones de depleción, por ejemplo, DEPLETION2.1.

Sin desear estar vinculado por una teoría particular, reduciendo el nivel de los reguladores negativos de las células inmunes (por ejemplo, la disminución del número de células inmunes no deseadas, por ejemplo, las células Treg), en un sujeto antes de la aféresis o durante la fabricación de un producto de células que expresan CAR se reduce significativamente el riesgo de recaída en el sujeto. Por ejemplo, se conocen en la técnica métodos de agotar las células Treg. Los métodos de la disminución de las células Treg incluyen, pero no se limitan a, ciclofosfamida, anticuerpo anti-GITR (un anticuerpo anti-GITR que se describe en este documento), agotamiento CD25, inhibidor de mTOR, y combinaciones de los mismos.

En algunas modalidades, los métodos de fabricación comprenden la reducción del número (por ejemplo, agotamiento) de células T_{REG} antes de la fabricación de la célula que expresa CAR. Por ejemplo, los métodos de fabricación comprenden poner en contacto la muestra, por ejemplo, la muestra de aféresis, con un anticuerpo anti-GITR y/o un anticuerpo anti-CD25 (o un fragmento del mismo, o un ligando de unión a CD25), por ejemplo, para agotar o reducir las células T_{REG} antes de la fabricación del producto de células que expresan CAR (por ejemplo, células T, células NK).

Sin desear estar vinculado por una teoría particular, reducir el nivel de los reguladores negativos de las células inmunes (por ejemplo, la disminución del número de células inmunes no deseadas, por ejemplo, las células Treg), en un sujeto antes de la aféresis o durante la fabricación de un producto de células que expresan CAR puede reducir el riesgo de una recaída T_{REG}. En una realización, un sujeto es pre-tratado con una o más terapias que reducen las células Treg antes de la recogida de las células para la fabricación de productos de células que expresan CAR, reduciendo así el riesgo de recaída sujeto al tratamiento con células que expresan CAR. En una realización, los métodos de la disminución de las células Treg incluyen, pero no se limitan a, la administración al sujeto de uno o más de ciclofosfamida, anticuerpo anti-GITR, agotamiento CD25, o una combinación de los mismos. En una realización, los métodos de la disminución de las células Treg incluyen, pero no se limitan a, la administración al sujeto de uno o más de ciclofosfamida, anti-anticuerpo GITR, agotamiento CD25, inhibidor de mTOR, o una combinación de los mismos. La administración de uno o más de ciclofosfamida, anticuerpo anti-GITR, agotamiento CD25, o una combinación de los mismos, pueden ocurrir antes, durante o después de una infusión del producto de células que expresan CAR. La administración de uno o más de ciclofosfamida, anticuerpo anti-GITR, agotamiento CD25-, inhibidor de mTOR, o una combinación de los mismos, puede ocurrir antes, durante o después de una infusión del producto de células que expresan CAR.

En algunas modalidades, los métodos de fabricación comprenden la reducción del número (por ejemplo, el agotamiento) de células T_{REG} antes de la fabricación de la célula que expresa CAR. Por ejemplo, los métodos de fabricación comprenden poner en contacto la muestra, por ejemplo, la muestra de aféresis, con un anticuerpo anti-GITR y/o un anticuerpo anti-CD25 (o un fragmento del mismo, o un ligando de unión a CD25), por ejemplo, para agotar o reducir las células T_{REG} antes de la fabricación del producto de células que expresan CAR (por ejemplo, células T, células NK).

En una modalidad, un sujeto recibe tratamiento previo con una o más terapias que reducen las células T_{REG} antes de recolectar las células para la fabricación del producto de células que expresan CAR, reduciendo así el riesgo de recaída del sujeto frente al tratamiento con células que expresan CAR. En una modalidad, los métodos para reducir las células T_{REG} incluyen, de manera enunciativa más no limitativa, la administración al sujeto de una o más de ciclofosfamida, anticuerpo anti-GITR, reducción de CD25, o una combinación de los mismos.

La administración de una o más de ciclofosfamida, anticuerpo anti-GITR, reducción de CD25, o una combinación de los mismos, puede ocurrir antes, durante o después de una infusión del producto de células que expresan CAR.

En una modalidad, un sujeto recibe tratamiento previo con ciclofosfamida antes de recolectar las células para la fabricación del producto de células que expresan CAR, reduciendo así el riesgo de recaída del sujeto frente al tratamiento con células que expresan CAR. En una modalidad, un sujeto recibe tratamiento previo con un anticuerpo anti-GITR antes de recolectar las células para la fabricación del producto de células que expresan CAR, reduciendo así el riesgo de recaída del sujeto frente al tratamiento con células que expresan CAR.

En una modalidad, la población de células a ser eliminado no está compuesta por células T reguladoras ni células tumorales, sino por células que afectan negativamente de otra manera la expansión y/o función de las células TCAR, por ejemplo, células que expresan CD14, CD11b, CD33, CD15 u otros marcadores expresados por células supresoras potencialmente inmunitarias. En una modalidad, se pretende la eliminación de estas células simultáneamente con células T reguladoras y/o células tumorales, o después de dicha reducción o agotamiento, o en otro orden.

Los métodos descritos en el presente documento pueden incluir más de un paso de selección, por ejemplo, más de un paso de agotamiento o reducción. El enriquecimiento de una población de células T mediante selección negativa se puede lograr, por ejemplo, mediante una combinación de anticuerpos dirigidos a marcadores de superficie únicos para las células seleccionadas negativamente. Un método es la clasificación y/o selección de células a través de inmunoadherencia magnética negativa o citometría de flujo, que usa un cóctel de anticuerpos monoclonales dirigidos a marcadores de superficie celular presentes en las células seleccionadas negativamente. Por ejemplo, para incrementar células CD4+ por selección negativa, un cóctel de anticuerpos monoclonales puede incluir anticuerpos para CD14, CD20, CD11b, CD16, HLA-DR y CD8.

Los métodos descritos en el presente documento pueden incluir además la eliminación de células de la población que expresan un antígeno tumoral, por ejemplo, un antígeno tumoral que no comprende CD25, por ejemplo, CD19, CD30, CD38, CD123, CD20, CD14 o CD11b, para proporcionar así una población con depleción de células T reguladoras, por ejemplo, con depleción de células CD25+, y células con depleción de antígeno tumoral que son adecuadas para la expresión de un CAR, por ejemplo, un CAR descrito en el presente documento. En una

modalidad, las células que expresan antígeno tumoral se eliminan simultáneamente con las células T reguladoras, por ejemplo, células CD25+. Por ejemplo, un anticuerpo anti-C25, o un fragmento del mismo, y un anticuerpo de antígeno anti-tumoral, o fragmento del mismo, se pueden unir al mismo sustrato, por ejemplo, esfera, que se puede usar para eliminar las células; o un anticuerpo anti-CD25, o fragmento del mismo, o el anticuerpo de antígeno anti-tumoral, o fragmento del mismo, se puede unir a esferas diferentes, usando una mezcla de estas para eliminar las células. En otras modalidades, la eliminación de células T reguladoras, por ejemplo, células CD25+, y la eliminación de las células que expresan antígeno tumoral es secuencial, y puede ocurrir, por ejemplo, en cualquier orden.

El presente documento también proporciona procedimientos que incluyen la eliminación de células de la población que expresan un inhibidor de punto de control, por ejemplo, un inhibidor de punto de control descrito en el presente documento, por ejemplo, una o más de células PD1+, células LAG3+ y células TIM3+, para proporcionar de este modo una población con depleción de células T reguladoras, por ejemplo, con depleción de células CD25+, y células con depleción de inhibidor de punto de control, por ejemplo, células con depleción de PD1+, LAG3+ y/o TIM3+. Ejemplos de inhibidores de puntos de control ejemplares incluyen PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (por ejemplo., CEACAM-1, CEACAM-3 y/o CEACAM-5), LAG3, VISTA, BTLA, TIGIT, CTLA-4, BTLA y LAIR1.LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 o CD270), KIR, A2aR, CMH clase I, CMH clase II, GAL9, adenosina, y TGFR (e.g., TGFRbeta), por ejemplo, como se describen en el presente documento. En una modalidad, el inhibidor de punto de control de las células que expresan se elimina simultáneamente con las células T reguladoras, por ejemplo, células CD25+. Por ejemplo, un anticuerpo anti-C25, o un fragmento del mismo, y un anticuerpo de inhibidor anti-punto de control, o fragmento del mismo, se pueden unir a la misma esfera, que se puede usar para eliminar las células; o un anticuerpo anti-CD25, o fragmento del mismo, o anticuerpo de inhibidor anti-punto de control, o fragmento del mismo, se puede unir a esferas diferentes, usando una mezcla de estas para eliminar las células. En otras modalidades, la eliminación de células T reguladoras, por ejemplo, células CD25+, y la eliminación de las células que expresan el inhibidor de puto de control es secuencial, y puede ocurrir, por ejemplo, en cualquier orden.

Métodos descritos en el presente documento pueden incluir un paso de selección

positiva, por ejemplo, se pueden aislar células T mediante incubación con esferas conjugadas anti-CD3/anti-CD28 (por ejemplo, 3x28), tales como DYNABEADS® M-450 CD3/CD28 T, durante un período de tiempo suficiente para la selección positiva de las células T deseadas. En un aspecto, el período de tiempo es de aproximadamente 30 minutos. En un aspecto adicional, el período de tiempo varía entre 30 minutos y 36 horas o más, y todos los valores enteros comprendidos en este rango. En un aspecto adicional, el período de tiempo es de al menos 1, 2, 3, 4, 5 o 6 horas. En aún otro aspecto, el período de tiempo es entre 10 y 24 horas. En un aspecto, el período de incubación es de 24 horas. Períodos de incubación más largos pueden ser usados para aislar células T en cualquier situación donde hay pocas células T en comparación con otros tipos de células, tales como el aislamiento de linfocitos infiltrantes de tumor (TIL) a partir de tejido tumoral o de individuos inmunocomprometidos. Además, el uso de períodos de incubación más largos puede aumentar la eficiencia de la captura de las células T CD8+. Así, simplemente acortando o alargando el período de tiempo en el que se permite a las células T unirse a las esferas CD3/CD28 y/o aumentando o disminuyendo la relación de esferas a células T (como se describe en detalle en el presente documento), subpoblaciones de células T se pueden seleccionar preferentemente a favor o en contra al inicio del cultivo o en otros momentos durante el proceso. Además, aumentando o disminuyendo la relación de anticuerpos anti-CD3 y/o anti-CD28 en las esferas u otra superficie, subpoblaciones de células T se pueden seleccionar preferentemente a favor o en contra al inicio del cultivo o en otros momentos deseados.

En una modalidad, una población de células T se puede seleccionar que expresa una o más de IFN-γ, TNFa, IL-17A, IL-2, IL-3, IL-4, GM-CSF, IL-10, IL-13, granzima B y perforina, u otras moléculas apropiadas, por ejemplo, otras citoquinas. Se pueden determinar métodos para detectar la expresión celular, por ejemplo, mediante los métodos descritos en la Publicación PCT No.: WO 2013/126712.

Para el aislamiento de una población deseada de células mediante selección positiva o negativa, se pueden variar la concentración de células y la superficie (por ejemplo, partículas tales como esferas). En ciertos aspectos, puede ser deseable disminuir significativamente el volumen al que se mezclan las esferas y las células (es decir, aumentar la concentración de células), para asegurar el contacto máximo de las células y las esferas. Por ejemplo, en un aspecto, se usa una concentración de aproximadamente 10 mil millones de células/ml, 9 mil millones de células/ml, 8 mil millones de células/ml, 7 mil millones de células/ml, 6 mil

millones de células/ml o 5 mil millones de células/ml. Por ejemplo, en un aspecto, se usa una concentración de 1 mil millones de células/ml. En un aspecto, se usa una concentración de células de 75, 80, 85, 90, 95 o 100 millones de células/ml. En aspectos adicionales, se puede usar concentraciones de 125 o 150 millones de células/ml.

El uso de altas concentraciones puede resultar en mayor rendimiento celular, activación de células y expansión celular. Además, el uso de altas concentraciones de células permite la captura más eficiente de células que pueden expresar débilmente los antígenos blanco de interés, tales como células T negativas para CD28, o de muestras donde hay presencia de muchas células tumorales (por ejemplo, sangre leucémica, tejido tumoral, etc.). Estas poblaciones celulares pueden tener valor terapéutico y sería deseable obtenerlas. Por ejemplo, usar una concentración alta de células permite una selección más eficaz de células T CD8+ que normalmente tienen una expresión de CD28 más débil.

En un aspecto relacionado, puede ser deseable usar concentraciones más bajas de células. Al diluir significativamente la mezcla de células T y superficie (por ejemplo, partículas tales como esperas), las interacciones entre las partículas y las células se reducen al mínimo. Esto selecciona las células que expresan altas cantidades de los antígenos deseados para unión a las partículas. Por ejemplo, las células T CD4+ expresan altos niveles de CD28 y son capturadas de manera más eficiente que las células T CD8+ en concentraciones diluidas. En un aspecto, la concentración de células usada es 5 x 10^6/ml. En otros aspectos, la concentración usada puede ser entre aproximadamente 1 x 10^5/ml y 1 x 10^6/ml, y cualquier número entero entre este rango de valores.

En otros aspectos, las células pueden incubarse en un rotador durante distintos períodos de tiempo a distintas velocidades o bien a 2-10ºC o a temperatura ambiente.

Las células T para la estimulación también se pueden congelar después de un paso de lavado. Al margen de las limitaciones que impone la teoría, la congelación y el posterior paso de descongelación ofrecen un producto más uniforme al eliminar los granulocitos y, hasta cierto punto, los monocitos en la población de células. Después del paso de lavado, que elimina el plasma y las plaquetas, las células se pueden suspender en una solución de congelación. Aunque muchas soluciones y parámetros de congelación son conocidos en la técnica y serán útiles en este contexto, un método implica el uso de PBS que contiene DMSO al 20 % y albúmina de suero humano al 8 %, o medios de cultivo que contienen dextrano 40 al 10 % y dextrosa al 5 %,

albúmina de suero humano al 20 % y DMSO al 7,5 %, o PlasmaLyte-A al 31,25 %, dextrosa al 5 %, NaCl al 0,45 %, dextrano 40 al 10 % y dextrosa al 5 %, albúmina de suero humano al 20% y DMSO al 7,5 % u otros medios de de congelación celular que contengan, por ejemplo, Hespan y PlasmaLyte A; a continuación, las células se congelan a -80°C a una velocidad de 1° por minuto y se almacenan en la fase de vapor de un tanque de almacenamiento de nitrógeno líquido. Se pueden usar otros métodos de congelación controlada, así como congelación no controlada inmediatamente a -20°C o en nitrógeno líquido.

En ciertos aspectos, las células criopreservadas se descongelan y se lavan tal como se describe en el presente documento y se dejan en reposo durante una hora a temperatura ambiente antes de la activación usando los métodos de la presente invención.

También se contempla en el contexto de la invención la recolección de muestras de sangre o producto de la aféresis de un sujeto en un período de tiempo antes del momento en el que las células expandidas que se describen en el presente documento sean necesarias. Como tal, la fuente de las células que serán expandidas puede ser recolectada en cualquier momento en que sea necesario, y las células deseadas, tales como células T, se pueden aislar y congelar para su uso posterior en la terapia con células efectoras inmunes para cualquier cantidad de enfermedades o condiciones que se puedan beneficiar de la terapia con células efectoras inmunes, tales como las descritas en el presente documento. En un aspecto, una muestra de sangre o una aféresis se toma de un sujeto generalmente sano. En ciertos aspectos, una muestra de sangre o una aféresis se toma de un sujeto generalmente sano que está en riesgo de desarrollar una enfermedad, pero que aún no ha desarrollado la enfermedad, y se congelan las células de interés para su uso posterior. En ciertos aspectos, las células T pueden ser expandidas, congeladas y usadas en un momento posterior. En ciertos aspectos, las muestras se recogen de un paciente poco después del diagnóstico de una enfermedad determinada, tal como se describe en el presente documento, pero antes de cualquier tratamiento. En un aspecto adicional, las células se aíslan de una muestra de sangre o una aféresis de un sujeto antes de cualquier número de modalidades de tratamiento relevantes, que incluyen, de manera enunciativa mas no limitativa, tratamiento con agentes como natalizumab, efalizumab, agentes antivirales, quimioterapia, radiación, agentes inmunosupresores tales como ciclosporina, azatioprina, metotrexato, micofenolato y FK506, anticuerpos, u otros agentes inmunoablativos tales como CAMPATH, anticuerpos anti-CD3, cytoxan, fludarabina, ciclosporina, FK506, rapamicina,

ácido micofenólico, esteroides, FR901228 y radiación.

En un aspecto adicional de la presente invención, las células T se obtienen de un paciente directamente tras el tratamiento que deja al sujeto con células T funcionales. En este sentido, se ha observado que después de ciertos tratamientos de cáncer, en particular los tratamientos con fármacos que afectan el sistema inmunitario, poco después del tratamiento, durante el período en el que los pacientes normalmente se recuperan del tratamiento, la calidad de las células T obtenidas puede ser óptima o mejorada por su capacidad para expandirse ex vivo. Del mismo modo, tras la manipulación ex vivo, usando los métodos descritos en el presente documento, estas células pueden estar en un estado preferido para injerto y expansión in vivo mejorados. Por lo tanto, en el contexto de la presente invención se contempla recolectar células sanguíneas, incluyendo células T, células dendríticas u otras células de linaje hematopoyético, durante esta fase de recuperación. Además, en ciertos aspectos, se pueden usar regímenes de movilización (por ejemplo, movilización con GM-CSF) y de acondicionamiento para crear una condición en un sujeto en el que la repoblación, la recirculación, la regeneración y/o la expansión de tipos particulares de células se favorece, especialmente durante un período definido después de la terapia. Ejemplos de tipos de células incluyen células T, células B, células dendríticas y otras células del sistema inmune.

En una modalidad, las células efectoras inmunes que expresan una molécula de CAR, por ejemplo, una molécula de CAR descrita en el presente documento, se obtienen de un sujeto que recibió una dosis potenciadora inmune baja de un inhibidor de mTOR. En una modalidad, la población de células efectoras inmunes, por ejemplo, células T, que serán modificadas para expresar CAR, se cultivan durante un tiempo suficiente, o después de recibir una dosis potenciadora inmune baja suficiente de un inhibidor de mTOR, tal que el nivel de células efectoras inmunes PD1 negativas, por ejemplo, células T, o la relación de células efectoras inmunes PD1 negativas, por ejemplo, células T/células efectoras inmunes PD1 positivas, por ejemplo, células T, en el sujeto o recolectadas del sujeto, se ha aumentado, al menos transitoriamente.

En otras modalidades, la población de células efectoras inmunes, por ejemplo, células T, que han sido modificadas o serán modificadas para expresar CAR, pueden ser tratadas ex vivo por contacto con una cantidad de un inhibidor de mTOR que aumenta el número de células efectoras inmunes PD1 negativas, por ejemplo, células T, o aumenta la relación de células

efectoras inmunes PD1 negativas, por ejemplo, células T/células efectoras inmunes PD1 positivas, por ejemplo, células T.

En una modalidad, una población de células T es deficiente de diacilglicerol quinasa (DGK). Las células deficientes de DGK incluyen células que no expresan proteína o ARN de DGK, o que han reducido o inhibido la actividad de DGK. Las células deficientes de DGK pueden ser generadas mediante métodos genéticos, por ejemplo, la administración de agentes de ARN interferente, por ejemplo, ARNsi, ARNsh, ARNmi, para reducir o evitar la expresión de DGK. Alternativamente, las células deficientes de DGK se pueden generar mediante tratamiento con inhibidores de DGK descritos en el presente documento.

En una modalidad, una población de células T deficiente de Ikaros. Las células deficientes de Ikaros incluyen células que no expresan proteína o ARN de Ikaros, o que han reducido o inhibido la actividad de Ikaros. Las células deficientes de Ikaros pueden ser generadas mediante métodos genéticos, por ejemplo, la administración de agentes de ARN interferente, por ejemplo, ARNsi, ARNsh, ARNmi, para reducir o prevenir la expresión Ikaros. Alternativamente, las células deficientes de Ikaros se pueden generar mediante tratamiento con inhibidores de Ikaros, por ejemplo, lenalidomida.

En algunas modalidades, una población de células T es deficiente de DGK y deficiente de Ikaros, por ejemplo, no expresa DGK y Ikaros, o ha reducido o inhibido la actividad de DGK y Ikaros. Dichas células deficientes de Ikaros y DGK pueden ser generadas mediante cualquiera de los métodos descritos en el presente documento.

En una modalidad, las células NK se obtienen del sujeto. En otra modalidad, las células NK son una línea celular NK, por ejemplo, línea celular NK-92 (Conkwest).

CAR alogénico

En algunas modalidades descritas en el presente documento, la célula efectora inmune puede ser una célula efectora inmune alogénica, por ejemplo, una célula T o una célula NK. Por ejemplo, la célula puede ser una célula T alogénica, por ejemplo, una célula T alogénica que carece de expresión de un receptor de células T (TCR) funcional y/o un antígeno leucocitario humano (HLA), por ejemplo, HLA clase I y/o HLA clase II.

Una célula T que carece de un TCR funcional puede ser, por ejemplo, modificada de tal

manera que no exprese ningún TCR funcional en su superficie, modificada de tal manera que no exprese una o más subunidades que comprenden un TCR funcional (por ejemplo, modificada de manera que no expresa (o muestra una expresión reducida) de TCR alfa, TCR beta, TCR gamma, TCR delta, TCR épsilon y/o TCR zeta) o modificada de tal manera que produzca muy pocos TCR funcionales en su superficie (por ejemplo, modificada de tal manera que no exprese (o que exhiba expresión reducida) de TCR alfa, TCR beta, TCR gama, TCR gamma, TCR épsilon y/o TCR zeta). Alternativamente, la célula T puede expresar un TCR sustancialmente deteriorado, por ejemplo, mediante la expresión de formas mutadas o truncadas de una o más de las subunidades del TCR. El término "TCR sustancialmente deteriorado" significa que este TCR no provocará una reacción inmune adversa en un huésped.

Una célula T descrita en el presente documento puede ser, por ejemplo, modificada de tal manera que no exprese un HLA funcional en su superficie. Por ejemplo, una célula T descrita en el presente documento puede ser modificada de tal manera que el HLA de expresión en superficie celular, por ejemplo, un HLA clase I y/o HLA clase II, es regulado a la baja. En algunas modalidades, la regulación a la baja de HLA se puede lograr mediante la reducción o eliminación de la expresión de beta-2 microglobulina (B2M).

En algunas modalidades, la célula T puede carecer de un TCR funcional y un HLA funcional, por ejemplo, HLA clase I y/o HLA clase II.

Las células T modificadas que carecen de expresión de un TCR y/o HLA funcional se pueden obtener a través de cualquier medio adecuado, incluyendo un bloqueo o inactivación de una o más subunidades de TCR o HLA. Por ejemplo, la célula T puede incluir una inactivación de TCR y/o HLA usando ARNsi, ARNsh, una repetición palindrómica corta agrupada y regularmente interespaciada (CRISPR), una nucleasa efectora de tipo activador de transcripción (TALEN) o una endonucleasa de dedo de zinc (ZFN).

En algunas modalidades, la célula alogénica puede ser una célula que no expresa una molécula inhibidora o la expresa a niveles bajos, por ejemplo, una célula modificada mediante cualquier método descrito en el presente documento. Por ejemplo, la célula puede ser una célula que no expresa una molécula inhibidora o la expresa a niveles bajos, por ejemplo, que puede disminuir la capacidad de una célula que expresa un CAR para montar una respuesta efectora inmune. Ejemplos de moléculas inhibidoras incluyen PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (por ejemplo, CEACAM-1, CEACAM-3 y/o CEACAM-5), LAG3, VISTA, BTLA,

TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), CMH de clase B7-H4 (VTCN1), Hvem (TNFRSF14 o CD270), KIR, A2AR, CMH de clase I, II, GAL9, adenosina y TGFR (Por ejemplo, TGFR beta). La inhibición de una molécula inhibidora, por ejemplo, mediante inhibición a nivel del ADN, ARN o proteína, puede optimizar el desempeño de una célula que expresa CAR. En alguna repetición palindrómica corta agrupada y regularmente interespaciada (CRISPR), una nucleasa efectora de tipo activador de transcripción (TALEN) un repetido corto palindrómico aglomerado regularmente interespaciado (CRISPR), una nucleasa efectora de tipo activador de transcripción (TALEN) o una endonucleasa de dedo de zinc (ZFN), por ejemplo, tal como se describe en el presente documento.

ARNsi y ARNsh para inhibir TCR o HLA

En algunas modalidades, la expresión de TCR y/o la expresión de HLA se puede inhibir usando ARNsi o ARNsh que se dirige a un ácido nucleico que codifica un TCR y/o HLA, y/o una molécula inhibidora descrita en el presente documento (por ejemplo, PD1, PD-L1, PD- L2, CTLA4, TIM3, CEACAM (por ejemplo, CEACAM-1, CEACAM-3 y/o CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 o CD270), KIR, A2AR, CMH clase I, CMH clase II, GAL9, adenosina, y TGFR beta), en una célula T.

Los sistemas de expresión de ARNsi y ARNsh y los ANshs ejemplaresse describen en, por ejemplo, los párrafos 649 y 650 de la Solicitud Internacional WO2015/142675, presentada el 13 de marzo de 2015, la cual se incorpora en la presente en su totalidad como referencia.

CRISPR para inhibir TCR o HLA

"CRISPR" o "CRISPR para TCR y/o HLA" o "CRISPR para inhibir TCR y/o HLA", tal como se usa en el presente documento, se refiere a un conjunto de repeticiones palindrómicas cortas agrupadas y regularmente interespaciadas o a un sistema que comprende un conjunto de dichas repeticiones. "Cas", tal como se usa en el presente documento, se refiere a una proteína asociada a CRISPR. Un sistema de "CRISPR/Cas" se refiere a un sistema derivado de CRISPR y Cas puede ser usado para silenciar o mutar un gen TCR y/o HLA, y/o una molécula inhibidora

descrita en el presente documento (por ejemplo, PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (por ejemplo, CEACAM-1, CEACAM-3 y/o CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 o CD270), KIR, A2aR, CMH clase I, CMH clase II, GAL9, adenosina y TGFR beta).

Los sistemas CRISPR/Cas, y usos de los mismos, se describen, por ejemplo en los párrafos 651-658 de la solicitud internacional WO2015/142675, presentada el 13 de marzo de 2015, la cual se incorpora en la presente en su totalidad como referencia.

TALEN para inhibir TCR y/o HLA

"TALEN" o "TALEN para HLA y/o TCR" o "TALEN para inhibir HLA y/o TCR" se refiere a una nucleasa efectora de tipo activador de transcripción, una nucleasa artificial que se puede usar para editar el gen HLA y/o TCR, y/o una molécula inhibidora de la descrita en el presente documento (por ejemplo, PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (por ejemplo, CEACAM-1, CEACAM-3 y/o CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 o CD270), KIR, A2aR, CMH clase I, CMH clase II, GAL9, adenosina y TGFR beta).

Los TALEs y usos de los mismos, se describen, por ejemplo en los párrafos 659-665 de la solicitud internacional WO2015/142675, presentada el 13 de marzo de 2015, la cual se incorpora en la presente en su totalidad como referencia.

Nucleasa de dedo de zinc para inhibir HLA y/o TCR

"ZFN" o "nucleasa de dedo de zinc" o "ZFN para HLA y/o TCR" o "ZFN para inhibir HLA y/o TCR" se refiere a una nucleasa de dedo de zinc, una nucleasa artificial que puede ser usada para editar el gen HLA y/o TCR, y/o una molécula inhibidora de la descrita en este documento (por ejemplo, PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (por ejemplo, CEACAM-1, CEACAM-3 y/o CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 o CD270), KIR, A2aR, CMH clase I, CMH clase II, GAL9, adenosina y TGFR beta).

Los ZFNs y usos de los mismos, se describen, por ejemplo en los párrafos 666-671 de la

solicitud internacional WO2015/142675, presentada el 13 de marzo de 2015, la cual se incorpora en la presente en su totalidad como referencia.

Expresión de la telomerasa

Al margen de las limitaciones que imponen teorías particulares, en algunas modalidades, una célula T terapéutica tiene persistencia a corto plazo en un paciente debido a los telómeros acortados en la célula T; en consecuencia, la transfección con un gen de la telomerasa puede alargar los telómeros de la célula T y mejorar la persistencia de la célula T en el paciente. Véase Carl June, "Adoptive T cell therapy for cancer in the clinic", Journal of Clinical Investigation, 117: 1466-1476 (2007). Por lo tanto, en una modalidad, una célula efectora inmune, por ejemplo, una célula T, expresa de manera ectópica una subunidad de la telomerasa, por ejemplo, la subunidad catalítica de la telomerasa, por ejemplo, terc, por ejemplo, hTERT. En algunos aspectos, esta divulgación proporciona un método para producir una célula que expresa CAR, el cual comprende poner en contacto una célula con un ácido nucleico que codifica una subunidad de la telomerasa, por ejemplo, la subunidad catalítica de la telomerasa, por ejemplo, terc, por ejemplo, hTERT. La célula puede ponerse en contacto con el ácido nucleico antes de, simultáneamente con o después de ser puesta en contacto con un constructo que codifica un CAR.

En un aspecto, la divulgación presenta un método de fabricación de una población de células efectoras inmunes (por ejemplo, células T o células NK). En una modalidad, el método comprende: proporcionar una población de células efectoras inmunes (por ejemplo, células T o células NK), poner en contacto la población de células efectoras inmunes con un ácido nucleico que codifica un CAR; y poner en contacto la población de células efectoras inmunes con un ácido nucleico que codifica una subunidad de la telomerasa, por ejemplo, hTERT, en condiciones que permitan la expresión de la telomerasa y el CAR.

En una modalidad, el ácido nucleico que codifica la subunidad de telomerasa es ADN. En una modalidad, el ácido nucleico que codifica la subunidad de la telomerasa comprende un promotor capaz de dirigir la expresión de la subunidad de la telomerasa.

En una modalidad, hTERT tiene la secuencia de aminoácidos de GenBank ID de Proteína AAC51724.1 (Meyerson et al., "hEST2, the Putative Human Telomerase Catalytic Subunit Gene, Is Up-Regulated in Tumor Cells and during Immortalization" Cell Volume 90,

Edición 4, 22 agosto 1997, páginas 785–795) así:

MPRAPRCRAVRSLLRSHYREVLPLATFVRRLGPQGWRLVQRGDPAAFRALVAQ
CLVCVPWDARPPPAAPSFRQVSCLKELVARVLQRLCERGAKNVLAFGFALLDGARGGP
PEAFTTSVRSYLPNTVTDALRGSGAWGLLLRRVGDDVLVHLLARCALFVLVAPSCAYQ
VCGPPLYQLGAATQARPPPHASGPRRRLGCERAWNHSVREAGVPLGLPAPGARRRGGS
ASRSLPLPKRPRRGAAPEPERTPVGQGSWAHPGRTRGPSDRGFCVVSPARPAEEATSLE
GALSGTRHSHPSVGRQHHAGPPSTSRPPRPWDTPCPPVYAETKHFLYSSGDKEQLRPSFL
LSSLRPSLTGARRLVETIFLGSRPWMPGTPRRLPRLPQRYWQMRPLFLELLGNHAQCPY
GVLLKTHCPLRAAVTPAAGVCAREKPQGSVAAPEEEDTDPRRLVQLLRQHSSPWQVYG
FVRACLRRLVPPGLWGSRHNERRFLRNTKKFISLGKHAKLSLQELTWKMSVRGCAWLR
RSPGVGCVPAAEHRLREEILAKFLHWLMSVYVVELLRSFFYVTETTFQKNRLFFYRKSV
WSKLQSIGIRQHLKRVQLRELSEAEVRQHREARPALLTSRLRFIPKPDGLRPIVNMDYVV
GARTFRREKRAERLTSRVKALFSVLNYERARRPGLLGASVLGLDDIHRAWRTFVLRVR
AQDPPPELYFVKVDVTGAYDTIPQDRLTEVIASIIKPQNTYCVRRYAVVQKAAHGHVRK
AFKSHVSTLTDLQPYMRQFVAHLQETSPLRDAVVIEQSSSLNEASSGLFDVFLRFMCHH
AVRIRGKSYVQCQGIPQGSILSTLLCSLCYGDMENKLFAGIRRDGLLLRLVDDFLLVTPH
LTHAKTFLRTLVRGVPEYGCVVNLRKTVVNFPVEDEALGGTAFVQMPAHGLFPWCGL
LLDTRTLEVQSDYSSYARTSIRASLTFNRGFKAGRNMRRKLFGVLRLKCHSLFLDLQVN
SLQTVCTNIYKILLLQAYRFHACVLQLPFHQQVWKNPTFFLRVISDTASLCYSILKAKNA
GMSLGAKGAAGPLPSEAVQWLCHQAFLLKLTRHRVTYVPLLGSLRTAQTQLSRKLPGT
TLTALEAAANPALPSDFKTILD (SEQ ID NO.: 1332)

En una modalidad, hTERT tiene una secuencia al menos 80 %, 85 %, 90 %, 95 %, 96 %, 97 %, 98 % o 99 % idéntica a la secuencia de SEQ ID NO.: 1332. En una modalidad, hTERT tiene una secuencia de SEQ ID NO.: 1332. En una modalidad, hTERT comprende una deleción (por ejemplo, de no más de 5, 10, 15, 20 o 30 aminoácidos) en el extremo N-terminal, el extremo C-terminal, o ambos. En una modalidad, hTERT comprende una secuencia de aminoácidos transgénica (por ejemplo, de no más de 5, 10, 15, 20 o 30 aminoácidos) en el extremo N-terminal, el extremo C-terminal, o ambos.

En una realización, hTERT está codificada por la secuencia de ácido nucleico con No. de Acceso GenBank AF018167 (Meyerson et al., “hEST2, the Putative Human Telomerase Catalytic Subunit Gene, Is Up-Regulated in Tumor Cells and during Immortalization”Cell

Volumen 90, Edición 4, 22 de agosto 1997, páginas 785–795):

1 caggcagcgt ggtcctgctg cgcacgtggg aagccctggc cccggccacc cccgcgatgc

61 cgcgcgctcc ccgctgccga gccgtgcgct ccctgctgcg cagccactac cgcgaggtgc

121 tgccgctggc cacgttcgtg cggcgcctgg ggccccaggg ctggcggctg gtgcagcgcg

181 gggacccggc ggctttccgc gcgctggtgg cccagtgcct ggtgtgcgtg ccctgggacg

241 cacggccgcc ccccgccgcc ccctccttcc gccaggtgtc ctgcctgaag gagctggtgg

301 cccgagtgct gcagaggctg tgcgagcgcg gcgcgaagaa cgtgctggcc ttcggcttcg

361 cgctgctgga cggggcccgc gggggccccc ccgaggcctt caccaccagc gtgcgcagct

421 acctgcccaa cacggtgacc gacgcactgc gggggagcgg ggcgtggggg ctgctgttgc

481 gccgcgtggg cgacgacgtg ctggttcacc tgctggcacg ctgcgcgctc tttgtgctgg

541 tggctcccag ctgcgcctac caggtgtgcg ggccgccgct gtaccagctc ggcgctgcca

601 ctcaggcccg gcccccgcca cacgctagtg gaccccgaag gcgtctggga tgcgaacggg

661 cctggaacca tagcgtcagg gaggccgggg tccccctggg cctgccagcc ccgggtgcga

721 ggaggcgcgg gggcagtgcc agccgaagtc tgccgttgcc caagaggccc aggcgtggcg

781 ctgcccctga gccggagcgg acgcccgttg ggcaggggtc ctgggcccac ccgggcagga

841 cgcgtggacc gagtgaccgt ggtttctgtg tggtgtcacc tgccagaccc gccgaagaag

901 ccacctcttt ggagggtgcg ctctctggca cgcgccactc ccacccatcc

gtgggccgcc

961 agcaccacgc gggcccccca tccacatcgc ggccaccacg tccctgggac acgccttgtc

1021 ccccggtgta cgccgagacc aagcacttcc tctactcctc aggcgacaag gagcagctgc

1081 ggccctcctt cctactcagc tctctgaggc ccagcctgac tggcgctcgg aggctcgtgg

1141 agaccatctt tctgggttcc aggccctgga tgccagggac tccccgcagg ttgccccgcc

1201 tgccccagcg ctactggcaa atgcggcccc tgtttctgga gctgcttggg aaccacgcgc

1261 agtgccccta cggggtgctc ctcaagacgc actgcccgct gcgagctgcg gtcaccccag

1321 cagccggtgt ctgtgcccgg gagaagcccc agggctctgt ggcggccccc gaggaggagg

1381 acacagaccc ccgtcgcctg gtgcagctgc tccgccagca cagcagcccc tggcaggtgt

1441 acggcttcgt gcgggcctgc ctgcgccggc tggtgccccc aggcctctgg ggctccaggc

1501 acaacgaacg ccgcttcctc aggaacacca agaagttcat ctccctgggg aagcatgcca

1561 agctctcgct gcaggagctg acgtggaaga tgagcgtgcg gggctgcgct tggctgcgca

1621 ggagcccagg ggttggctgt gttccggccg cagagcaccg tctgcgtgag gagatcctgg

1681 ccaagttcct gcactggctg atgagtgtgt acgtcgtcga gctgctcagg tctttctttt

1741 atgtcacgga gaccacgttt caaaagaaca ggctcttttt ctaccggaag agtgtctgga

1801 gcaagttgca aagcattgga atcagacagc acttgaagag ggtgcagctg cgggagctgt

1861 cggaagcaga ggtcaggcag catcgggaag ccaggcccgc

cctgctgacg tccagactcc

1921 gcttcatccc caagcctgac gggctgcggc cgattgtgaa catggactac gtcgtgggag

1981 ccagaacgtt ccgcagagaa aagagggccg agcgtctcac ctcgagggtg aaggcactgt

2041 tcagcgtgct caactacgag cgggcgcggc gccccggcct cctgggcgcc tctgtgctgg

2101 gcctggacga tatccacagg gcctggcgca ccttcgtgct gcgtgtgcgg gcccaggacc

2161 cgccgcctga gctgtacttt gtcaaggtgg atgtgacggg cgcgtacgac accatccccc

2221 aggacaggct cacggaggtc atcgccagca tcatcaaacc ccagaacacg tactgcgtgc

2281 gtcggtatgc cgtggtccag aaggccgccc atgggcacgt ccgcaaggcc ttcaagagcc

2341 acgtctctac cttgacagac ctccagccgt acatgcgaca gttcgtggct cacctgcagg

2401 agaccagccc gctgagggat gccgtcgtca tcgagcagag ctcctccctg aatgaggcca

2461 gcagtggcct cttcgacgtc ttcctacgct tcatgtgcca ccacgccgtg cgcatcaggg

2521 gcaagtccta cgtccagtgc caggggatcc cgcagggctc catcctctcc acgctgctct

2581 gcagcctgtg ctacggcgac atggagaaca agctgtttgc ggggattcgg cgggacgggc

2641 tgctcctgcg tttggtggat gatttcttgt tggtgacacc tcacctcacc cacgcgaaaa

2701 ccttcctcag gaccctggtc cgaggtgtcc ctgagtatgg ctgcgtggtg aacttgcgga

2761 agacagtggt gaacttccct gtagaagacg aggccctggg tggcacggct tttgttcaga

2821 tgccggccca cggcctattc ccctggtgcg gcctgctgct

ggatacccgg accctggagg

2881 tgcagagcga ctactccagc tatgcccgga cctccatcag agccagtctc accttcaacc

2941 gcggcttcaa ggctgggagg aacatgcgtc gcaaactctt tggggtcttg cggctgaagt

3001 gtcacagcct gtttctggat ttgcaggtga acagcctcca gacggtgtgc accaacatct

3061 acaagatcct cctgctgcag gcgtacaggt ttcacgcatg tgtgctgcag ctcccatttc

3121 atcagcaagt ttggaagaac cccacatttt tcctgcgcgt catctctgac acggcctccc

3181 tctgctactc catcctgaaa gccaagaacg cagggatgtc gctgggggcc aagggcgccg

3241 ccggccctct gccctccgag gccgtgcagt ggctgtgcca ccaagcattc ctgctcaagc

3301 tgactcgaca ccgtgtcacc tacgtgccac tcctggggtc actcaggaca gcccagacgc

3361 agctgagtcg gaagctcccg gggacgacgc tgactgccct ggaggccgca gccaacccgg

3421 cactgccctc agacttcaag accatcctgg actgatggcc acccgcccac agccaggccg

3481 agagcagaca ccagcagccc tgtcacgccg ggctctacgt cccagggagg gaggggcggc

3541 ccacacccag gcccgcaccg ctgggagtct gaggcctgag tgagtgtttg gccgaggcct

3601 gcatgtccgg ctgaaggctg agtgtccggc tgaggcctga gcgagtgtcc agccaagggc

3661 tgagtgtcca gcacacctgc cgtcttcact tccccacagg ctggcgctcg gctccacccc

3721 agggccagct tttcctcacc aggagcccgg cttccactcc ccacatagga atagtccatc

3781 cccagattcg ccattgttca cccctcgccc tgccctcctt

tgccttccac ccccaccatc

3841 caggtggaga ccctgagaag gaccctggga gctctgggaa tttggagtga ccaaaggtgt

3901 gccctgtaca caggcgagga ccctgcacct ggatgggggt ccctgtgggt caaattgggg

3961 ggaggtgctg tgggagtaaa atactgaata tatgagtttt tcagttttga aaaaaaaaaa

4021 aaaaaaa (SEQ ID NO.: 1333)

En una modalidad, hTERT es codificada por un ácido nucleico que tiene una secuencia al menos 80 %, 85 %, 90 %, 95 %, 96 %, 97 %, 98 % o 99 % idéntica a la secuencia de SEQ ID NO.: 1333. En una modalidad, hTERT es codificada por un ácido nucleico de SEQ ID NO.: 1333.

Activación y expansión de células efectoras inmunes (por ejemplo, células T)

Las células efectoras inmunes pueden ser activadas y ampliadas por lo general usando métodos tales como los descritos, por ejemplo, en las patentes de Estados Unidos 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; y en la Publicación de Solicitud de Patente de Estados Unidos No. 20060121005.

El procedimiento para la expansión *ex vivo* de células madre hematopoyéticas y células progenitoras descrito en la Patente de Estados Unidos No. 5,199,942, que se incluye en el presente documento a manera de referencia, se puede aplicar a las células de la presente invención. Otros métodos adecuados son conocidos en la técnica, por lo tanto, la presente invención no se limita a ningún método particular de expansión ex vivo de células. Brevemente, el cultivo y la expansión ex vivo de células T puede comprender: (1) la recolección de células madre y progenitoras hematopoyéticas CD34+ de un mamífero a partir de la recolección de sangre periférica o de explantes de médula ósea; y (2) la expansión de dichas células ex vivo. Además de los factores de crecimiento celular descritos en la Patente de estados Unidos No. 5,199,942, otros factores tales como flt3-L, IL-1, IL-3 y ligando c-kit se pueden usar para el cultivo y la expansión de células.

Generalmente, una población de células efectoras inmunes puede ser expandida por

contacto con una superficie que tiene fijada a ella un agente que estimula una señal asociada a un complejo CD3/TCR y un ligando que estimula una molécula coestimuladora en la superficie de las células T. En particular, las poblaciones de células T pueden ser estimuladas tal como se describe en el presente documento, por ejemplo, por contacto con un anticuerpo anti-CD3, o fragmento del mismo, o un fragmento de unión a antígeno del mismo, o un anticuerpo anti-CD2 inmovilizado sobre una superficie, o por contacto con un activador de la proteína quinasa C (por ejemplo, briostatina) en conjunción con un ionóforo de calcio. Para la co-estimulación de una molécula accesoria en la superficie de las células T, se usa un ligando que une la molécula accesoria. Por ejemplo, se puede contactar una población de células T con un anticuerpo anti-CD3 y un anticuerpo anti-CD28, en condiciones apropiadas para estimular la proliferación de las células T. Para estimular la proliferación de cualquiera de las células T CD4+ o células T CD8+, se pueden usar un anticuerpo anti-CD3 y un anticuerpo anti-CD28. Ejemplos de un anticuerpo anti-CD28 incluyen 9,3, B-T3, XR-CD28 (Diaclone, Besançon, Francia), que se pueden usar al igual que otros métodos conocidos comúnmente en la técnica (Berg et al., Transplant Proc. 30(8): 3975-3977, 1998; Haanen et al., J. Exp. Med. 190(9): 13191328, 1999; Garland et al., J. Immunol Meth. 227(1-2): 53-63, 1999).

En algunas modalidades, las células efectoras inmunes (tales como PBMC o células T) se expanden y se estimulan poniendo en contacto las células con uno o ambos de un anticuerpo anti-CD3 e IL-2. En algunas modalidades, las células se expanden sin esferas anti-CD28 o anti-CD3.

En ciertos aspectos, la señal primaria de estimulación y la señal coestimuladora para la célula T pueden ser proporcionadas mediante diferentes protocolos. Por ejemplo, los agentes que proporcionan cada señal pueden estar en solución o acoplados a una superficie. Cuando están acoplados a una superficie, los agentes pueden estar acoplados a la misma superficie (es decir, en formación "cis") o a superficies separadas (es decir, en formación "trans"). Alternativamente, un agente puede estar acoplado a una superficie y el otro agente estar en solución. En un aspecto, el agente que proporciona la señal coestimuladora está unido a una superficie celular y el agente que proporciona la señal primaria de activación está en solución o acoplado a una superficie. En ciertos aspectos, ambos agentes pueden estar en solución. En un aspecto, los agentes pueden estar en forma soluble, y luego reticulados a una superficie, tal como una célula que expresa receptores de Fc o un anticuerpo u otro agente de unión que se unirá a los agentes.

En este sentido, véanse, por ejemplo, las Publicaciones de Solicitud de Patente de Estados Unidos No. 20040101519 y 20060034810 para células presentadoras de antígeno artificiales (aAPCs) que se contemplan para uso en la activación y expansión de células T en la presente invención.

En un aspecto, los dos agentes están inmovilizados en esferas, ya sea en la misma esfera, es decir, "cis", o en esferas separadas, es decir, "trans". A modo de ejemplo, el agente que proporciona la señal primaria de activación es un anticuerpo anti-CD3 o un fragmento de unión a antígeno del mismo y el agente que proporciona la señal coestimuladora es un anticuerpo anti-CD28 o fragmento de unión a antígeno del mismo; y los dos agentes están co-inmovilizados en la misma esfera en cantidades moleculares equivalentes. En un aspecto, se usa una relación de 1:1 de cada anticuerpo unido a las esferas para la expansión de células T CD4+ y el crecimiento de células T. En ciertos aspectos, se usa una relación de anticuerpos anti CD3:CD28 unidos a las esferas de tal manera que se observa un aumento en la expansión de células T en comparación con la expansión observada cuando se usa la relación 1:1. En un aspecto particular, se observa un aumento de aproximadamente 1 a aproximadamente 3 veces en comparación con la expansión observada usando una relación 1:1. En un aspecto, la relación de anticuerpos CD3:CD28 unidos a las esferas oscila entre 100:1 y 1:100, y todos los valores enteros contenidos entre estos valores. En un aspecto, hay más anticuerpo anti-CD28 unido a las partículas que anticuerpo anti-CD3, es decir, la relación CD3:CD28 es menor que uno. En ciertos aspectos, la relación de anticuerpo anti-CD28 a anticuerpo anti-CD3 unidos a las esferas es mayor que 2:1. En un aspecto particular, se usa una relación 1:100 de anticuerpos CD3:CD28 unidos a las esferas. En un aspecto particular, se usa una relación 1:75 de anticuerpos CD3:CD28 unidos a las esferas. En un aspecto particular, se usa una relación 1:50 de anticuerpos CD3:CD28 unidos a las esferas. En un aspecto particular, se usa una relación 1:30 de anticuerpos CD3:CD28 unidos a las esferas. En un aspecto particular, se usa una relación 1:10 de anticuerpos CD3:CD28 unidos a las esferas. En un aspecto particular, se usa una relación 1:3 de anticuerpos CD3:CD28 unidos a las esferas. En un aspecto particular, se usa una relación 3:1 de anticuerpos CD3:CD28 unidos a las esferas.

Relaciones de partículas a células entre 1:500 y 500:1 y cualquier número entero entre estos valores se pueden usar para estimular células T u otras células blanco. Como un experto en la técnica puede comprender fácilmente, la relación de partículas a células puede depender del

tamaño de la partícula con respecto a la célula blanco. Por ejemplo, las esferas de tamaño pequeño solo pueden unir unas pocas células, mientras que las esferas más grandes pueden unir muchas. En ciertos aspectos, la relación de células a partículas varía entre 1:100 y 100:1, y cualquier número entero entre estos valores; y en otros aspectos, la relación comprende entre 1:9 y 9: 1, y cualquier número entero entre estos valores, también se puede usar para estimular células T. La relación de partículas acopladas anti-CD3 y anti CD-28 a células T que produce la estimulación de células T puede variar tal como se señaló anteriormente. Sin embargo, ciertos valores adecuados incluyen 1:100, 1:50, 1:40, 1:30, 1:20, 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1 y 15:1, con una relación adecuada de al menos 1:1 partículas por célula T. En un aspecto, se usa una relación de partículas a células de 1:1 o inferior. En un aspecto específico, se usa una relación de partículas a células adecuada de 1:5. En otros aspectos, la relación de partículas a células puede variar dependiendo del día de la estimulación. Por ejemplo, en un aspecto, la relación de partículas a células es entre 1:1 y 10:1 durante el primer día y se agregan partículas adicionales a las células cada día o cada día de por medio a partir de ese momento hasta por 10 días, con relaciones finales entre 1:1 y 1:10 (con base en los recuentos de células en el día de la adición). En un aspecto particular, la relación de partículas a células es de 1:1 en el primer día de estimulación y se ajusta a 1:5 en el tercer y quinto días de estimulación. En un aspecto, se agregan partículas cada día o cada día de por medio con base en una relación final de 1:1 en el primer día y 1:5 en el tercer y quinto días de estimulación. En un aspecto particular, la relación de partículas a células es de 2:1 en el primer día de estimulación y se ajusta a 1:10 en el tercer y quinto días de estimulación. En un aspecto, se agregan partículas cada día o cada día de por medio con base en una relación final de 1:1 en el primer día y 1:10 en el tercer y quinto días de estimulación. Un experto en la técnica observará que un amplio número de otras relaciones pueden ser adecuadas para uso en la presente invención. En particular, las relaciones variarán dependiendo del tamaño de las partículas y del tamaño y el tipo de células. En un aspecto, las relaciones más típicas para uso son cercanas a 1:1, 2:1 y 3:1 en el primer día.

En otros aspectos de la presente invención, las células, tales como las células T, se combinan con esferas recubiertas con agente, posteriormente se separan las esferas y las células, y luego se cultivan las células. En un aspecto alternativo, antes del cultivo, las esferas recubiertas con agente y las células no se separan, sino que se cultivan juntas. En un aspecto adicional, las esferas y las células se concentran primero mediante aplicación de una fuerza,

como una fuerza magnética, lo que resulta en un aumento de la ligadura de marcadores de superficie celular, induciendo con ello la estimulación de células.

A modo de ejemplo, las proteínas de la superficie celular se pueden ligar permitiendo que esferas paramagnéticas a las que están fijados anti-CD3 y anti-CD28 (esferas 3x28) entren en contacto con las células T. En un aspecto, las células (por ejemplo, células T 10^4 a 10^9) y las esferas (por ejemplo, esferas paramagnéticas T CD3/CD28 M-450 Dynabeads® en una relación 1:1) se combinan en un tampón, por ejemplo, PBS (sin cationes divalentes, tales como calcio y magnesio). Una vez más, los expertos en la técnica pueden entender fácilmente que es posible usar cualquier concentración de células. Por ejemplo, la célula blanco puede ser muy escasa en la muestra y comprender solamente 0,01 % de la muestra, o la totalidad de la muestra (es decir, el 100 %) puede comprender la célula blanco de interés. En consecuencia, cualquier número de células está dentro del contexto de la presente invención. En ciertos aspectos, puede ser deseable disminuir significativamente el volumen al que se mezclan las partículas y las células (es decir, aumentar la concentración de células), para asegurar el contacto máximo de las células y las partículas. Por ejemplo, en un aspecto, se usa una concentración de aproximadamente 10 mil millones de células/ml, 9 mil millones de células/ml, 8 mil millones de células/ml, 7 mil millones de células/ml, 6 mil millones de células/ml o 5 mil millones de células/ml o 2 mil millones de células/ml. En un aspecto, se usan más de 100 millones de células/ml. En un aspecto adicional, se usa una concentración de células de 10, 15, 20, 25, 30, 35, 40, 45 o 50 millones de células/ml. En otro aspecto, se usa una concentración de células de 75, 80, 85, 90, 95 o 100 millones de células ml. En aspectos adicionales, se puede usar concentraciones de 125 o 150 millones de células/ml. El uso de altas concentraciones puede resultar en mayor rendimiento celular, activación de células y expansión celular. Además, el uso de altas concentraciones de células permite la captura más eficiente de células que pueden expresar débilmente los antígenos blanco de interés, tales como células T negativas para CD28. Estas poblaciones de células pueden tener valor terapéutico y sería deseable obtenerlas en ciertos aspectos. Por ejemplo, usar una concentración alta de células permite una selección más eficaz de células T CD8+ que normalmente tienen una expresión de CD28 más débil.

En una modalidad, las células transducidas con un ácido nucleico que codifica un CAR, por ejemplo, un CAR descrito en el presente documento, se expanden, por ejemplo, a través de un método descrito en el presente documento. En una modalidad, las células se expanden en

cultivo durante un periodo entre varias horas (por ejemplo, aproximadamente 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 18, 21 horas) y aproximadamente 14 días (por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 o 14 días). En una modalidad, las células se expanden durante un período entre 4 y 9 días. En una modalidad, las células se expanden durante un período de 8 días o menos, por ejemplo, 7, 6 o 5 días. En una modalidad, las células, por ejemplo, una célula CAR descrita en el presente documento, se expanden en cultivo durante 5 días, y las células resultantes son más potentes que las mismas células expandidas en cultivo durante 9 días bajo las mismas condiciones de cultivo. La potencia se puede definir, por ejemplo, mediante diferentes funciones de las células T, por ejemplo, proliferación, destrucción de células blanco, producción de citoquinas, activación, migración, o combinaciones de las mismas. En una modalidad, las células, por ejemplo, una célula CAR de CD19 descritas en el presente documento, expandida durante 5 días, exhiben un incremento de al menos una, dos, tres o cuatro veces en las duplicaciones de células tras la estimulación con antígeno en comparación con las mismas células expandidas en cultivo durante 9 días bajo las mismas condiciones de cultivo. En una modalidad, las células, por ejemplo, las células que expresan CAR descritas en el presente documento, se expanden en cultivo durante 5 días, y las células resultantes exhiben una mayor producción de citoquinas proinflamatorias, por ejemplo, niveles de IFN-γ y/o GM-CSF, en comparación a las mismas células expandidas en cultivo durante 9 días bajo las mismas condiciones de cultivo. En una modalidad, las células, por ejemplo, una célula CAR descrita en el presente documento, se expanden en cultivo durante 5 días y exhiben un incremento de al menos una, dos, tres, cuatro, cinco, diez veces en pg/ml de producción de citoquinas proinflamatorias, por ejemplo, niveles de IFN-γ y/o GM-CSF, en comparación a las mismas células expandidas en cultivo durante 9 días bajo las mismas condiciones de cultivo.

En un aspecto de la presente invención, la mezcla puede ser cultivada durante un período que puede durar entre varias horas (alrededor de 3 horas) y aproximadamente 14 días o cualquier número entero entre estos valores. En un aspecto, la mezcla se puede cultivar durante 21 días. En un aspecto de la invención, las esferas y las células T se cultivan juntas durante aproximadamente ocho días. En un aspecto, las esferas y las células T se cultivan juntas durante 2-3 días. También puede ser deseable usar varios ciclos de estimulación de manera que el tiempo de cultivo de las células T puede ser de 60 días o más. Las condiciones apropiadas para el cultivo de células T incluyen un medio apropiado (por ejemplo, Medio Esencial Mínimo o

Medio RPMI 1640 o X-Vivo 15, (Lonza)) que puede contener factores necesarios para la proliferación y la viabilidad, incluyendo suero (por ejemplo, suero fetal humano o bovino), interleuquina-2 (IL-2), insulina, IFN-γ, IL-4, IL-7, GM-CSF, IL-10, IL-12, IL-15, TGF y TNF-α, o cualquier otro aditivo para el crecimiento celular conocido por un experto en la materia. Otros aditivos para el crecimiento celular incluyen, de manera enunciativa mas no limitativa, tensioactivo, plasmanato y agentes reductores tales como N-acetil-cisteína y 2-mercaptoetanol. Los medios pueden incluir RPMI 1640, AIM-V, DMEM, MEM, α-MEM, F-12, X-Vivo 15, y X-Vivo 20, optimizador, con aminoácidos añadidos, piruvato de sodio y vitaminas, ya sean libres de suero o complementados con una cantidad adecuada de suero (o plasma) o un conjunto definido de hormonas y/o una cantidad de citoquina(s) suficiente para el crecimiento y la expansión de las células T. Los antibióticos, por ejemplo, la penicilina y la estreptomicina, se incluyen solo en cultivos experimentales, no en cultivos de células que serán infundidas en un sujeto. Las células blanco se mantienen bajo condiciones necesarias para apoyar el crecimiento, por ejemplo, una temperatura (por ejemplo, 37° C) y atmósfera (por ejemplo, aire más 5% de CO_2) apropiadas.

En una modalidad, las células se expanden en un medio apropiado (por ejemplo, medios descritos en el presente documento), el cual incluye una o más interleuquinas que producen un aumento de al menos 200 veces (por ejemplo, 200 veces, 250 veces, 300 veces, 350 veces) de las células durante un período de expansión de 14 días, por ejemplo, medido a través de un método descrito en el presente documento, tal como la citometría de flujo. En una modalidad, las células se expanden en presencia de IL-15 y/o IL-7 (por ejemplo, IL-15 e IL-7).

En algunas modalidades, una célula que expresa un CAR descrita en el presente documento (por ejemplo, una célula T tal como una célula T CD4+ o una célula T CD8+) se pone en contacto con una composición que comprende un polipéptido de interleuquina-15 (IL-15), un polipéptido de receptor alfa de interleuquina-15 (IL-15Ra), o una combinación de un polipéptido IL-15 y un polipéptido de IL-15Ra, por ejemplo, hetIL- 15, durante la fabricación de la célula que expresa CAR, por ejemplo, ex vivo. En algunas modalidades, la célula que expresa un CAR descrita en el presente documento se pone en contacto con una composición que comprende un polipéptido de IL-15 durante la fabricación de la célula que expresa CAR, por ejemplo, ex vivo. En algunas modalidades, la célula que expresa un CAR descrita en el presente documento se pone en contacto con una composición que comprende una combinación de un

polipéptido de IL-15 y un polipéptido de IL-15a durante la fabricación de la célula que expresa CAR, por ejemplo, ex vivo. En algunas modalidades, la célula que expresa un CAR descrita en el presente documento se pone en contacto con una composición que comprende un hetIL-15 durante la expansión ex vivo.

En una modalidad, la célula que expresa un CAR (por ejemplo, una célula T o una célula NK) descrita en el presente documento se pone en contacto con una composición que comprende hetIL-15 durante la expansión ex vivo. En una modalidad, la célula que expresa un CAR descrita en el presente documento se pone en contacto con una composición que comprende un polipéptido de IL-15 durante la expansión ex vivo. En una modalidad, la célula que expresa un CAR descrita en el presente documento se pone en contacto con una composición que comprende un polipéptido de IL-15 y un polipéptido de IL-15Ra durante la expansión ex vivo. En una modalidad, la puesta en contacto tiene como resultando la supervivencia y la proliferación de una subpoblación de linfocitos, por ejemplo, células T CD8+.

En una modalidad, el método de fabricación descrito en la presente invención comprende además poner en contacto la población de células efectoras inmunes (por ejemplo, células T o células NK) con un ácido nucleico que codifica una subunidad de telomerasa, por ejemplo, hTERT. El ácido nucleico que codifica la subunidad de telomerasa puede ser ADN.

Las células T que han sido expuestas a diversas estimulaciones pueden presentar características diferentes. Por ejemplo, los productos de células mononucleares de sangre periférica sometida a aféresis o sangre típica tienen una población de células T colaboradoras (TH, CD4+) mayor que la población de células T supresoras o citotóxicas (TC, CD8+). La expansión ex vivo de células T mediante estimulación de los receptores CD3 y CD28 produce una población de células T que antes de aproximadamente 8-9 días contiene predominantemente células TH, mientras que después de aproximadamente 8-9 días, la población de células T comprende una población cada vez mayor de células TC. En consecuencia, dependiendo del objetivo del tratamiento, infundir a un sujeto con una población de células T que comprende predominantemente células TH puede ser ventajoso. De manera similar, si se ha aislado un subconjunto de células T específico de antígeno puede ser beneficioso expandir aún más este subconjunto.

Además de los marcadores CD4 y CD8, otros marcadores fenotípicos varían significativamente, pero en gran medida de forma reproducible durante el curso del proceso de

expansión celular. Por lo tanto, esta reproducibilidad promueve la capacidad de adaptar un producto de células T activadas para propósitos específicos.

Después de producir un constructo de CAR, por ejemplo, un CAR de CD19, se pueden usar diversos ensayos para evaluar la actividad de la molécula, incluyendo, de manera enunciativa mas no limitativa, la capacidad de expandir células T después de la estimulación del antígeno, mantener la expansión de células T en ausencia de re-estimulación y actividades anti-cancerosas en modelos in vitro y animales apropiados. Ensayos para evaluar los efectos de un CAR, por ejemplo, un CAR de CD19, se describen en más detalle a continuación.

El análisis Western blot de la expresión de CAR en células T primarias se puede usar para detectar la presencia de monómeros y dímeros. Por ejemplo, como se describe en el párrafo 695 de la Solicitud Internacional WO2015/142675, presentada el 13 de marzo de 2015, la cual se incorpora en la presente como referencia en su totalidad.

La expansión *in vitro* de células T CAR^+ después de la estimulación de antígeno se puede medir mediante citometría de flujo. Por ejemplo, se estimula una mezcla de células T $CD4^+$ y $CD8^+$ se estimula con esferas αCD3/αCD28 y luego se transduce con vectores lentivirales que expresan GFP bajo el control de los promotores a ser analizados. Ejemplos de promotores incluyen el gen CMV IE, EF-1α, ubiquitina C o promotores de fosfoglicerato quinasa (PGK). La fluorescencia de GFP se evalúa en el día 6 de cultivo en los subconjuntos de células T $CD4^+$ y/o $CD8^+$ mediante citometría de flujo. Véase, *por ejemplo*, Milone *et al*., Molecular Therapy 17(8): 1453-1464 (2009). Alternativamente, una mezcla de células T $CD4^+$ y $CD8^+$ se estimula con esferas magnéticas recubiertas αCD3/αCD28 en el día 0, y se transduce con CAR en el día 1 usando un vector lentiviral bicistrónico que expresa un CAR junto con eGFP usando una secuencia de salto ribosomal 2A. Los cultivos se volvieron a estimular con células K562 $CD19^+$ (K562-CD19), células K562 de tipo silvestre (tipo silvestre) K562 o células K562 que expresan hCD32 y 4-1BBL en presencia de anticuerpo antiCD3 y anti-CD28 (K562-BBL-3/28) después del lavado. Se agrega IL-2 exógena a los cultivos cada día de por medio a 100UI/ml. Las células T GFP^+ se enumeran mediante citometría de flujo usando conteo basado en esferas. Véase, *por ejemplo*, Milone *et al*., Molecular Therapy 17(8): 1453-1464 (2009).

También es posible medir la expansión sostenida de células T CAR^+ en ausencia de re-estimulación. Véase, *por ejemplo*, Milone *et al*., Molecular Therapy 17(8): 1453-1464 (2009). Brevemente, el volumen medio de células T (fl) se mide en el día 8 de cultivo usando Coulter

Multisizer, Nexcelom Cellometer Vision o Millipore Scepter después de la estimulación con esferas magnéticas recubiertas αCD3/αCD28 en el día 0, y transducción con el CAR indicado en el día 1.

Para medir la actividad de una célula que expresa CAR también se pueden usar modelos animales. Por ejemplo, Por ejemplo, como se describe en el párrafo 698 de la Solicitud Internacional WO2015/142675, presentada el 13 de marzo de 2015, la cual se incorpora en la presente como referencia en su totalidad.

Se puede evaluar la respuesta a tratamientos con CAR dependientes de dosis. Por ejemplo, como se describe en el párrafo 699 de la Solicitud Internacional WO2015/142675, presentada el 13 de marzo de 2015, la cual se incorpora en la presente como referencia en su totalidad.

La evaluación de la proliferación celular y la producción de citoquinas se ha descrito previamente, por ejemplo, como se describe en el párrafo 700 de la solicitud internacional WO2015/142675, presentada el 13 de marzo 2015, que se incorpora aquí por referencia en su totalidad.

La citotoxicidad se puede evaluar mediante un ensayo de liberación de 51Cr estándar, por ejemplo, como se describe en el párrafo 701 de la solicitud internacional WO2015/142675, presentada el 13 de marzo 2015, que se incorpora aquí por referencia en su totalidad.

Se pueden utilizar tecnologías de imagen para evaluar el tráfico específico y la proliferación de los CAR en modelos animales portadores de tumores, por ejemplo, como se describe en el párrafo 702 de la solicitud internacional WO2015/142675, presentada el 13 de marzo de de 2015, que se incorpora aquí como referencia en su totalidad.

Otros ensayos incluyen aquellos descritos en la sección de Ejemplos en el presente documento, así como aquellos que son conocidos en la técnica que tsmbién pueden ser usados para evaluar a los CARs descritos en el presente documento.

Alternativamente, o en combinación con los métodos descritos en el presente documento, se divulgan métodos y composiciones para una o más de detección y/o cuantificación de células que expresan CAR (por ejemplo, in vitro o in vivo (por ejemplo, monitoreo clínico clínico)), expansión y/o activación de células inmunitarias, y/o selección específica de CAR, que implican

el uso de un ligando de CAR. En un ejemplo de modalidad, el ligando de CAR es un anticuerpo que se une a la molécula de CAR, por ejemplo, se une al dominio de unión a antígeno extracelular de CAR (por ejemplo, un anticuerpo que se une al dominio de unión a antígeno, por ejemplo, un anticuerpo anti-idiotípico; o un anticuerpo que se une a una región constante del dominio de unión extracelular). En otras modalidades, el ligando de CAR es una molécula de antígeno CAR (por ejemplo, una molécula de antígeno CAR tal como se describe en el presente documento).

En un aspecto, se divulga un método para detectar y/o cuantificar células que expresan CAR. Por ejemplo, el ligando de CAR se puede usar para detectar y/o cuantificar células que expresan CAR in vitro o in vivo (por ejemplo, monitoreo clínico de células que expresan CAR en un paciente o dosificación a un paciente). El método incluye:

proporcionar el ligando de CAR (opcionalmente, un ligando de CAR marcado, por ejemplo, un ligando de CAR que incluya una etiqueta, una esfera, un marcador radioactivo o fluorescente);

adquirir la célula que expresa un CAR (por ejemplo, adquirir una muestra que contiene células CAR que expresan, como una muestra de fabricación o de una muestra clínica);

poner en contacto la célula que expresa un CAR con el ligando de CAR en condiciones en las que ocurre la unión, para detectar así el nivel (por ejemplo, la cantidad) de células que expresan CAR presentes. La unión de la célula que expresa un CAR con el ligando de CAR se puede detectar usando técnicas estándar tales como FACS, ELISA y similares.

En otro aspecto, se describe un método de expansión y/o activación de células (por ejemplo, células efectoras inmunes). El método incluye:

proporcionar una célula que expresa un CAR (por ejemplo, una primera célula que expresa un CAR o una célula que expresa un CAR transitoriamente);

poner en contacto dicha célula que expresa un CAR con un ligando de CAR, por ejemplo, un ligando de CAR descrito en el presente documento), en condiciones donde ocurra la expansión y/o proliferación de células, produciendo así la población de células activadas y/o expandidas.

En ciertas modalidades, el ligando de CAR está presente (por ejemplo, está inmovilizado o unido a un sustrato, por ejemplo, un sustrato de origen no natural). En algunas modalidades, el

sustrato es un sustrato no celular. El sustrato no celular puede ser un soporte sólido elegido entre, por ejemplo, una placa (por ejemplo, una placa de microtitulación), una membrana (por ejemplo, una membrana de nitrocelulosa), una matriz, un chip o una esfera. En algunas modalidades, el ligando de CAR está presente en el sustrato (por ejemplo, en la superficie del sustrato). El ligando de CAR se puede inmovilizar, unir o asociar de manera covalente o no covalente (por ejemplo, reticulada) al sustrato. En una modalidad, el ligando de CAR está unido (por ejemplo, unido covalentemente) a una esfera. En las modalidades antes mencionadas, la población de células inmunitarias se puede expandir in vitro o ex vivo. El método puede incluir además el cultivo de la población de células inmunitarias en presencia del ligando de la molécula de CAR, por ejemplo, usando cualquiera de los métodos descritos en el presente documento.

En otras modalidades, el método de expansión y/o activación de las células comprende además la adición de una segunda molécula estimuladora, por ejemplo, CD28. Por ejemplo, el ligando de CAR y la segunda molécula estimuladora se pueden inmovilizar a un sustrato, por ejemplo, una o más esferas, proporcionando de este modo una mayor expansión y/o activación de las células.

En otras modalidades, se proporciona un método para seleccionar o aumentar para una célula que expresa CAR. El método incluye poner en contacto la célula que expresa un CAR con un ligando de CAR tal como se describe en el presente documento y seleccionar la célula con base en la unión del ligando de CAR.

En aún otras modalidades, se proporciona un método para agotar (por ejemplo, reducir y/o eliminar) una célula que expresa CAR. El método incluye poner en contacto la célula que expresa un CAR con un ligando de CAR tal como se describe en el presente documento y seleccionar la célula con base en la unión del ligando de CAR, reduciendo así la cantidad, y/o eliminando, la célula que expresa CAR. En una modalidad, el ligando de CAR está acoplado a un agente tóxico (por ejemplo, una toxina o un medicamento de ablación celular). En otra modalidad, el anticuerpo anti-idiotípico puede causar, actividad de células efectoras, por ejemplo, actividades de ADCC o de ADC.

Ejemplos de anticuerpos anti-CAR que se pueden usar en los métodos divulgados en el presente documento se describen, por ejemplo, en WO 2014/190273 y en Jena et al., “Chimeric Antigen Receptor (CAR)-Specific Monoclonal Antibody to Detect CD19-Specific T cells in

Clinical Trials", PLOS marzo 2013 8: 3 e57838, cuyos contenidos se incluyen en el presente documento a manera de referencia. En algunos aspectos y modalidades, las composiciones y métodos son optimizados en el presente documento para un conjunto específico de células T, por ejemplo, como se describe en la Solicitud No. U.S. PCT/US2015/043219 presentada el 31 de julio de 2015, los contenidos de la cual están incorporados en la presente como referencia en su totalidad. En algunas modadlidades, los conjuntos optimizados de células T muetsran una persistencia aumentada frente a una célula T control, por ejemplo, una célula T de un tipo diferente (por ejemplo CD8+ o CD4+) que expresan el mismo constructo.

En algunas formas de realización, una célula T CD4 + comprende un CAR que se describe en el presente documento, tal CAR comprende un dominio de señalización intracelular adecuado para (por ejemplo, optimizado para, por ejemplo, lo que lleva a la persistencia mejorada in) una célula T CD4 +, por ejemplo, un dominio de ICOS. En algunas formas de realización, una célula T CD8 + comprende un CAR que se describe en el presente documento, que CAR comprende un dominio de señalización intracelular adecuada para (por ejemplo, optimizado para, por ejemplo, lo que lleva a una mayor persistencia de) una célula T CD8 +, por ejemplo, un dominio de 4-1BB, un dominio de CD28, u otro dominio coestimulador que no sea un dominio ICOS. En algunas formas de realización, el CAR descrito en este documento comprende un dominio de unión a antígeno que se describe en el presente documento, por ejemplo, un CAR que comprende un dominio de unión a antígeno.

En un aspecto, se describe aquí un método de tratamiento de un sujeto, por ejemplo, un sujeto que tiene cáncer. El método incluye administrar a dicho sujeto, una cantidad eficaz de:

1) una célula T CD4 + que comprende un CAR (el CAR CD4 +) que comprende:

un dominio de unión a antígeno, por ejemplo, un dominio de unión a antígeno que se describe en el presente documento;

un dominio transmembrana; y

un dominio de señalización intracelular, por ejemplo, un primer dominio coestimulador, por ejemplo, un dominio de ICOS; y

2) una célula T CD8 + que comprende un CAR (el CAR CD8+) que comprende:

un dominio de unión a antígeno, por ejemplo, un dominio de unión a antígeno que se describe en el presente documento;

un dominio transmembrana; y

un dominio de señalización intracelular, por ejemplo, un segundo dominio coestimuladora, por ejemplo, un dominio de 4-1BB, un dominio de CD28, u otro dominio coestimuladora que no sea un dominio ICOS;

en el que el CAR CD4 + y el CAR CD8 + difieren uno de otro.

Opcionalmente, el método incluye además la administración de:

3) una segunda célula T CD8 + que comprende un CAR (el segundo CAR CD8 +) que comprende:

un dominio de unión a antígeno, por ejemplo, un dominio de unión a antígeno que se describe en el presente documento;

un dominio transmembrana; y

un dominio de señalización intracelular, en el que el segundo CAR CD8 + comprende un dominio de señalización intracelular, por ejemplo, un dominio de señalización coestimulador, no presente en el CAR CD8 +, y, opcionalmente, no comprende un dominio de señalización ICOS.

Métodos de Fabricación / Producción

En algunas realizaciones, los métodos descritos en este documento además incluyen la administración de un agente agotador de células T después del tratamiento con la célula (por ejemplo, una célula efectora inmune como se describe en el presente documento, por ejemplo, una célula efectora inmune que expresa un CAR conducido por un promotor PGK1 truncado), reduciendo de ese modo (por ejemplo, el agotamiento) las células que expresan CAR (por ejemplo, las células que expresan CAR CD19). Tales agentes agotadores de células T se pueden utilizar para agotar de manera efectiva a las células que expresan CAR (por ejemplo, células que expresan CAR CD19) para mitigar la toxicidad. En algunas formas de realización, las células que expresan CAR-fueron fabricadas de acuerdo con un método del presente documento, por ejemplo, se ensayó (por ejemplo, antes o después de la transfección o transducción) de acuerdo con un método de la presente memoria.

En algunas realizaciones, se administra el agente agotador de células T agente una, dos, tres, cuatro, o cinco semanas después de la administración de la célula, por ejemplo, la población de células efectoras inmunes, que se describen en este documento.

En una realización, la célula T agente de ozono es un agente que reduce las células que expresan CAR, por ejemplo, mediante la inducción de la citotoxicidad mediada por células dependiente de anticuerpos (ADCC) y/o la muerte celular inducida por el complemento. Por ejemplo, las células que expresan CAR descritas en este documento también pueden expresar un antígeno (por ejemplo, un antígeno diana) que es reconocido por moléculas capaces de inducir la muerte celular, por ejemplo, ADCC o la muerte celular inducida por el complemento. Por ejemplo, las células que expresan CAR descritas en este documento también pueden expresar una proteína diana (por ejemplo, un receptor) capaz de ser dirigida por un anticuerpo o fragmento de anticuerpo. Ejemplos de tales proteínas diana incluyen, pero no se limitan a, EpCAM, VEGFR, integrinas (por ejemplo, integrinas αvβ3, α4, αI3 / 4β3, α4β7, α5β1, αvβ3, αv), miembros de la superfamilia de receptores de TNF (por ejemplo, TRAIL R1, TRAIL-R2), receptor de PDGF, receptor de interferón, receptor de folato, GPNMB, ICAM-1, HLA-DR, CEA, CA-125, MUC1, TAG-72, receptor de IL-6, 5T4, GD2, GD3, CD2 , CD3, CD4, CD5, CD11, CD11a / LFA-1, CD15, CD18 / ITGB2, CD19, CD20, CD22, CD23 / IgE receptor, CD25, CD28, CD30, CD33, CD38, CD40, CD41, CD44, CD51, CD52, CD62L, CD74, CD80, CD125, CD147 / basigina, CD152 / CTLA-4, CD154 / CD40L, CD195 / CCR5, CD319 / SLAMF7, y EGFR, y versiones truncadas de los mismos (por ejemplo, versiones preservar uno o más epítopos extracelulares pero que carece de una o más regiones dentro del dominio citoplasmático).

En algunas realizaciones, la célula que expresa CAR co-expresa el CAR y la proteína diana, por ejemplo, se expresa de forma natural la proteína diana o está diseñada para expresar la proteína diana. Por ejemplo, la célula, por ejemplo, la población de células efectoras inmunes, puede incluir un ácido nucleico (por ejemplo, vector) que comprende el ácido nucleico de CAR (por ejemplo, un ácido nucleico de CAR tal como se describe en el presente documento) y un ácido nucleico que codifica la proteína diana.

En una realización, el agente agotador de la célula T es un inhibidor de CD52, por ejemplo, una molécula de anticuerpo anti-CD52, por ejemplo, alemtuzumab.

En otras realizaciones, la célula, por ejemplo, la población de células efectoras inmunes,

expresa una molécula de CAR como se describe aquí (por ejemplo, CAR CD19) y la proteína diana reconocida por el agente agotador de células T. En una realización, la proteína diana es CD20. En realizaciones en las que la proteína blanco es CD20, el agente agotador de las células T es un anticuerpo anti-CD20, por ejemplo, rituximab.

En realizaciones adicionales de cualquiera de los métodos mencionados anteriormente, los métodos incluyen además el trasplante de una célula, por ejemplo, una célula madre hematopoyética, o una médula ósea, en el mamífero.

En otro aspecto, la invención presenta un método de acondicionamiento de un mamífero antes de trasplante de células. El método incluye administrar al mamífero una cantidad efectiva de la célula que comprende un ácido nucleico o polipéptido de CAR, por ejemplo, un ácido nucleico o polipéptido de CAR CD19. En algunas formas de realización, el trasplante de células es un trasplante de células madre, por ejemplo, un trasplante de células madre hematopoyéticas, o un trasplante de médula ósea. En otras realizaciones, el acondicionamiento de un sujeto antes de trasplante de células incluye reducir el número de células que expresan el blanco en un sujeto, por ejemplo, expresión de CD19 expresión de las células normales o células cancerosas que expresan CD19.

Biopolimeros ejemplares se describen, por ejemplo, en lo spárrafos 1004-1006d ela solicitud internacional WO2015/142675, presentada el 13 de marzo de 2015, la cual se incorpora en el presente documento como referencia en su totalidad.

Aplicaciones terapéuticas

Enfermedades y/o trastornos asociados a CD19

En un aspecto, la invención métodos para el tratamiento de una enfermedad asociada a la expresión de CD19. En un aspecto, la invención proporciona métodos para tratar una enfermedad en la que parte del cáncer es negativo para CD19 y parte del cáncer es positivo para CD19. Por ejemplo, los métodos y composiciones de la invención son útiles para el tratamiento de sujetos que se han sometido a tratamiento para una enfermedad asociada a la expresión de CD19, donde el sujeto que ha sido sometido al tratamiento relacionado con la expresión de CD19, por ejemplo, tratamiento con un CAR de CD19, presenta una enfermedad asociada a la

expresión de CD19.

En otro aspecto, la invención proporciona métodos para tratar una enfermedad asociada a la expresión de un antígeno de células B, por ejemplo, uno o más de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1. En un aspecto, la invención proporciona métodos para tratar una enfermedad en la que parte del tumor es negativo para el antígeno de células B y parte del tumor es positivo para el antígeno de células B. Por ejemplo, las composiciones y métodos de la invención son útiles para el tratamiento de sujetos que se han sometido a tratamiento para una enfermedad asociada a la expresión del antígeno de células B, donde el sujeto que ha sido sometido al tratamiento relacionado con la expresión de un antígeno de células B, por ejemplo, tratamiento con un CAR dirigido a un antígeno de células B, presenta una enfermedad asociada a la expresión del antígeno de células B. En un tercer aspecto, la invención proporciona métodos para tratar una enfermedad asociada a la expresión del antígeno de células B, por ejemplo, asociado a la expresión de CD19 y uno o más otros antígenos de células B.

En otro aspecto, la invención se refiere a un vector que comprende un CAR de CD19 enlazado operativamente al promotor para la expresión en células de mamíferos, por ejemplo, células T o células NK. En un aspecto, la invención proporciona una célula recombinante, por ejemplo, una célula T o célula NK, que expresa el CAR de CD19 para su uso en el tratamiento de cánceres que expresan CD19, donde la célula T recombinante que expresa el CAR de CD19 se denomina TCAR de CD19. En un aspecto, el TCAR de CD19 descrito en el presente documento tiene la capacidad de poner en contacto una célula cancerosa con al menos un CAR de CD19 expresado en su superficie tal que el TCAR se dirige a la célula cancerosa y se inhibe el crecimiento del cáncer.

En un aspecto, la invención se refiere a un inhibidor de CD22, el cual es un TCAR de CD22, por ejemplo, una célula T, que expresa el CAR de CD22 para su uso en el tratamiento de tumores que expresan CD22 en combinación con TCARS de CD19, donde la célula T recombinante que expresa el CAR de CD22 se denomina TCAR de CD22. En un aspecto, el TCAR de CD22 descrito en el presente documento tiene la capacidad de poner en contacto una célula tumoral con al menos un CAR de CD22 expresado en su superficie tal que el TCAR de CD22 se dirige a la célula tumoral y se inhibe el crecimiento del tumor.

En un aspecto, la invención se refiere a un método para inhibir el crecimiento de una célula cancerosa que expresa CD19, que comprende poner en contacto la célula cancerosa con

una célula que expresa un CAR de CD19, por ejemplo, una célula TCAR de CD19 descrita en el presente documento, y una o más otras células que expresan CAR, por ejemplo, tal como se describe en el presente documento, tal que el TCAR se activa en respuesta al antígeno y se dirige a la célula cancerosa, donde se inhibe el crecimiento del cáncer. La célula que expresa un CAR de CD19, por ejemplo, célula T, se administra en combinación con un inhibidor de células B, por ejemplo, un inhibidor de células B descrito en el presente documento.

En algunas modalidades, el inhibidor de CD19 (por ejemplo, una o más células que expresan una molécula de CAR que une a CD19, por ejemplo, una molécula de CAR que une a CD19 descrita en el presente documento) y el inhibidor de células B (por ejemplo, uno o más inhibidores de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3 o ROR1, por ejemplo, tal como se describe en el presente documento) se administran simultáneamente. En algunas modalidades, el inhibidor de CD19 y el inhibidor de células B se infunden en un sujeto simultáneamente, por ejemplo, se mezclan en el mismo volumen de infusión. En otras modalidades, la administración simultánea comprende la administración por separado del inhibidor de CD19 y el inhibidor de células B, por ejemplo, la administración de cada uno se inicia en entre un intervalo de tiempo predeterminado (por ejemplo, entre 15, 30 o 45 minutos el uno del otro).

En algunas modalidades, el inicio de la entrega del inhibidor de CD19 y el inicio de la entrega del inhibidor de células B ocurren con 1, 2, 3, 4, 6, 12, 18 o 24 horas de diferencia, o con 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 60, 80 o 100 días de diferencia. En algunas modalidades, el final de la entrega del inhibidor de CD19 y el final de la entrega del inhibidor de células B ocurren con 1, 2, 3, 4, 6, 12, 18 o 24 horas de diferencia, o con 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 60, 80 o 100 días de diferencia. En algunas modalidades, la superposición en términos de administración entre la entrega del inhibidor de CD19 (por ejemplo, infusión) y el final de la entrega del inhibidor de células B (por ejemplo, infusión) es al menos 1, 2, 3, 4, 5, 10, 15, 20, 25, 30 o 45 minutos.

En algunas modalidades, el inhibidor de células B se administra mientras que las una o más células que expresan una molécula de CAR que se une CD19 están presentes (por ejemplo, en expansión) en el sujeto. En algunas modalidades, el inhibidor de CD19 se administra mientras que las una o más células que expresan una molécula de CAR que se une una o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a están presentes

(por ejemplo, en expansión) en el sujeto.

La invención incluye (entre otras cosas) un tipo de terapia celular en la que las células T se modifican genéticamente para expresar un Receptor Quimérico de Antígeno (CAR) y la célula TCAR se infunde a un sujeto receptor que lo necesite. La célula infundida tiene la capacidad de destruir las células tumorales en el receptor. A diferencia de las terapias con anticuerpos, las células T modificadas con CAR son capaces de reproducirse in vivo, lo que genera la persistencia a largo plazo que puede llevar a un control sostenido del tumor. En diversos aspectos, las células T administradas al paciente, o su progenie, persisten en el paciente durante al menos cuatro meses, cinco meses, seis meses, siete meses, ocho meses, nueve meses, diez meses, once meses, doce meses, trece meses, catorce meses, quince meses, dieciséis meses, diecisiete meses, dieciocho meses, diecinueve meses, veinte meses, veintiún meses, veintidós meses, veintitrés meses, dos años, tres años, cuatro años, o cinco años después de la administración de la célula T al paciente.

La invención también incluye un tipo de terapia celular en la que se modifican células efectoras inmunes, por ejemplo, se modifican células NK o células T, por ejemplo, por ARN transcrito *in vitro*, para expresar transitoriamente un Receptor Quimérico de Antígeno (CAR) y la célula que expresa un CAR (por ejemplo, TCAR) se infunde a un sujeto receptor que lo necesite. La célula infundida tiene la capacidad de destruir las células cancerosas en el receptor. Por lo tanto, en varios aspectos, las células que expresan CAR, por ejemplo, células T, administradas al paciente están presentes durante menos de un mes, por ejemplo, tres semanas, dos semanas, una semana, después de la administración de la célula que expresa CAR, por ejemplo, célula T, al paciente.

Al margen de las limitaciones que impone una teoría particular, la respuesta de inmunidad anti-cancerosa inducida por las células T modificadas con CAR puede ser una repuesta inmunitaria activa o pasiva, o alternativamente puede deberse a una respuesta inmune directa versus indirecta. En un aspecto, las células T transducidas con CAR (por ejemplo, CAR de CD19) exhiben una secreción específica de citoquinas proinflamatorias y una actividad citolítica potente en respuesta a las células cancerosas humanas que expresan el antígeno blanco (por ejemplo, CD19), resisten a la inhibición de antígeno blanco soluble, median la destrucción adyacente y median la regresión de un cáncer humano establecido. Por ejemplo, las células cancerosas sin antígeno dentro de un campo heterogéneo de cáncer que expresa antígeno blanco

pueden ser susceptibles a la destrucción indirecta por las células T redirigidas a antígeno blanco que han reaccionado previamente contra células cancerosas adyacentes positivas al antígeno.

En un aspecto, las células modificadas con CAR de la invención, por ejemplo, células TCAR completamente humanas, pueden ser un tipo de vacuna para inmunización *ex vivo* y/o terapia in vivo en un mamífero. En un aspecto, el mamífero es un humano.

Con respecto a la inmunización *ex vivo,* al menos una de las siguientes situaciones ocurre *in vitro* antes de la administración de la célula en un mamífero: i) expansión de las células, ii) introducción de un ácido nucleico que codifica un CAR a las células o iii) criopreservación de las células.

Los procedimientos *ex vivo* son bien conocidos en la técnica y se discuten en mayor detalle a continuación. Brevemente, se aíslan células mamífero (por ejemplo, un ser humano) y se modifican genéticamente (es decir, se transducen o transfectan in vitro) con un vector que expresa un CAR descrito en el presente documento. La célula modificada con CAR se puede administrar a un receptor mamífero para proporcionar un beneficio terapéutico. El receptor mamífero puede ser humano y la célula modificada con CAR puede ser autóloga con respecto al receptor. Alternativamente, las células pueden ser alogénicas, singénicas o xenogénicas con respecto al receptor.

El procedimiento para la expansión *ex vivo* de células madre hematopoyéticas y células progenitoras descrito en la Patente de Estados Unidos No. 5,199,942, que se incluye en el presente documento a manera de referencia, se puede aplicar a las células de la presente invención. Otros métodos adecuados son conocidos en la técnica, por lo tanto, la presente invención no se limita a ningún método particular de expansión *ex vivo* de células. Brevemente, el cultivo y la expansión *ex vivo* de células T puede comprender: (1) la recolección de células madre y progenitoras hematopoyéticas CD34+ de un mamífero a partir de sangre periférica o de explantes de médula ósea; y (2) la expansión de dichas células *ex vivo*. Además de los factores de crecimiento celular descritos en la Patente de estados Unidos No. 5,199,942, otros factores tales como flt3-L, IL-1, IL-3 y ligando c-kit se pueden usar para el cultivo y la expansión de células.

Además de usar una vacuna basada en células en términos de una inmunización *ex vivo*, los métodos descritos en el presente documento también incluyen composiciones y métodos para

la inmunización *in vivo* para provocar una respuesta inmune dirigida contra un antígeno en un paciente.

Generalmente, las células activadas y expandidas, tal como se describen en el presente documento, se pueden usar en el tratamiento y la prevención de enfermedades que se presentan en individuos inmunocomprometidos. En particular, las células que expresan CAR descritas en el presente documento se usan en el tratamiento de enfermedades, trastornos y afecciones asociadas con la expresión de uno o más antígenos de células B. En ciertos aspectos, las células se usan en el tratamiento de pacientes en riesgo de desarrollar enfermedades, trastornos y afecciones asociadas a la expresión de uno o más antígenos de células B. Por lo tanto, la presente invención proporciona (entre otras cosas) métodos para el tratamiento o la prevención de enfermedades, trastornos y afecciones asociados a la expresión de un antígeno de células B, que comprende administrar a un sujeto que lo necesita una cantidad terapéuticamente eficaz de células que expresan CAR de CD19 descritas en el presente documento en combinación con uno o más inhibidores de células B descritos en el presente documento.

La presente invención también proporciona métodos para inhibir la proliferación o reducir una población de células que expresan CD19, los cuales comprenden contactar una población de células que comprende una célula que expresa CD19 con una célula que expresa un CAR anti-CD19 descrita en el presente documento que se une a la célula que expresa CD19, y contactar la población de células que expresan CD19 con uno o más de los inhibidores de células B descritos en el presente documento. En un aspecto específico, la presente invención proporciona métodos para inhibir la proliferación o reducir la población de células cancerosas que expresan CD19, los cuales comprenden contactar la población de células cancerosas con una célula que expresa un CAR anti-CD19 descrita en el presente documento que se une a la célula que expresa CD19, y contactar la población de células que expresan CD19 con uno o más de los inhibidores de células B descritos en el presente documento. En un aspecto, la presente invención proporciona métodos para inhibir la proliferación o reducir la población de células cancerosas que expresan CD19, los cuales comprenden contactar la población de células cancerosas con una célula que expresa un CAR anti-CD19 descrita en el presente documento que se une a la célula que expresa CD19, y contactar la población de células que expresan CD19 con uno o más de los inhibidores de células B descritos en el presente documento. En ciertos aspectos, la combinación de la célula que expresa un CAR anti-CD19 descrita en el presente

documento y uno o más inhibidores de células B descritos en el presente documento reduce la cantidad, número, monto o porcentaje de células y/o células cancerosas en al menos 25%, al menos 30%, al menos 40%, al menos 50%, al menos 65 %, al menos 75%, al menos 85%, al menos 95% o al menos 99% en un sujeto con o en un modelo animal para cáncer hematológico u otro cáncer asociado a células que expresan CD19 en relación con un control negativo. En un aspecto, el sujeto es humano.

La presente invención también proporciona métodos para inhibir la proliferación o reducir una población de células que comprende células que expresan CD19 y células que expresan un segundo antígeno de células B. En un aspecto, CD19 y el segundo antígeno de células B son expresados por las mismas células de la población. En otro aspecto, CD19 y el segundo antígeno de células B son expresados por subconjuntos diferentes de células de la población. En otro aspecto, CD19 y el segundo antígeno de células B son expresados por subconjuntos superpuestos de células de la población, de forma que algunas células expresan CD19 y el segundo antígeno de células B, y algunas células expresan CD19, y algunas células expresan el segundo antígeno de células B.

La presente invención también proporciona métodos para inhibir la proliferación o reducir una población de células que expresan CD19 y un segundo antígeno de células B, los cuales comprenden (i) contactar una población de células que comprende una célula que expresa CD19 con una célula que expresa un CAR anti-CD19 descrita en el presente documento que se une a la célula que expresa CD19, y (ii) contactar la célula que expresa el segundo antígeno de células B con una célula que expresa un segundo CAR descrito en el presente documento que se une a la célula que expresa el segundo antígeno de células B. En un aspecto específico, la presente invención proporciona métodos para inhibir la proliferación o reducir una población de células cancerosas que expresan CD19 y un segundo antígeno de células B, los cuales comprenden (i) contactar la población de células cancerosas que expresan anti-CD19 con una célula que expresa anti-CD19 descrita en el presente documento que se une a la célula que expresa CD19, y (ii) contactar la población de células que expresan el segundo antígeno que expresa células B con una célula que expresa un segundo CAR descrito en el presente documento que se une al célula que expresa el segundo antígeno de células B. En un aspecto, la presente invención proporciona métodos para inhibir la proliferación o reducir una población de células cancerosas que expresan CD19 y/o un segundo antígeno de células B, los cuales

comprenden (i) contactar la población de células cancerosas que expresan anti-CD19 con una célula que expresa anti-CD19 descrita en el presente documento que se une a la célula que expresa CD19, y (ii) contactar la población de células que expresan el segundo antígeno que expresa células B con una célula que expresa un segundo CAR descrito en el presente documento que se une al célula que expresa el segundo antígeno de células B. En ciertos aspectos, la combinación de la célula que expresa un CAR anti-CD19 descrita en el presente documento y la célula que expresa el segundo CAR descrito en el presente documento reduce la cantidad, número, monto o porcentaje de células y/o células cancerosas en al menos 25%, al menos 30%, al menos 40%, al menos 50%, al menos 65 %, al menos 75%, al menos 85%, al menos 95% o al menos 99% en un sujeto con o en un modelo animal para cáncer hematológico u otro cáncer asociado a células que expresan CD19 y/o las células que expresa el segundo antígeno de células B en relación con un control negativo. En un aspecto, el sujeto es un humano.

La presente invención también proporciona métodos para prevenir, tratar y/o manejar una enfermedad asociada a células que expresan CD19 (por ejemplo, un cáncer hematológico o un cáncer atípico que expresa CD19), los métodos que comprenden administrar a un sujeto que lo necesita una célula que expresa un CAR anti-CD19, la cual se une a la célula que expresa CD19 y a un inhibidor de células B. En un aspecto, el sujeto es humano. Ejemplos no limitativos de trastornos asociados a células que expresan CD19 incluyen trastornos autoinmunes (tales como lupus), trastornos inflamatorios (tales como alergias y asma) y cánceres (tales como cánceres hematológicos o cánceres atípicos que expresan CD19).

La presente invención también proporciona métodos para prevenir, tratar y/o manejar una enfermedad asociada a CD19 y/o células que expresan un segundo antígeno de células B (por ejemplo, un cáncer hematológico o un cáncer atípico que expresa CD19 y/o un segundo antígeno de células B), los métodos que comprenden administrar a un sujeto que lo necesita una célula que expresa un CAR anti-CD19, la cual se une a la célula que expresa CD19 y a un inhibidor de células B.

La presente invención también proporciona métodos para prevenir, tratar y/o manejar una enfermedad asociada a células que expresan CD19, los cuales comprenden administrar a un sujeto que lo necesita una célula TCAR de anti-CD19 de la invención que se une a la célula que expresa CD19. En un aspecto, el sujeto es humano.

La presente invención también proporciona métodos para prevenir recaídas de cáncer asociado a células que expresan CD19, los cuales comprenden administrar a un sujeto que lo necesita un TCAR anti-CD19 de la invención que se une a la célula que expresa CD19. En un aspecto, los métodos comprenden administrar al sujeto que lo necesita una cantidad eficaz de un TCAR anti-CD19 descrito en el presente documento que se une a la célula que expresa CD19 en combinación con una cantidad eficaz de otra terapia.

En un aspecto, la invención se refiere a un método para tratamiento de cáncer en un sujeto. El método comprende administrar al sujeto una célula que expresa un CAR de CD19, por ejemplo, célula T, descrita el presente documento, en combinación con un inhibidor de células B, de manera tal que se trate el cáncer en el sujeto. Un ejemplo de un cáncer que es tratable a través de los métodos descritos en el presente documento es un cáncer asociado a la expresión de CD19. En una modalidad, la enfermedad es un tumor sólido o un tumor líquido. En una modalidad, la enfermedad es un cáncer hematológico, por ejemplo, como se describe en el presente documento.

Indicaciones no relacionadas con cáncer asociadas con la expresión de CD19 incluyen, pero no se limitan a, por ejemplo, enfermedad autoinmune, (por ejemplo, lupus), trastornos inflamatorios (alergia y el asma) y trasplante.

En algunas realizaciones, un cáncer que puede ser tratado con la combinación descrita en el presente documento es el mieloma múltiple. El mieloma múltiple es un cáncer de la sangre, que se caracteriza por la acumulación de un clon de células plasmáticas en la médula ósea. Las terapias actuales para el mieloma múltiple incluyen, pero no se limitan a, tratamiento con lenalidomida, que es un análogo de la talidomida. La lenalidomida tiene actividades que incluyen la actividad anti-tumor, inhibición de la angiogénesis, y la inmunomodulación. En algunas realizaciones, un CAR CD19, por ejemplo, como se describe en el presente documento, se puede utilizar para dirigirse a las células de mieloma. En algunas realizaciones, la combinación descrita en la presente memoria se puede utilizar con una o más terapias adicionales, por ejemplo, tratamiento con lenalidomida.

Las células que expresan CAR descritas en este documento se pueden administrar ya sea solas, o como una composición farmacéutica en combinación con diluyentes y/o con otros componentes, tales como IL-2 u otras citoquinas o poblaciones de células.

Los cánceres hematológicos

Las condiciones del cáncer hematológico son los tipos de cáncer, como leucemia, linfoma y condiciones linfoproliferativos malignos que afectan a la sangre, la médula ósea y el sistema linfático.

En una modalidad, el cáncer hematológico es una leucemia. En una modalidad, el cáncer se selecciona del grupo que consiste en una o más leucemias agudas incluyendo, de manera enunciativa mas no limitativa, por ejemplo, leucemia linfoide aguda de células B ("LLA B"), leucemia linfoide aguda de células T ("LLA T"), linfoma linfocítico pequeño (LLP), leucemia linfoide aguda (LLA); una o más leucemias crónicas incluyendo, de manera enunciativa mas no limitativa, por ejemplo, leucemia mielógena crónica (LMC), leucemia linfocítica crónica (LLC); otros cánceres hematológicos o condiciones hematológicas incluyen, de manera enunciativa mas no limitativa, linfoma de células del manto (LCM), leucemia prolinfocítica de células B, neoplasia blástica de células dendríticas plasmocitoides, linfoma de Burkitt, linfoma difuso de células B grandes, linfoma folicular, leucemia de células pilosas, linfoma folicular de células pequeñas o grandes, afecciones linfoproliferativas malignas, linfomas tipo MALT, linfoma MALT, linfoma de la zona marginal, mieloma múltiple, mielodisplasia y síndrome mielodisplásico, linfoma no Hodgkin, linfoma plasmablástico, neoplasia de células dendríticas plasmocitoides, macroglobulinemia de Waldenstrom y "pre-leucemia", las cuales son una colección diversa de condiciones hematológicas que tienen en común la producción ineficaz (o displasia) de células sanguíneas mieloides, y similares, y a enfermedades asociadas a la expresión de CD19, CD20 o CD22 que incluyen, de manera enunciativa más no limitativa, cánceres atípicos y/o no clásicos, tumores malignos, afecciones pre-cancerosas o enfermedades proliferativas que expresan CD19, CD20 o CD22; y cualquier combinación de las mismas.

La leucemia se puede clasificar como leucemia aguda y leucemia crónica. La leucemia aguda se puede clasificar adicionalmente como leucemia mielógena aguda (LMA) y leucemia linfoide aguda (LLA). La leucemia crónica incluye la leucemia mieloide crónica (LMC) y la leucemia linfoide crónica (LLC). Otras enfermedades relacionadas incluyen síndromes mielodisplásicos (MDS, antes conocido como "pre-leucemia"), que son una colección diversa de afecciones hematológicas que tienen en común la producción ineficaz (o displasia) de células sanguíneas mieloides y el riesgo de transformarse en LMA.

El linfoma es un grupo de tumores de células de la sangre que se desarrollan a partir de

linfocitos. Ejemplos de linfomas incluyen el linfoma no Hodgkin y linfoma de Hodgkin.

En un aspecto, la invención se refiere a un método de tratamiento de un mamífero que padece de linfoma de Hodgkin, el cual comprende administrar al mamífero una cantidad eficaz de células que expresan una molécula de CAR de CD19, por ejemplo, una molécula de CAR de CD19 descrita en el presente documento y un inhibidor de células B.

En un aspecto, las composiciones y las células TCAR o las células NK que expresan CAR de la presente invención son particularmente útiles para el tratamiento de tumores malignos de células B, tales como linfomas no Hodgkin, por ejemplo, DLBCL, linfoma folicular, o CLL.

El linfoma no Hodgkin (LNH) es un grupo de cánceres de linfocitos, formados a partir de cualquiera de las células B o T. LNH ocurre a cualquier edad y con frecuencia se caracterizan por ganglios linfáticos más grandes de lo normal, la pérdida de peso y fiebre. Los diferentes tipos de linfomas no Hodgkin se clasifican como tipos indolentes (de crecimiento lento) y agresivo (de crecimiento rápido). Linfomas no Hodgkin de células B incluyen el linfoma de Burkitt, la leucemia linfocítica crónica / linfoma de linfocitos pequeños (CLL / SLL), Linfoma difuso de células B grandes (DLBCL), linfoma folicular, linfoma de células grandes inmunoblástico, linfoma de células B precursoras linfoblásticas, y el linfoma de células del manto. Ejemplos de linfomas de células T no Hodgkin incluyen micosis fungoide, linfoma anaplásico de células grandes, y precursor de linfoma T-linfoblástica. Los linfomas que se producen después de médula ósea o de células madre son típicamente linfomas no Hodgkin de células B. Véase, por ejemplo, Maloney. NEJM. 366.21 (2012): 2008-16.

El linfoma difuso de células B grandes (DLBCL) es una forma de linfoma no Hodgkin que se desarrolla a partir de células B. El DLBCL es un linfoma agresivo que puede surgir en los ganglios linfáticos o en el exterior del sistema linfático, por ejemplo, en el tracto gastrointestinal, testículos, tiroides, piel, mama, hueso, o el cerebro. Se observan comúnmente tres variantes de la morfología celular en DLBCL: centroblástico, inmunoblástico, y anaplásico. La morfología centroblástico es más común y tiene la apariencia de linfocitos de mediano a gran tamaño con citoplasma mínimo. Hay varios subtipos de DLBCL. Por ejemplo, linfoma primario del sistema nervioso central es un tipo de DLBCL que sólo afecta al cerebro que se llama y es tratado de manera diferente que el DLBCL que afecta a áreas fuera del cerebro. Otro tipo de DLBCL es el linfoma mediastínico primario de células B, que a menudo se produce en los pacientes más

jóvenes y crece rápidamente en el pecho. Los síntomas de DLBCL incluyen una hinchazón rápida indolora en el cuello, las axilas o la ingle, que es causada por ganglios linfáticos agrandados. En algunos objetos, la hinchazón puede ser dolorosa. Otros síntomas de DLBCL incluyen sudores nocturnos, fiebre sin explicación, y la pérdida de peso. Aunque la mayoría de los pacientes con DLBCL son adultos, esta enfermedad se produce a veces en los niños. El tratamiento para el DLBCL incluye quimioterapia (por ejemplo, ciclofosfamida, doxorrubicina, vincristina, prednisona, etopósido), los anticuerpos (por ejemplo, Rituxan), radiación, o trasplantes de células madre.

El linfoma folicular es un tipo de linfoma no Hodgkin y es un linfoma de centro folículo células B (centrocitos y centroblastos), que tiene al menos un patrón parcialmente folicular. Las células de linfoma folicular expresan los marcadores CD10, CD19, CD20, y CD22 de células B. Las células de linfoma folicular son comúnmente CD5negativas. Morfológicamente, un tumor de linfoma folicular se compone de folículos que contienen una mezcla de centrocitos (también llamadas células escindido centro de folículo o células pequeñas) y centroblastos (también llamado células grandes no hendidas centro de folículo o células grandes). Los folículos están rodeados por células no malignas, en su mayoría células T. Los folículos predominantemente contienen centrocitos con una minoría de centroblastos.La Organización Mundial de la Salud (OMS) ordenó morfológicamente los grados de la enfermedad de la siguiente manera: grado 1 (<5 centroblastos por campo de alta potencia (hpf), grado 2 (6-15 centroblastos / hpf) ; grado 3 (> 15 centroblastos / hpf) el grado 3 se subdivide en los siguientes grados: grado 3A (centrocitos todavía presentes); grado 3B (los folículos se componen casi en su totalidad de centroblastos) el tratamiento del linfoma folicular incluye quimioterapia, por ejemplo, agentes alquilantes, análogos de nucleósidos, regímenes que contienen antraciclina, por ejemplo, una terapia combinada llamada CHOP-ciclofosfamida, doxorrubicina, vincristina, prednisona / prednisolona, anticuerpos (por ejemplo, rituximab), radioinmunoterapia, y el trasplante de células madre hematopoyéticas.

CLL es una enfermedad maligna de células B caracterizada por la proliferación neoplásica de células y la acumulación en la médula ósea, sangre, ganglios linfáticos y el bazo. La mediana de edad al momento del diagnóstico de la LLC es de unos 65 años. Los tratamientos actuales incluyen quimioterapia, radioterapia, terapia biológica, o trasplante de médula ósea. A veces los síntomas son tratados quirúrgicamente (por ejemplo, la eliminación de la

esplenectomía de bazo agrandado) o por radioterapia (por ejemplo, aumento de volumen de los ganglios linfáticos). Los agentes quimioterapéuticos para el tratamiento de CLL incluyen, por ejemplo, fludarabina, 2-clorodesoxiadenosina (cladribina), clorambucilo, vincristina, pentostatina, ciclofosfamida, alemtuzumab (Campath-1H), doxorubicina y prednisona. La terapia biológica para la CLL incluye anticuerpos, por ejemplo, el alemtuzumab, rituximab, y ofatumumab; así como tratamientos inhibidores de la tirosina quinasa. Un número de criterios puede ser usado para clasificar etapa de CLL, por ejemplo, el sistema de Rai o Binet. El sistema Rai describe la LLC tiene cinco etapas: Etapa 0 en que sólo está presente linfocitosis; la etapa I donde la linfadenopatía está presente; fase II, donde la esplenomegalia, linfadenopatía, o ambos están presentes; fase III donde la anemia, organomegalia, o ambos están presentes (la progresión se define por la pérdida de peso, fatiga, fiebre, organomegalia masiva, y un rápido aumento del número de linfocitos); y la etapa IV donde la anemia, trombocitopenia, organomegalia, o una combinación de los mismos están presentes. En el marco del sistema de estadificación Binet, hay tres categorías: etapa A, donde la linfocitosis está presente y menos de tres nódulos linfáticos están agrandados (esta etapa es inclusiva de todas las etapas de pacientes Rai 0, uno con un medio de Rai pacientes en estadio I, y un tercio de la etapa II Rai pacientes); etapa B, donde hay tres o más ganglios linfáticos involucrados; y la etapa C en el que la anemia o trombocitopenia, o ambos están presentes. Estos sistemas de clasificación se pueden combinar con las mediciones de la mutación de los genes de inmunoglobulina para proporcionar una caracterización más precisa del estado de la enfermedad. La presencia de genes de inmunoglobulina mutados se correlaciona con un mejor pronóstico.

En otra realización, las células que expresan CAR de la presente invención se utilizan para tratar cánceres o leucemias, por ejemplo, con las células madre de la leucemia. Por ejemplo, las células madre de la leucemia son células de leucemia $CD34^+/CD38^-$.

Enfermedades y/o trastornos asociados a *CD20 y CD22*

La presente invención proporciona, entre otras cosas, composiciones y métodos para tratar una enfermedad asociada con la expresión de CD20 o CD22 o una condición asociada con las células que expresan CD20 o CD22, incluyendo, por ejemplo, una enfermedad proliferativa tal como cáncer o un tumor maligno o una afección precancerosa ; o una indicación relacionada con el cáncer asociado con las células que expresan CD20 o CD22. En un aspecto, un cáncer

asociado con la expresión de CD22 es un cáncer hematológico, por ejemplo, un cáncer hematológico que se describe aquí.

Indicaciones no relacionadas con cáncer asociadas con la expresión de CD20 o CD22 también pueden ser incluidos. indicaciones no relacionadas con cáncer asociadas con la expresión de CD20 o CD22 incluyen, pero no se limitan a, por ejemplo, enfermedad autoinmune, (por ejemplo, lupus, artritis reumatoide, anemia hemolítica autoinmune esclerosis múltiple, aplasia pura de células rojas, púrpura trombocitopénica idiopática, síndrome de Evans , vasculitis, trastornos de la piel bullosa, diabetes mellitus tipo 1, síndrome de Sjogren, la encefalitis anti-receptor de NMDA y la enfermedad de Devic, oftalmopatía de Graves, y pancreatitis autoinmunitaria), trastornos inflamatorios (alergia y asma) y de órganos sólidos o trasplante de células hematopoyéticas.

Las composiciones y métodos descritos en este documento pueden usarse para tratar enfermedades hematológicas, incluyendo, pero no limitado a mielodisplasia, anemia, hemoglobinuria paroxística nocturna, anemia aplásica, adquirió anemia pura de glóbulos rojos, anemia Diamon-Blackfan, anemia de Fanconi, citopenia, trombocitopenia amegakaryotic, trastornos mieloproliferativos , policitemia vera, trombocitosis esencial, mielofibrosis, hemoglobinopatías, anemia de células falciformes, β talasemia mayor, entre otros.

En un aspecto, la invención proporciona métodos para tratar una enfermedad asociada con la expresión de CD22. En un aspecto, la invención proporciona métodos para tratar una enfermedad en la que una parte del tumor es negativo para CD20 o CD22 y una parte del tumor es positivo para CD20 o CD22. Por ejemplo, el CAR de la invención es útil para el tratamiento de sujetos que se han sometido a tratamiento para una enfermedad asociada con la expresión de CD20 o CD22, en el que el tema que ha sido objeto de tratamiento relacionado con la expresión de CD20 o CD22 exhibe una enfermedad asociada con la expresión de CD20 o CD22.

En un aspecto, la invención se refiere a un método para inhibir el crecimiento de un CD20 o células tumorales que expresan CD22, comprende poner en contacto la célula tumoral con una célula CAR CD20 o CD22 (por ejemplo, células T o células NK) de la presente invención de modo que el CAR es activado en respuesta al antígeno y se dirige a la célula de cáncer, en donde el crecimiento del tumor es inhibido.

En un aspecto, la invención se refiere a un método para tratar cáncer en un sujeto. El método comprende administrar al sujeto una célula que expresa CAR CD20 o CD22 (por ejemplo, células T o células NK) de la presente invención tal que el cáncer es tratado en el sujeto. Un ejemplo de un cáncer que se puede tratar por las células que expresan CAR CD20 o CD22 (por ejemplo, células T o células NK) de la invención es un cáncer asociado con la expresión de CD20 o CD22. Un ejemplo de un cáncer que se puede tratar por la célula que expresa el CAR CD20 o CD22 (por ejemplo, células T o células NK) de la invención incluyen pero no se limita a un cáncer hematológico que se describe aquí.

La invención incluye un tipo de terapia celular donde las células (por ejemplo, células T o células NK) se modifican genéticamente para expresar un receptor quimérico de antígeno (CAR) y la célula que expresa CAR (por ejemplo, células T o células NK) se infunde a un destinatario en necesidad del mismo. La célula infundida es capaz de matar las células tumorales en el receptor. A diferencia de las terapias de anticuerpos, las células CAR-modificadas (por ejemplo, células T o células NK) son capaces de replicarse in vivo si resulta en persistencia a largo plazo que pueden dar lugar a control tumoral sostenido. En diversos aspectos, las células (por ejemplo, células T o células NK) administradas al paciente, o su progenie, persisten en el paciente durante al menos cuatro meses, cinco meses, seis meses, siete meses, ocho meses, nueve meses, diez meses, once meses, doce meses, trece meses, catorce meses, quince meses, dieciséis meses, diecisiete meses, dieciocho meses, diecinueve meses, veinte meses, veintiún meses, veintidós meses, veintitrés meses, dos años, tres años, cuatro años, o cinco años después de la administración de la célula T al paciente.

La invención incluye también un tipo de terapia celular donde se modifican las células efectoras inmunes, por ejemplo, las células NK o células T, por ejemplo, in vitro transcrito de ARN, para expresar transitoriamente un receptor quimérico de antígeno (CAR) y el CAR que expresan (por ejemplo, célula T CAR o células NK que expresan CAR) se infunde a un receptor que lo necesite. La célula infundida es capaz de matar las células de cáncer en el receptor. Por lo tanto, en varios aspectos, las células que expresan CAR, por ejemplo, células T o células NK, se administran al paciente, está presente en menos de un mes, por ejemplo, tres semanas, dos semanas, una semana después de la administración de la célula que expresa CAR, por ejemplo, las células T o células NK, para el paciente.

Sin desear estar ligado por ninguna teoría en particular, la respuesta de inmunidad anti-tumor provocada por las células CAR-modificadas (por ejemplo, células T o células NK) puede ser una respuesta inmune activa o pasiva, o alternativamente puede ser debido a una respuesta inmune directa vs indirecta. En un aspecto, las células CAR transducidas (por ejemplo, células T o células NK) muestran la secreción de citoquinas proinflamatorias específicas y la actividad citolítica potente en respuesta a las células de cáncer humano que expresan CD20 o CD22, resisten la inhibición CD20 o CD22 soluble, median la eliminación y mediar la regresión de un tumor humano establecido. Por ejemplo, los antígenos de células tumorales dentro de un campo heterogéneo de un tumor que expresa CD20 o CD22 pueden ser susceptibles a la destrucción indirecta por células T CD20 o CD22-redirigidas que ha reaccionado previamente contra las células cancerosas positivas al antígeno adyacentes.

En un aspecto, las células CAR-modificadas (por ejemplo, células T o células NK) de la invención, por ejemplo, las células que expresan CAR plenamente humanos, pueden ser un tipo de vacuna ex vivo lara la inmunización y/o terapia in vivo en un mamífero . En un aspecto, el mamífero es un humano.

Con respecto a la inmunización ex vivo, ocurre al menos una de las siguientes situaciones in vitro antes de la administración de la célula en un mamífero: i) expansión de las células, ii) la introducción de un ácido nucleico que codifica un CAR a las células o iii) la criopreservación de la Células.

Los procedimientos ex in vivo son bien conocidos en la técnica y se discuten con más detalle a continuación. Brevemente, las células se aíslan de un mamífero (por ejemplo, un ser humano) y son modificadas genéticamente (es decir, se transducen o transfectan in vitro) con un vector que expresa un CAR descrito en este documento. La célula CAR-modificada puede ser administrada a un receptor mamífero para proporcionar un beneficio terapéutico. El receptor mamífero puede ser la célula CAR-modificada puede ser autólogo con respecto al receptor humano y. Alternativamente, las células pueden ser alogénicas, singénicas o xenogénicas con respecto al receptor.

El procedimiento para la expansión ex vivo de células madre y hematopoyéticas progenitoras se describe en la patente de EE.UU.. No. 5.199.942, incorporada aquí por referencia, se puede aplicar a las células de la presente invención. Otros métodos adecuados son conocidos en la técnica, por lo tanto, la presente invención no se limita a ningún método

particular de la expansión ex vivo de las células. Brevemente, ex vivo cultivo y expansión de las células T comprende: (1) la recolección de células madre y progenitoras hematopoyéticas CD34 + a partir de un mamífero de la cosecha de sangre periférica o de médula ósea explantes; y (2) expandir tales células ex vivo. Además de los factores de crecimiento celular descritos en la patente de EE.UU.. No. 5.199.942, otros factores tales como flt3L, IL-1, IL-3 y el ligando c-kit, se puede utilizar para el cultivo y la expansión de las células.

Además de usar una vacuna basada en células en términos de inmunización ex vivo, la presente invención también proporciona composiciones y métodos para la inmunización in vivo para provocar una respuesta inmune dirigida contra un antígeno en un paciente.

Generalmente, las células activadas y expandidas como se describe en el presente documento se pueden utilizar en el tratamiento y prevención de enfermedades que surgen en individuos inmunocomprometidos. En particular, las células CAR-modificadas (por ejemplo, células T o células NK) de la invención se utilizan en el tratamiento de enfermedades, trastornos y afecciones asociadas con la expresión de CD20 o CD22. En ciertos aspectos, las células de la invención se utilizan en el tratamiento de pacientes en riesgo de desarrollar enfermedades, trastornos y afecciones asociadas con la expresión de CD20 o CD22. Por lo tanto, la presente invención proporciona métodos para el tratamiento o la prevención de enfermedades, trastornos y afecciones asociadas con la expresión de CD20 o CD22 que comprende administrar a un sujeto en necesidad del mismo, una cantidad terapéuticamente eficaz de las células CAR-modificadas (por ejemplo, células T o células NK) de la invención.

En un aspecto, las células que expresan CAR de la invención pueden ser utilizadas para tratar una enfermedad proliferativa, tal como un cáncer o tumor maligno o una condición precancerosa. En un aspecto, un cáncer asociado con la expresión de CD20 o CD22 es un preleucemia hematológica cáncer, trastorno hiperproliferativo, hiperplasia o displasia, que se caracteriza por el crecimiento anormal de células.

Las células CAR-modificadas de la presente invención se pueden administrar ya sea solas, o como una composición farmacéutica en combinación con diluyentes y/o con otros componentes, tales como IL-2 u otras citoquinas o las poblaciones de células.

La presente invención también métodos para inhibir la proliferación o la reducción de una población de células que expresan CD20 o CD22, los métodos comprenden poner en

contacto una población de células que comprenden células que expresan CD20 o CD22 con una célula de la invención que expresa CAR CD20 o CD22 que se une a las células que expresan CD20 o CD22. En un aspecto específico, la presente invención proporciona métodos para inhibir la proliferación o la reducción de la población de células cancerosas que expresan CD20 o CD22, los métodos comprenden poner en contacto la población de células cancerosas que expresan CD22 o CD20 con una célula de la invención que expresa CAR CD20 o CD22 que se une a las células que expresan CD20 o CD22. En un aspecto, la presente invención proporciona métodos para inhibir la proliferación o la reducción de la población de células cancerosas que expresan CD20 o CD22, los métodos comprenden poner en poner en contacto la población de células cancerosas que expresan CD22 o CD20 con una célula de la invención que expresa CAR CD20 o CD22 de la invención que se unen al CD20 o CD22 de las células que los expresan. En ciertos aspectos, la célula que expresa el CAR CD20 o CD22 de la invención reduce la cantidad, número, cantidad o porcentaje de células y/o células de cáncer de por lo menos 25%, al menos 30%, al menos 40%, al menos 50% , al menos 65%, al menos 75%, al menos 85%, al menos 95%, o al menos 99% en un sujeto con o modelo animal para la enfermedad maligna de células B u otro cáncer asociado con que expresan CD20 o CD22 relativa a un control negativo. En un aspecto, el sujeto es un humano.

La presente invención proporciona métodos para la prevención de la recaída de cáncer asociado con células que expresan CD20 o CD22, los métodos comprenden administrar a un sujeto en necesidad del mismo una célula que expresa CAR CD20 o CD22 de la invención que se une a las células que expresan CD20 o CD22. En un aspecto, los procedimientos comprenden la administración al sujeto en necesidad del mismo una cantidad eficaz de una célula que expresa CAR CD20 o CD22 que se describe en este documento que se une a las células que expresan CD20 o CD22 en combinación con una cantidad eficaz de otra terapia.

En algunas realizaciones, la célula que expresa CD22 expresa CD19, CD123, FLT-3, ROR-1, CD79b, CD179b, CD79a, CD10, CD34, y/o CD20. En ciertas realizaciones, la célula que expresa CD22 expresa CD19. En algunas realizaciones, la célula que expresa CD22 no expresa CD19. En algunas realizaciones, la célula que expresa CD20 expresa CD19, CD123, FLT-3, ROR-1, CD79b, CD179b, CD79a, CD10, CD34, y/o CD22. En ciertas realizaciones, la célula que expresa CD20 expresa CD19. En algunas realizaciones, la célula que expresa CD20 no expresa CD19.

En algunas realizaciones, el sujeto es un no respondedor a la terapia CAR CD19. En algunas realizaciones, el sujeto es un respondedor parcial a la terapia CAR CD19. En algunas realizaciones, el sujeto es un respondedor completo a la terapia CAR CD19. En algunas realizaciones, el sujeto es un no-reincidente a la terapia CAR CD19. En algunas realizaciones, el sujeto es un reincidente parcial a la terapia CAR CD19. En algunas realizaciones, el sujeto es un reincidente completoa a la terapia CAR CD19.

En algunas realizaciones, un cáncer u otra condición que antes era sensible al tratamiento con células CD19 que expresan CAR-no expresa CD19. En algunas realizaciones, un cáncer u otra condición que antes era sensible al tratamiento con células CAR que expresan CD19 tiene un 10%, 20%, 30%, 40%, 50% o más de reducción en los niveles de expresión CD19 en relación con cuando el cáncer o otra condición era sensible al tratamiento con las células que expresan CAR CD19. En algunas realizaciones, un cáncer u otra condición que antes era sensible al tratamiento con células CD19 que expresan CAR-expresa CD20, CD22, CD123, o cualquier combinación de los mismos.

En algunas realizaciones, la célula que expresa el CAR CD20 o CD22 de la invención se administra después de la reincidencia de un cáncer u otra condición previamente tratada con células que expresan CAR CD19. En algunas formas de realización, una célula expresa CAR CD19 y se administran simultáneamente una célula que expresa CAR CD20 o CD22, como se describe en el presente documento.

La ablación de médula ósea

En un aspecto, la presente invención proporciona composiciones y métodos para la ablación de médula ósea. Por ejemplo, en un aspecto, la invención proporciona composiciones y métodos para la erradicación de al menos una porción de la médula ósea existente en un sujeto. Se describe en este documento que, en ciertos casos, célula que expresa el CAR CD19, C20, o CD22 que comprende un CAR de la presente invención erradica células progenitoras mieloides de la médula ósea CD19 C20, o CD22, positivas.

En un aspecto, la invención proporciona un método de ablación de la médula ósea que comprende administrar una célula que expresa CAR CD19, C20, o CD22 (por ejemplo, células

T o células NK) de la invención a un sujeto en necesidad de la ablación de la médula ósea. Por ejemplo, el presente método se puede utilizar para erradicar algunos o todos de la médula ósea existente de un sujeto que tiene una enfermedad o trastorno en el que el trasplante de médula ósea o de reacondicionamiento de médula ósea es una estrategia beneficiosa de tratamiento. En un aspecto, el método de ablación de la médula ósea de la invención, que comprende la administración de una, célula que expresa CAR CD19 C20, o CD22 (por ejemplo, células T o células NK) que se describen en otra parte en este documento, se realiza en un sujeto antes de trasplante de médula ósea. Por lo tanto, en un aspecto, el método de la invención proporciona un régimen de acondicionamiento celular antes de la médula ósea o trasplante de células madre. En un aspecto, el trasplante de médula ósea comprende el trasplante de una célula madre. El trasplante de médula ósea puede comprender el trasplante de células autólogas o alogénicas.

La presente invención proporciona un método para tratar una enfermedad o trastorno que comprende la administración de una célula que expresa CAR CD19, C20, o CD22 (por ejemplo, células T o células NK) de la invención para erradicar al menos una porción de la médula ósea existente. El método puede utilizarse como al menos una parte de un régimen de tratamiento para el tratamiento de cualquier enfermedad o trastorno en el que el trasplante de médula ósea es beneficioso. Es decir, el presente método puede ser utilizado en cualquier sujeto en necesidad de un trasplante de médula ósea. En un aspecto, la ablación de médula ósea que comprende la administración de una, célula que expresa CAR CD19 C20, o CD22 (por ejemplo, células T o células NK) es útil en el tratamiento de AML. En ciertos aspectos, la médula ósea de ablación por medio del presente método es útil en el tratamiento de un cáncer hematológico, un tumor sólido, una enfermedad hematológica, un trastorno metabólico, VIH, HTLV, un trastorno de almacenamiento lisosomal, y una inmunodeficiencia.

Las composiciones y métodos descritos aquí se pueden usar para erradicar al menos una porción de la médula ósea existente para el tratamiento de cánceres hematológicos incluyendo, pero no limitados a, los cánceres descritos en este documento, por ejemplo, leucemia, linfoma, mieloma, ALL, AML, CLL, CML, linfoma Hodgkin, linfoma no Hodgkin (por ejemplo, el DLBCL o linfoma folicular) y mieloma múltiple.

En un aspecto, la presente invención proporciona un método para tratar cáncer que comprende la médula ósea acondicionada, donde al menos una porción de la médula ósea del sujeto que se erradique por la célula CAR CD22 (por ejemplo, células T o células NK) de la

invención. Por ejemplo, en ciertos casos, la médula ósea del sujeto comprende una célula maligna precursora que puede ser dirigido y se elimina por la actividad de la célula CAR CD20 o CD22 (por ejemplo, células T o células NK). En un aspecto, una terapia de acondicionamiento de la médula ósea que comprende administrar una médula ósea o trasplante de células madre para el sujeto después de la erradicación de la médula ósea nativa. En un aspecto, la terapia de reacondicionamiento de la médula ósea se combina con uno o más de otras terapias contra el cáncer, incluyendo, pero no limitado a las terapias anti-tumorales CAR, la quimioterapia, la radiación, y similares.

En un aspecto, la erradicación de las células que expresan CAR CD19, CD20, o CD22 administradas puede ser necesaria antes de la infusión de la médula ósea o trasplante de células madre. La erradicación de la célula que expresa CAR CD19 CD20, o CD22 (por ejemplo, células T o células NK) se puede realizar usando cualquier estrategia o tratamiento adecuado, incluyendo, pero no limitado a, el uso de un gen suicida, la persistencia CAR limitada, usando ARN que codifica los CAR, o modalidades de células T anti- que incluyen anticuerpos o quimioterapia.

Terapias de combinación

La combinación de un CAR descrita en el presente documento (por ejemplo, una célula que Expresa un CAR CD19, CAR CD20 o CAR CD22, por ejemplo, tal como se describe en el presente documento) se puede usar en combinación con otros agentes y terapias conocidos.

Una célula que expresa un CAR de CD29 descrita en el presente documento, (por ejemplo, una célula que Expresa un CAR CD19, CAR CD20 o CAR CD22) opcionalmente, el uno o más inhibidores de células B y/o el al menos un agente terapéutico adicional se pueden administrar simultáneamente, en la misma composición o en composiciones separadas, o de manera secuencial. Para la administración secuencial, la célula que expresa un CAR descrita en el presente documento (por ejemplo, una célula que expresa un CAR de CD19, CAR de CD20 o CAR de CD22) se puede administrar primero y luego se puede administrar el agente adicional, o el orden de administración puede ser invertido.

La terapia con CAR y/u otros agentes (tal como una segunda terapia con CAR),

procedimientos o modalidades terapéuticos se puede administrar durante períodos en los que la enfermedad está activa, o durante períodos de remisión o en los que la enfermedad está menos activa. La terapia con CAR se puede administrar antes de administrar el otro tratamiento, de manera simultánea con el otro tratamiento, después de administrar el otro tratamiento o durante la remisión de la enfermedad.

Por ejemplo, en algunas modalidades, la terapia con CAR se administra a un sujeto que tiene una enfermedad asociada con la expresión de CD19, CD20 o CD22 por ejemplo, un cáncer. El sujeto puede ser sometido a ensayo para detectar indicadores de la capacidad de respuesta o recaída. En algunas modalidades, cuando el sujeto muestra uno o más signos de recaída, por ejemplo, un desplazamiento del marco y/o codón de terminación prematuro en CD19, se administra una terapia adicional. En algunas modalidades, la terapia adicional es un inhibidor de células B. La terapia con CD19 se puede continuar (por ejemplo, cuando todavía hay algunas células cancerosas que expresan CD19 detectables en el sujeto) o se puede interrumpir (por ejemplo, cuando un análisis de riesgo-beneficio favorece la interrupción del tratamiento).

Cuando se administra junto con otro tratamiento, la terapia con CAR y el agente adicional (por ejemplo, el segundo o tercer agente), o todos, se pueden administrar en una cantidad o una dosis mayor, menor o igual a la cantidad o dosis de cada agente cuando se usa individualmente, por ejemplo, como una monoterapia. En ciertas modalidades, la cantidad o la dosis administrada de la terapia con CAR, el agente adicional (por ejemplo, el segundo o tercer agente), o todos, es menor (por ejemplo, al menos 20 %, al menos 30 %, al menos 40 % o al menos 50 % menor) que la cantidad o la dosis de cada agente cuando se usa individualmente, por ejemplo, como una monoterapia. En otras modalidades, la cantidad o la dosis de la terapia con CAR, el agente adicional (por ejemplo, el segundo o tercer agente), o todos, que produce un efecto deseado (por ejemplo, tratamiento del cáncer) es menor (por ejemplo, al menos 20 %, al menos 30 %, al menos 40 % o al menos 50 % menor) que la cantidad o la dosis requerida de cada agente cuando se usa de manera individual, por ejemplo, como una monoterapia, para conseguir el mismo efecto terapéutico.

En algunas modalidades, uno o más de los agentes terapéuticos en la terapia de combinación es una molécula de anticuerpo. Los antígenos de cáncer se pueden seleccionar como blanco con terapia de anticuerpos monoclonales. Se ha demostrado que la terapia con

anticuerpos monoclonales (mAb) tiene potentes efectos antitumorales a través de múltiples mecanismos, incluyendo la citotoxicidad dependiente de complementos (CDC), la citotoxicidad celular dependiente de anticuerpos (ADCC) y la inhibición celular directa o los efectos inductores de apoptosis en células tumorales que sobre-expresan las moléculas blanco.

En otros aspectos, la combinación de la célula que expresa un CAR de CD19 descrita en el presente documento (por ejemplo, una célula que expresa un CAR CD20, un CAR CD22, o unCAR CD19, opcionalmente en combinación con uno o más inhibidores de células B) se puede usar un régimen de tratamiento en combinación con cirugía, quimioterapia, radiación, un inhibidor de la vía de mTOR, agentes inmunosupresores, tales como ciclosporina, azatioprina, metotrexato, micofenolato y FK506, anticuerpos, u otros agentes inmunoablativos tales como CAMPATH, anticuerpos anti-CD3 u otras terapias con anticuerpos, citoxina, fludarabina, ciclosporina, FK506, rapamicina, ácido micofenólico, esteroides, FR901228, citoquinas e irradiación, vacuna de péptidos, como los que se describen en Izumoto et al. 2008 J Neurosurg 108: 963-971.

En una modalidad, la combinación de una célula que expresa un CAR de CD19, CD20 o CD22 descrita en el presente documento (por ejemplo, y uno o más inhibidores de células B) puede ser usada en combinación con un agente quimioterapéutico. Los agentes quimioterapéuticos ejemplares incluyen antraciclinas (por ejemplo, doxorrubicina (por ejemplo, doxorubicina liposomal)); alcaloides de la vinca (por ejemplo, vinblastina, vincristina, vindesina, vinorelbina); agentes alquilantes (por ejemplo, ciclofosfamida, decarbazina, melfalán, ifosfamida, temozolomida); anticuerpos de células del sistema inmune (por ejemplo, alemtuzumab, gemtuzumab, rituximab, tositumomab); antimetabolitos (incluyendo, por ejemplo, antagonistas del ácido fólico, análogos de pirimidina; análogos de purina e inhibidores de adenosina desaminasa (por ejemplo, fludarabina)); agonistas de la proteína relacionada con TNFR inducida por glucocorticoides (GITR); inhibidores de proteasoma (por ejemplo, aclacinomicina A, gliotoxina o bortezomib); inmunomoduladores, tales como talidomida o un derivado de la talidomida (por ejemplo, lenalidomida).

Los agentes quimioterapéuticos generales considerados para uso en terapias de combinación incluyen anastrozol (Arimidex®), bicalutamida (Casodex®), sulfato de bleomicina (Blenoxane®), busulfano (Myleran®), busulfano en inyecciones (Busulfex®), capecitabina (Xeloda®), N4-pentoxicarbonilo-5-desoxi-5-fluorocitidina, carboplatino (Paraplatin®),

carmustina (BiCNU®), clorambucilo (Leukeran®), cisplatino (Platinol®), cladribina (Leustatin®), ciclofosfamida (Cytoxan® o Neosar®), citarabina, citosina arabinósido (Cytosar-U®), inyección liposomal de citarabina (DepoCyt®), dacarbazina (DTIC-Dome®), dactinomicina (Actinomycin D, Cosmegan), clorhidrato de daunorubicina (Cerubidine®), inyección liposomal de citrato de daunorubicina (DaunoXome®), dexametasona, docetaxel (Taxotere®, US 2004073044), clorhidrato de doxorrubicina (Adriamycin®, Rubex®), etopósido (Vepesid®), fosfato de fludarabina (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), flutamida (Eulexin®), tezacitibina, Gemcitabina (difluorodeoxycitidina), hidroxiurea (Hydrea®), Idarrubicina (Idamycin®), ifosfamida (IFEX®), irinotecan (Camptosar®), L-asparaginasa (ELSPAR®), leuvocorina cálcica, melfalan (Alkeran®), 6-mercaptopurina (Purinethol®), metotrexato (Folex®), mitoxantrona (Novantrone®), mylotarg, paclitaxel (Taxol®), nab-paclitaxel (Abraxane®), phoenix (Yttrium90/MX- DTPA), pentostatina, polifeprosan 20 con implante de carmustina (Gliadel®), citrato de tamoxifeno (Nolvadex ®), teniposida (Vumon®), 6-tioguanina, tiotepa, tirapazamina (Tirazone®), clorhidrato de topotecan para inyección (Hycamptin®), vinblastina (Velban®), vincristina (Oncovin®) y vinorelbina (Navelbine®).

El tratamiento con una combinación de un agente quimioterapéutico y una célula que expresa una molécula de CAR descrito en este documento puede ser utilizado para tratar un cáncer hematológico en el presente documento se describe, por ejemplo, AML. En formas de realización, la combinación de un agente quimioterapéutico y una célula que expresa un CAR es útil para la orientación, por ejemplo, matando a, las células madre de cáncer, por ejemplo, células madre leucémicas, por ejemplo, en sujetos con AML. En formas de realización, la combinación de un agente quimioterapéutico y una célula CAR-expresión es útil para el tratamiento de la enfermedad residual mínima (MRD). MRD se refiere al pequeño número de células cancerosas que quedan en un sujeto durante el tratamiento, por ejemplo, quimioterapia, o después del tratamiento. MRD es a menudo una de las principales causas de recaída. La presente invención proporciona un método para tratar el cáncer, por ejemplo, MRD, que comprende la administración de un agente quimioterapéutico en combinación con una célula que expresa CAR, por ejemplo, como se describe en el presente documento.

En una realización, el agente quimioterapéutico se administra antes de la administración de la célula que expresa una molécula de CAR, por ejemplo, una molécula de CAR se describe aquí. En regímenes de quimioterapia donde se desea más de una administración del agente

quimioterapéutico, el régimen de quimioterapia se inició o finalizó antes de la administración de una célula que expresa una molécula de CAR, por ejemplo, una molécula de CAR se describe aquí. En realizaciones, el agente quimioterapéutico se administra al menos 1 día, 2 días, 3 días, 4 días, 5 días, 6 días, 7 días, 8 días, 9 días, 10 días, 11 días, 12 días, 13 días, 14 días, 15 días, 20 días, 25 días o 30 días antes de la administración de la célula que expresa la molécula de CAR. En realizaciones, el régimen de quimioterapia se inició o finalizó al menos 1 día, 2 días, 3 días, 4 días, 5 días, 6 días, 7 días, 8 días, 9 días, 10 días, 11 días, 12 días, 13 días , 14 días, 15 días, 20 días, 25 días o 30 días antes de la administración de la célula que expresa la molécula de CAR. En formas de realización, el agente quimioterapéutico es un agente quimioterapéutico que aumenta la expresión de CD19, CD20, o CD22 en las células cancerosas, por ejemplo, las células tumorales, por ejemplo, en comparación con la expresión en células normales o no cancerosas. La expresión puede determinarse, por ejemplo, por tinción inmunohistoquímica o citometría de flujo análisis. Por ejemplo, el agente quimioterapéutico es la citarabina (Ara-C).

Los agentes anti-cáncer de especial interés para las combinaciones con los compuestos de la presente invención incluyen: antimetabolitos; fármacos que inhiben o bien la calcineurina fosfatasa dependiente de calcio o la p70S6 quinasa FK506) o inhiben la p70S6 quinasa; agentes alquilantes; inhibidores de mTOR; inmunomoduladores; antraciclinas; alcaloides de la vinca; inhibidores de proteosoma; agonistas GITR; inhibidores de la tirosina proteína fosfatasa; un inhibidor de CDK4 quinasa; un inhibidor de quinasa BTK; un inhibidor de quinasa MKN; un inhibidor de la quinasa DGK; o un virus oncolítico.

antimetabolitos incluyen a modo de ejemplo, sin limitación, antagonistas del ácido fólico (también denominado aquí como antifolatos), análogos de pirimidina, análogos de purina e inhibidores de adenosina deaminasa): metotrexato (Rheumatrex®, Trexall®), 5-fluorouracilo (Adrucil®, Efudex®, Fluoroplex ®), floxuridina (FUDF®), citarabina (Cytosar-U®, Tarabine PFS), 6-mercaptopurina (Puri-Nethol®)), 6-tioguanina (thioguanine Tabloid®), fosfato de fludarabina (Fludara®), pentostatina (Nipent ®), pemetrexed (Alimta®), raltitrexed (Tomudex®), cladribina (Leustatin®), clofarabina (Clofarex®, Clolar®), mercaptopurina (Puri-Nethol®), capecitabina (Xeloda®), nelarabina (Arranon®), azacitidina (Vidaza®) y gemcitabina (Gemzar®). antimetabolitos preferidos incluyen, por ejemplo, 5-fluorouracilo (Adrucil®, Efudex®, Fluoroplex®), floxuridina (FUDF®), capecitabina (Xeloda®), pemetrexed (Alimta®), raltitrexed (Tomudex®) y gemcitabina (Gemzar®).

Ejemplos de agentes de alquilación incluyen, de manera enunciativa mas no limitativa, mostazas nitrogenadas, derivados de etilenimina, alquil sulfonatos, nitrosoureas y triazenos: mostaza de uracilo (Aminouracil Mustard®, Chlorethaminacil®, Demethyldopan®, Desmethyldopan®, Haemanthamine®, Nordopan®, Uracil Nitrogen Mustard®, Uracillost®, Uracilmostaza®, Uramustin®, Uramustine®), clormetina (Mustargen®), ciclofosfamida (Cytoxan®, Neosar®, Clafen®, Endoxan®, Procytox®, Revimmune™), ifosfamida (Mitoxana®), melfalán (Alkeran®), clorambucil (Leukeran®), pipobromano (Amedel®, Vercyte®), trietilenmelamina (Hemel®, Hexalen®, Hexastat®), trietilentiofosforamina, temozolomida (Temodar®), tiotepa (Thioplex®), busulfán (Busilvex®, Myleran®), carmustina (BiCNU®), lomustina (CeeNU®), estreptozocina (Zanosar®) y dacarbazina (DTIC-Dome®). Ejemplos de agentes alquilantes adicionales incluyen, de manera enunciativa mas no limitativa, oxaliplatino (Eloxatin®); temozolomida (Temodar® y Temodal®); dactinomicina (también conocidacomo actinomicina-D, Cosmegen®); melfalán (también conocido como L-PAM, L-sarcolisina, y mostaza de fenilalanina, Alkeran®); altretamina (también conocida como hexametilmelamina (HMM), Hexalen®); carmustina (BiCNU®); bendamustina (Treanda®); busulfán (Busulfex® y Myleran®); carboplatino (Paraplatin®); lomustina (también conocida como CCNU, CeeNU®); cisplatino (también conocido como CDDP, Platinol® y Platinol®-AQ); clorambucil (Leukeran®); ciclofosfamida (Cytoxan® y Neosar®); dacarbazina (también conocida como DTIC, DIC y carboxamida imidazol, DTIC-Dome®); altretamina (también conocida como hexametilmelamina (HMM), Hexalen®); ifosfamida (Ifex®); prednumustina; procarbazina (Matulane®); mecloretamina (también conocida como mostaza de nitrógeno, mustina e hidrocloruro de mecloroetamina, Mustargen®); estreptozocina (Zanosar®); tiotepa (también conocida como tiofosfoamida, TESPA y TSPA, Thioplex®); ciclofosfamida (Endoxan®, Cytoxan®, Neosar®, Procytox®, Revimmune®); y HCl bendamustina (Treanda®).

En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con fludarabina, ciclofosfamida, y/o rituximab. En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con fludarabina, ciclofosfamida y rituximab (FCR). En las realizaciones, el sujeto tiene CLL. Por ejemplo, el sujeto tiene una deleción en el brazo corto del cromosoma 17 (del (17p), por ejemplo, en una célula leucémica). En otros ejemplos, el sujeto no tiene una expresión

del (17p). En realizaciones, el sujeto comprende una célula leucémica que comprende una mutación en el gen de inmunoglobulina región variable- de cadena pesada (IgVH). En otras realizaciones, el sujeto no comprende una célula leucémica que comprende una mutación en el gen de inmunoglobulina región variable de cadena pesada (IgVH). En formas de realización, la fludarabina se administra a una dosis de aproximadamente 10 a 50 mg/m^2 (por ejemplo, aproximadamente 10-15, 15-20, 20-25, 25-30, 30-35, 35-40, 40-45, o 45-50 mg / m^2), por ejemplo, por vía intravenosa. En formas de realización, la ciclofosfamida se administra a una dosis de aproximadamente 200 a 300 mg / m^2 (por ejemplo, aproximadamente 200 a 225, 225 a 250, 250 a 275, o 275 a 300 mg / m^2), por ejemplo, por vía intravenosa. En realizaciones, el rituximab se administra a una dosis de aproximadamente 400 a 600 mg / m^2 (por ejemplo, 400-450, 450-500, 500-550, o 550 a 600 mg / m^2), por ejemplo, por vía intravenosa.

En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con bendamustina y rituximab. En las realizaciones, el sujeto tiene CLL. Por ejemplo, el sujeto tiene una deleción en el brazo corto del cromosoma 17 (del (17p), por ejemplo, en una célula leucémica). En otros ejemplos, el sujeto no tiene una expresión del (17p). En realizaciones, el sujeto comprende una célula leucémica que comprende una mutación en el gen de inmunoglobulina de cadena pesada variable-región (IgVH). En otras realizaciones, el sujeto no comprende una célula leucémica que comprende una mutación en el gen de inmunoglobulina de cadena pesada variable-región (IgVH). En formas de realización, la bendamustina se administra a una dosis de aproximadamente 70 a 110 mg/m^2 (por ejemplo, 70-80, 80-90, 90-100, o 100-110 mg/m^2), por ejemplo, por vía intravenosa. En realizaciones, el rituximab se administra a una dosis de aproximadamente 400 a 600 mg / m2 (por ejemplo, 400-450, 450-500, 500-550, o 550 a 600 mg / m^2), por ejemplo, por vía intravenosa.

En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con rituximab, ciclofosfamida, doxorubicina, vincristina, y/o un corticosteroide (por ejemplo, prednisona). En formas de realización, una célula que expresa CARdescrito en este documento se administra a un sujeto en combinación con rituximab, ciclofosfamida, doxorubicina, vincristina y prednisona (R-CHOP). En realizaciones, el sujeto tiene linfoma de células B grandes (DLBCL) difusa. En las realizaciones, el sujeto tiene DLBCL estadio limitado no voluminoso (por ejemplo, comprende un tumor que tiene un tamaño / diámetro de menos de 7 cm). En formas de realización, el sujeto es tratado con radiación en combinación

con el R-CHOP. Por ejemplo, se administra al sujeto R-CHOP (por ejemplo, 1-6 ciclos, por ejemplo, 1, 2, 3, 4, 5, o 6 ciclos de R-CHOP), seguido por la radiación. En algunos casos, se administra al sujeto R-CHOP (por ejemplo, 1-6 ciclos, por ejemplo, 1, 2, 3, 4, 5, o 6 ciclos de R-CHOP) después de la radiación.

En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con etopósido, prednisona, vincristina, ciclofosfamida, doxorrubicina, y/o rituximab. En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con etopósido, prednisona, vincristina, ciclofosfamida, doxorubicina y rituximab (EPOCH-R). En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con dosis ajustada de EPOCH-R (DA-EPOCH-R). En las realizaciones, el sujeto tiene un linfoma de células B, por ejemplo, un linfoma de células B agresivo reordenado-Myc.

En formas de realización, una célula que expresa CAR descrito en este documento se administra a un sujeto en combinación con rituximab y/o lenalidomida. La lenalidomida ((RS) -3- (4-amino-1-oxo 1,3-dihidro-2H-isoindol- 2-il) piperidina-2,6-diona) es un inmunomodulador. En formas de realización, una célula que expresa CAR descrito en este documento se administra a un sujeto en combinación con rituximab y lenalidomida. En las realizaciones, el sujeto tiene linfoma folicular (FL), o linfoma de células del manto (MCL). En las realizaciones, el sujeto tiene FL y no ha sido previamente tratado con una terapia del cáncer. En formas de realización, la lenalidomida se administra a una dosis de aproximadamente 10 a 20 mg (por ejemplo, 10 a 15 o 15 a 20 mg), por ejemplo, todos los días. En formas de realización, el rituximab se administra a una dosis de aproximadamente 350 a 550 mg / m2 (por ejemplo, 350-375, 375-400, 400-425, 425-450, 450-475, o 475 a 500 mg / m2), por ejemplo, por vía intravenosa.

inhibidores de mTOR ejemplares incluyen, por ejemplo, temsirolimus; ridaforolimus (formalmente conocido como deferolimus, (1R, 2R, 4S) -4 - [(2R) -2 [(1R, 9S, 12S, 15R, 16E, 18R, 19R, 21R, 23S, 24E, 26E, 28Z, 30S , 32S, 35R) -1,18-dihidroxi-19,30-dimetoxi-15,17,21,23, 29,35-hexametil-2,3,10,14,20-pentaoxo-11,36-dioxa- 4-azatriciclo [30.3.1.04,9] hexatriaconta-16,24,26,28-tetraen-12-il] propil] -2-dimetilfosfinato metoxiciclohexilo, también conocido como AP23573 y MK8669, y se describe en la publicación PCT No. WO 03 / 064.383); everolimus (RAD001 o Afinitor®); rapamicina (AY22989, Sirolimus®); simapimod (CAS 164301-51-3); emsirolimus, (5-{2,4-bis [(3S) -3-metilmorfolin-4-il] pirido [2,3-d]

pirimidin-7-il} -2-metoxifenil) metanol (AZD8055); 2-Amino-8-[trans-4-(2-hidroxietoxi)ciclohexil]-6-(6-metoxi-3-pyridinyl)-4-metil-pirido[2,3-d]pirimidin-7(8H)-ona (PF04691502, CAS 1013101-36-4); y N2-[1,4-dioxo-4-[[4-(4-oxo-8-fenil-4H-1-benzopiran-2-il)morfolinio-4-il]metoxi]butil]-L-arginilglicil-L-α-aspartilL-serina-, sal interna (SF1126, CAS 936487-67-1) (SEQ ID NO: 1316), y XL765.

Ejemplos de inmunomoduladores incluyen, por ejemplo, afutuzumab (comercializado por Roche®); pegfilgrastim (Neulasta®); lenalidomida (CC-5013, Revlimid®); talidomida (Thalomid®), ACTIMID (CC4047); y IRX-2 (mezcla de citoquinas humanas incluyendo interleuquina 1, interleuquina 2 e interferón γ, CAS 951209-71-5, comercializado por IRX Therapeutics).

Ejemplos de antraciclinas incluyen, por ejemplo, doxorrubicina (Adriamycin® y Rubex®); bleomicina (lenoxane®); daunorrubicina (clorhidrato de daunorrubicina, daunomicina y clorhidrato de rubidomicina, Cerubidine®); daunorrubicina liposomal (liposoma de citrato de daunorrubicina, DaunoXome®); mitoxantrona (DHAD, Novantrone®); epirubicina (Ellence™); idarrubicina (Idamycin®, Idamycin PFS®); mitomicina C (Mutamycin®); geldanamicina; herbimicina; ravidomicina y desacetilravidomicina.

Ejemplos de alcaloides de la vinca incluyen, por ejemplo, tartrato de vinorelbina (Navelbine®), vincristina (Oncovin®) y vindesina (Eldisine®); vinblastina (también conocida como sulfato de vinblastina, vincaleucoblastina y VLB, Alkaban-AQ® y Velban®); y vinorelbina (Navelbine®).

Ejemplos de inhibidores de proteosomas incluyen bortezomib (Velcade®); carfilzomib (PX-171-007, (*S*)-4-metil-*N*-((*S*)-1-(((*S*)-4-metil-1-((*R*)-2-metiloxiran-2-il)-1-oxopentan-2-il)amino)-1-oxo-3-fenilpropan-2-il)-2-((*S*)-2-(2-morfolinoacetamido)-4-fenillbutanamido)-pentanamida); marizomib (NPI-0052); ixazomib citrato (MLN-9708); delanzomib (CEP-18770); y *O*-metil-*N*-[(2-metil-5-tiazolil)carbonil]-L-seril-*O*-metil-*N*-[(1*S*)-2-[(2*R*)-2-metil-2-oxiranil]-2-oxo-1-(fenilmetil)etil]- L-serinamida (ONX-0912).

En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con vedotina. Brentuximab es un conjugado anticuerpo-fármaco de anticuerpo anti-CD30 y monometil auristatina E. En realizaciones, el sujeto tiene linfoma de

Hodgkin (HL), por ejemplo, en recaída o refractario HL. En realizaciones, el sujeto comprende CD30 + HL. En realizaciones, el sujeto se ha sometido a un trasplante autólogo de células madre (ASCT). En realizaciones, el sujeto no ha sido sometida a un TACM. En formas de realización, vedotina se administra a una dosis de aproximadamente 1-3 mg / kg (por ejemplo, aproximadamente 1 a 1,5, 1,5 a 2, 2 a 2,5, o 2,5 a 3 mg / kg), por ejemplo, por vía intravenosa, por ejemplo, cada 3 semanas.

En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con vedotina y dacarbazina o en combinación con vedotina y bendamustina. Dacarbazina es un agente alquilante con un nombre químico de 5-(3,3-dimetil-1-triazenil) imidazol-4-carboxamida. Bendamustina es un agente alquilante con un nombre químico de ácido 4- [5- [bis (2-cloroetil) amino] -1-metilbenzoimidazol-2-il] butanoico. En realizaciones, el sujeto tiene linfoma de Hodgkin (HL). En realizaciones, el sujeto no ha sido previamente tratado con una terapia del cáncer. En realizaciones, el sujeto tiene al menos 60 años de edad, por ejemplo, 60, 65, 70, 75, 80, 85, o más. En formas de realización, dacarbazina se administra a una dosis de aproximadamente 300 a 450 mg / m^2 (Por ejemplo, aproximadamente 300-325, 325-350, 350-375, 375-400, 400-425, 425-450, o mg / m2), por ejemplo, por vía intravenosa. En formas de realización, bendamustina se administra a una dosis de aproximadamente 75 a 125 mg / m2 (por ejemplo, 75 a 100 o 100 a 125 mg / m2, por ejemplo, aproximadamente 90 mg / m2), por ejemplo, por vía intravenosa. En formas de realización, vedotina se administra a una dosis de aproximadamente 1-3 mg / kg (por ejemplo, aproximadamente 1 a 1,5, 1,5 a 2, 2 a 2,5, o 2,5 a 3 mg / kg), por ejemplo, por vía intravenosa, por ejemplo, cada 3 semanas.

En algunas formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con un inhibidor de CD20, por ejemplo, un anticuerpo anti-CD20 (por ejemplo, un anticuerpo mono- o biespecíficos anti-CD20) o un fragmento del mismo. anticuerpos anti-CD20 de ejemplo incluyen pero no se limitan a rituximab, ofatumumab, ocrelizumab, veltuzumab, obinutuzumab, TRU-015 (Trubion Pharmaceuticals), ocaratuzumab, y Pro131921 (Genentech). Véase, por ejemplo, Lim et al. Haematologica. 95.1 (2010): 135-43.

En algunas realizaciones, el anticuerpo anti-CD20 comprende rituximab. Rituximab es un kappa de ratón / humano quimérico monoclonal IgG1 anticuerpo que se une a CD20 y causa

la citolisis de una célula que expresa CD20, por ejemplo, como se describe en www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf. En formas de realización, una célula que expresa CARdescrito en este documento se administra a un sujeto en combinación con rituximab. En las realizaciones, el sujeto tiene CLL o SLL.

En algunas realizaciones, rituximab se administra por vía intravenosa, por ejemplo, como una infusión intravenosa. Por ejemplo, cada infusión proporciona alrededor de 500 a 2000 mg (por ejemplo, aproximadamente 500 a 550, 550 a 600, 600 a 650, 650 a 700, 700 a 750, 750 a 800, 800 a 850, 850 a 900, 900 a 950 , 950-1000, 1000-1100, 1100-1200, 1200-1300, 1300-1400, 1400-1500, 1500-1600, 1600-1700, 1700-1800, 1800-1900, 1900-2000 o mg) de rituximab. En algunas realizaciones, rituximab se administra a una dosis de 150 mg / m^2 a 750 mg / m2, por ejemplo, aproximadamente 150-175 mg / m2, 175-200 mg / m2, 200-225 mg / m2, 225-250 mg / m2, 250-300 mg / m2, 300-325 mg / m2 , 325-350 mg / m2, 350-375 mg / m2, 375-400 mg / m2, 400-425 mg / m2, 425-450 mg / m2, 450-475 mg / m2, 475 a 500 mg / m2, 500-525 mg / m2, 525 a 550 mg / m2, 550-575 mg / m2, 575 a 600 mg / m2, 600 a 625 mg / m2, 625 a 650 mg / m2, 650 a 675 mg / m2, o 675-700 mg / m2, donde m2 indica el área de superficie corporal del sujeto. En algunas realizaciones, rituximab se administra en un intervalo de dosificación de al menos 4 días, por ejemplo, 4, 7, 14, 21, 28, 35 días, o más. Por ejemplo, el rituximab se administra en una intervalo de dosificación de al menos 0,5 semanas, por ejemplo, 0,5, 1, 2, 3, 4, 5, 6, 7, 8 semanas, o más. En algunas realizaciones, rituximab se administra a una dosis y el intervalo de dosificación descrito en el presente documento durante un periodo de tiempo, por ejemplo, al menos 2 semanas, por ejemplo, al menos 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 semanas, o más. Por ejemplo, el rituximab se administra a una dosis y el intervalo de dosificación descrito en la presente memoria para un total de al menos 4 dosis por ciclo de tratamiento (por ejemplo, al menos 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, o más dosis por ciclo de tratamiento).

En algunas realizaciones, el anticuerpo anti-CD20 comprende ofatumumab. Ofatumumab es un anticuerpo monoclonal humano anti-CD20 IgG1k con un peso molecular de aproximadamente 149 kDa. Por ejemplo, ofatumumab se genera utilizando la tecnología de ratones transgénicos y de hibridoma y se expresa y se purifica a partir de una línea celular murina recombinante (NS0). Véase, por ejemplo, www.accessdata.fda.gov/drugsatfda_docs/label/2009/125326lbl.pdf; and Clinical Trial número

identificador NCT01363128, NCT01515176, NCT01626352 y NCT01397591. En formas de realización, una célula que expresa CARdescrito en este documento se administra a un sujeto en combinación con ofatumumab. En las realizaciones, el sujeto tiene CLL o SLL.

En algunas realizaciones, ofatumumab se administra como una infusión intravenosa. Por ejemplo, cada infusión proporciona alrededor de 150 a 3000 mg (por ejemplo, aproximadamente 150 a 200, 200 a 250, 250 a 300, 300 a 350, 350 a 400, 400 a 450, 450 a 500, 500 a 550, 550 a 600 , 600-650, 650-700, 700-750, 750-800, 800-850, 850-900, 900-950, 950-1000, 1000-1200, 1200-1400, 1400-1600, 1600-1800, 1800 -2000, 2000-2200, 2200-2400, 2400-2600, 2600-2800, 2800-3000 o mg) de ofatumumab. En formas de realización, ofatumumab se administra a una dosis inicial de alrededor de 300 mg, seguido de 2000 mg, por ejemplo, durante aproximadamente 11 dosis, por ejemplo, durante 24 semanas. En algunas realizaciones, ofatumumab se administra en una intervalo de dosificación de al menos 4 días, por ejemplo, 4, 7, 14, 21, 28, 35 días, o más. Por ejemplo, ofatumumab se administra en un intervalo de dosificación de al menos 1 semana, por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 26, 28, 20, 22, 24, 26, 28, 30 semanas o más. En algunas realizaciones, ofatumumab se administra a una dosis y el intervalo de dosificación descrito en el presente documento durante un periodo de tiempo, por ejemplo, al menos 1 semana, por ejemplo, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 26, 28, 30, 40, 50, 60 semanas o más, o 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 meses o más, o 1, 2, 3, 4, 5 años o más. Por ejemplo, ofatumumab se administra a una dosis y el intervalo de dosificación descrito en la presente memoria para un total de al menos 2 dosis por ciclo de tratamiento (por ejemplo, al menos 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, o más dosis por ciclo de tratamiento).

En algunos casos, el anticuerpo anti-CD20 comprende ocrelizumab. Ocrelizumab es un anticuerpo monoclonal humanizado anti-CD20, por ejemplo, como se describe en los ensayos clínicos Identificador Nos. NCT00077870, NCT01412333, NCT00779220, NCT00673920, NCT01194570, y Kappos et al. Lanceta. 19.378 (2011): 1779-1787.

En algunos casos, el anticuerpo anti-CD20 comprende veltuzumab. Veltuzumab es un anticuerpo monoclonal humanizado contra CD20. Véase, por ejemplo, de ensayos clínicos Identificador Nº NCT00547066, NCT00546793, NCT01101581 y Goldenberg et al. Leuk Lymphoma. 51 (5) (2010): 747-55.

En algunos casos, el anticuerpo anti-CD20 comprende GA101. GA101 (también llamado

obinutuzumab o RO5072759) es un anticuerpo monoclonal humanizado y glico-ingeniería anti-CD20. Véase, por ejemplo, Robak. Curr. Opin. Investig. Los fármacos. 10.6 (2009): 588-96; Clinical Trial números de identificador: NCT01995669, NCT01889797, NCT02229422 y NCT01414205; y www.accessdata.fda.gov/drugsatfda_docs/label/2013/125486s000lbl.pdf.

En algunos casos, el anticuerpo anti-CD20 comprende AME-133V. AME-133V (también llamado LY2469298 o ocaratuzumab) es un anticuerpo IgG1 monoclonal humanizado contra CD20 con una mayor afinidad por el receptor FcRIIIa y una actividad dependiente de anticuerpo mejorado la citotoxicidad celular (ADCC), en comparación con rituximab. Véase, por ejemplo, Robak et al. Biofármacos 25.1 (2011): 13-25; y Forero-Torres et al. Clin Cancer Res. 18.5 (2012): 1395-403.

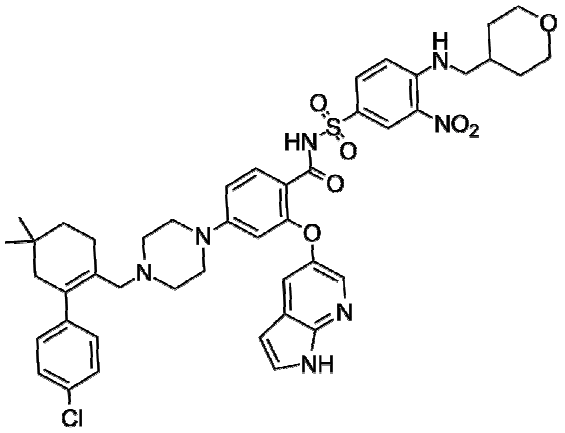
En algunos casos, el anticuerpo anti-CD20 comprende PRO131921. PRO131921 es un anticuerpo monoclonal anti-CD20 humanizado diseñado para tener una mejor unión a FcRIIIa y una mayor ADCC en comparación con rituximab. Véase, por ejemplo, Robak et al. Biofármacos 25.1 (2011): 13-25; y Casulo et al. Clin Immunol. 154.1 (2014): 37-46; y Ensayos Clínicos Identificador Nº NCT00452127.

En algunos casos, el anticuerpo anti-CD20 comprende TRU-015. TRU-015 es una proteína de fusión anti-CD20 derivada de los dominios de un anticuerpo contra CD20. TRU-015 es más pequeño que los anticuerpos monoclonales, pero conserva las funciones efectoras mediadas por Fc. Véase, por ejemplo, Robak et al. Biofármacos 25.1 (2011): 13-25. TRU-015 contiene un anticuerpo de cadena sencilla anti-CD20 (scFv) unido a IgG1 humana de la bisagra, los dominios CH2 y CH3, pero carece de los dominios CH1 y CL.

En algunas realizaciones, un anticuerpo anti-CD20 descrito en este documento se conjuga o de otro modo unido a un agente terapéutico, por ejemplo, un agente quimioterapéutico (por ejemplo, Cytoxan, fludarabina, inhibidor de la histona desacetilasa, agente de desmetilación, vacuna de péptidos, antibióticos anti-tumor, inhibidor de tirosina quinasa, agente alquilante, anti-microtúbulos o agente anti-mitótico), agente anti-alérgica, anti-náuseas agente (o antiemético), analgésico, o agente citoprotector descritos en el presente documento.

En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con un linfoma de células B 2 (-2 BCL) inhibidor (por ejemplo, venetoclax, también llamado ABT-199 o GDC-0199;) y / o rituximab . En formas de

realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con venetoclax y rituximab. Venetoclax es una pequeña molécula que inhibe la proteína anti-apoptótica, Bcl-2. La estructura de venetoclax (4- (4 -{[2- (4-clorofenil) -4,4-dimetilciclohex-1-en-1-il] metil} piperazin-1-il) -*N*-({3-nitro-4-[(tetrahidro-2H-piran-4-ilmetil)amino]fenil}sulfonil)-2-(1H-pirrolo[2,3-b]piridin-5-iloxi)benzamida) se muestra a continuación.



En las realizaciones, el sujeto tiene CLL. En realizaciones, el sujeto ha recaído CLL, por ejemplo, el sujeto ha sido previamente administrada una terapia del cáncer. En formas de realización, venetoclax se administra a una dosis de aproximadamente 15 a 600 mg (por ejemplo, 15-20, 20-50, 50-75, 75-100, 100-200, 200-300, 300-400, 400-500, o 500 a 600 mg), por ejemplo, diariamente. En formas de realización, el rituximab se administra a una dosis de aproximadamente 350 a 550 mg / m2 (por ejemplo, 350-375, 375-400, 400-425, 425-450, 450-475, o 475 a 500 mg / m2), por ejemplo, , por vía intravenosa, por ejemplo, mensual.

En algunas realizaciones, una o más células que expresan CAR descritas en este documento se administran en combinación con un virus oncolítico. En formas de realización, los virus oncolíticos son capaces de replicarse selectivamente en y provocando la muerte o retardando el crecimiento de una célula cancerosa. En algunos casos, los virus oncolíticos no tienen ningún efecto o un efecto mínimo sobre las células no cancerosas. Un virus oncolítico incluye pero no se limita a un adenovirus oncolítico, oncolítico Herpes Simplex Virus, retrovirus oncolítico, parvovirus oncolítico, virus vaccinia oncolítico, virus Sinbis oncolítico, virus de la gripe oncolítico, o virus de ARN oncolítico (por ejemplo, reovirus oncolítico, oncolítico virus de la enfermedad Newcastle (NDV), virus del sarampión oncolíticos, o virus de la estomatitis

vesicular oncolítico (VSV)).

En algunas realizaciones, el virus oncolítico es un virus, por ejemplo, virus oncolítico recombinante, se describe en US2010 / 0178684 A1, que se incorpora aquí por referencia en su totalidad. En algunas realizaciones, un virus oncolítico recombinante comprende una secuencia de ácido nucleico (por ejemplo, secuencia de ácido nucleico heterólogo) que codifica un inhibidor de una respuesta inmune o inflamatoria, por ejemplo, como se describe en US2010 / 0178684 A1, incorporada aquí por referencia en su totalidad. En formas de realización, el virus oncolítico recombinante, por ejemplo, oncolítico NDV, se compone de una proteína pro-apoptótica (por ejemplo, apoptina), una citoquina (por ejemplo, GM-CSF, interferón gamma, interleucina-2 (IL-2), factor de necrosis tumoral alfa), una inmunoglobulina (por ejemplo, un anticuerpo contra ED-B firbonectin) antígeno, asociado a un tumor, una proteína adaptadora biespecífico (por ejemplo, anticuerpo biespecífico o fragmento de anticuerpo dirigido contra la proteína NDV HN y un receptor de la célula T co-estimuladoras, tales como proteína o fusión entre la IL-2 humana y anticuerpo de cadena sencilla dirigido contra la proteína NDV HN); CD3 o CD28. Véase, por ejemplo, Zamarin et al. Futuro Microbiol. 7.3 (2012): 347-67, que se incorpora aquí por referencia en su totalidad. En algunas realizaciones, el virus oncolítico es un NDV quimérico oncolítico se describe en US 8.591.881 B2, US 2012/0122185 A1 o US 2014/0271677 A1, cada una de las cuales se incorpora aquí por referencia en su totalidad.

En algunas realizaciones, el virus oncolítico comprende un adenovirus condicionalmente replicativa (VAO), que está diseñado para replicar exclusivamente en células cancerosas. Véase, por ejemplo, Alemany et al. Nature Biotechnol. 18 (2000): 723-27. En algunas formas de realización, un adenovirus oncolítico comprende uno describen en la Tabla 1 en la página 725 de Alemany et al., Incorporada aquí por referencia en su totalidad.

virus oncolíticos ejemplares incluyen pero no se limitan a los siguientes:

Grupo B Adenovirus oncolíticos (ColoAd1) (PsiOxus Terapéutica Ltd) (véase, por ejemplo, ensayo clínico Identificador: NCT02053220);

Oncos-102 (anteriormente llamado CGTG-102), que es un adenovirus que comprende el factor estimulante de colonias de granulocitos-macrófagos (GM-CSF) (Oncos Terapéutica) (véase, por ejemplo, ensayo clínico Identificador: NCT01598129);

VCN-01, que es un oncolítico adenovirus humano que codifica PH20 humana

hialuronidasa modificado genéticamente (VCN Biosciences, S.L.) (véase, por ejemplo, identificadores de ensayo clínico: NCT02045602 y NCT02045589);

Condicionalmente Adenovirus ICOVIR-5 replicativo, que es un virus derivado de adenovirus de tipo silvestre humano serotipo 5 (hAd5) que ha sido modificado para replicar selectivamente en las células cancerosas con una vía E2F retinoblastoma / desregulado (Institut Català d'Oncologia) (véase, por ejemplo, ensayo clínico Identificador: NCT01864759);

Celyvir, que comprende células derivadas de médula ósea autólogo de células madre mesenquimales (MSC) infectado con ICOVIR5, un adenovirus oncolítico (Hospital Infantil Universitario Niño Jesús, Madrid, España / Ramón Alemany) (véase, por ejemplo, Clinical Trial Identificador: NCT01844661);

CG0070, que es un serotipo 5 de adenovirus oncolítico de replicación condicional (Ad5) en donde que humano E2F-1 promotor dirige la expresión de los genes virales esenciales E1a, restringiendo así la replicación viral y la citotoxicidad para las células tumorales de la ruta defectuosa Rb (Cold Genesys, Inc.) (véase, por ejemplo, Clinical Trial Identificador: NCT02143804); o

DNX-2401 (anteriormente llamado Delta-24-RGD), que es un adenovirus que ha sido diseñado para replicar selectivamente en retinoblastoma (Rb) -pathway células deficientes y para infectar las células que expresan ciertas integrinas RGD de unión de manera más eficiente (Clinica Universidad de Navarra, Universidad de Navarra / DNAtrix, Inc.) (véase, por ejemplo, ensayo clínico Identificador: NCT01956734).

En algunas realizaciones, un virus oncolítico describe en este documento es la administración por inyección, por ejemplo, subcutánea, intra-arterial, intravenosa, intramuscular, intratecal, o inyección intraperitoneal. En formas de realización, un virus oncolítico describe en este documento se administra por vía intratumoral, por vía transdérmica, transmucosa, oral, intranasal, o mediante la administración pulmonar.

En una realización, las células que expresan un CAR se describe en el presente documento se administran a un sujeto en combinación con una molécula que disminuye la población de células Treg. Métodos que disminuyen el número de (por ejemplo, agotar) células Treg son conocidos en la técnica e incluyen, por ejemplo, agotamiento de CD25, la administración de ciclofosfamida, modulación de la función GITR. Sin desear estar limitado por

la teoría, se cree que la reducción del número de células Treg en un sujeto antes de la aféresis o antes de la administración de una célula CAR-expresión descrito en este documento reduce el número de células inmunitarias no deseadas (por ejemplo, células T reguladoras) en el microambiente tumoral y reduce el riesgo del sujeto de la recaída.

En una modalidad, una célula que expresa un CAR descrita en el presente documento se administra a un sujeto en combinación con una molécula que disminuye la población de células Treg. Métodos que disminuyen la cantidad (por ejemplo, agotan) de células Treg son conocidos en la técnica e incluyen, por ejemplo, agotamiento de CD25, administración de ciclofosfamida y modulación de la función GITR. Al margen de las limitaciones que impone la teoría, se cree que la reducción del número de células Treg en un sujeto antes de la aféresis o antes de la administración de una célula que expresa un CAR descrita en el presente documento reduce la cantidad de células inmunitarias no deseadas (por ejemplo, células T reguladoras) en el microambiente tumoral y reduce el riesgo de recaída del sujeto. En una modalidad, células que expresan CAR descritas en el presente documento se administran a un sujeto en combinación con una molécula que se dirige a GITR y/o que modula las funciones de GITR, tal como un agonista de GITR y/o un anticuerpo de GITR que reduce células T reguladoras (Tregs). En una modalidad, células que expresan CAR descritas en el presente documento se administran a un sujeto en combinación con ciclofosfamida. En una modalidad, molécula de unión a GITR y/o molécula que modula las funciones de GITR (por ejemplo, un agonista de GITR y/o anticuerpos de GITR que reducen células Treg) se administra antes de la célula que expresa CAR. Por ejemplo, en una modalidad, el agonista de GITR puede ser administrado antes de la aféresis de las células. En algunas modalidades, la ciclofosfamida se administra al sujeto antes de la administración (por ejemplo, infusión o re-infusión) de la célula que expresa un CAR o antes de la aféresis de las células. En algunas modalidades, la ciclofosfamida y un anticuerpo anti-GITR se administran al sujeto antes de la administración (por ejemplo, infusión o re-infusión) de la célula que expresa un CAR o antes de la aféresis de las células. En una modalidad, el sujeto tiene cáncer (por ejemplo, un cáncer sólido o un cáncer hematológico tal como LLA o LLC). En una modalidad, el sujeto tiene LLC. En algunas modalidades, el sujeto tiene un cáncer sólido, por ejemplo, un cáncer sólido descrito en este documento.

En una modalidad, la combinación de una célula que expresa un CAR descrita en el

presente documento y uno o más inhibidores de células B descritos en el presente documento se administra a un sujeto en combinación con un agonista de GITR, por ejemplo, un agonista de GITR descrito en el presente documento. En una modalidad, el agonista de GITR se administra antes de la célula que expresa CAR, por ejemplo, células que expresan CAR de CD19. Por ejemplo, en una modalidad, el agonista de GITR puede ser administrado antes de la aféresis de las células. En una modalidad, el sujeto tiene LLC.

En una realización, una célula que expresa CAR CD19 que se describe en este documento se administra a un sujeto en combinación con un agonista de GITR, por ejemplo, un agonista GITR describe en este documento. En una realización, el agonista GITR se administra antes de la célula CAR que expresan. Por ejemplo, en una realización, el agonista GITR se puede administrar antes de la aféresis de las células.

Los agonistas GITR de ejemplo incluyen, por ejemplo, proteínas de fusión GITR y anticuerpos anti-GITR (por ejemplo, anticuerpos bivalentes anti-GITR) tales como, por ejemplo, una proteína de fusión GITR describe en la patente de Estados Unidos No .: 6.111.090, la Patente Europea No .: 090505B1, US Patente No .: 8.586.023, la publicación PCT nº .: WO 2010/003118 y 2011/090754, o un anticuerpo anti-GITR describe, por ejemplo, en la Patente de Estados Unidos No .: 7.025.962, la Patente Europea No .: 1947183B1, Patente de Estados Unidos No .: 7.812.135, Patente de Estados Unidos No .: 8.388.967, Patente de Estados Unidos No .: 8.591.886, la Patente Europea No .: EP 1.866.339, la publicación PCT WO 2011/028683 No .:, publicación PCT No .: WO 2013/039954, la publicación PCT No .: WO2005 / 007190, Publicación PCT No .: WO 2007/133822, la publicación PCT No .: WO2005 / 055808, la Publicación PCT WO 99/40196 No .:, Publicación PCT No .: WO 2001 / 03720, publicación PCT No .: WO99 / 20758, publicación PCT No .: WO2006 / 083289, publicación PCT No .: WO 2005/115451, patente de Estados Unidos No .: 7.618.632, y la publicación PCT WO 2011/051726

En una realización, una célula que expresa CAR descrito en este documento se administra a un sujeto en combinación con un inhibidor de la proteína tirosina fosfatasa, por ejemplo, un inhibidor de la proteína tirosina fosfatasa describe en este documento. En una realización, el inhibidor de la tirosina proteína fosfatasa es un inhibidor de SHP-1, por ejemplo, un inhibidor de la SHP-1 descrito en este documento, tal como, por ejemplo, estibogluconato de sodio. En una realización, el inhibidor de la tirosina proteína fosfatasa es un inhibidor de SHP-2, por ejemplo,

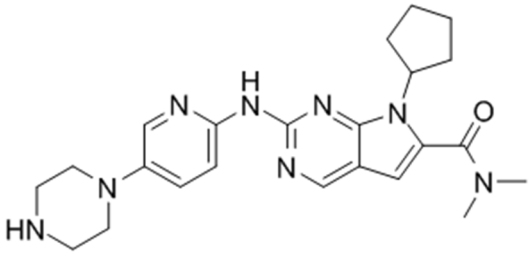
un inhibidor de la SHP-2 descrito en el presente documento.

En una realización, una célula que expresa CAR describe en este documento, opcionalmente en combinación con uno o más inhibidores de células B se pueden usar en combinación con un inhibidor de la quinasa. En una modalidad, el inhibidor de quinasa es un inhibidor de CDK4, por ejemplo, un inhibidor de CDK4 descrito en el presente documento, por ejemplo, un inhibidor de CD4/6, tal como, por ejemplo, 6-acetil-8-ciclopentil-5-metil-2-(5-piperazin-1-il-piridin-2-ilamino)-8*H*-pirido[2,3-*d*]pirimidin-7-ona, clorhidrato (también conocido como palbociclib o PD0332991). En una modalidad, el inhibidor de quinasa es un inhibidor de BTK, por ejemplo, un inhibidor de BTK descrito en el presente documento, tal como, por ejemplo, ibrutinib. En una modalidad, el inhibidor de quinasa es un inhibidor de mTOR, por ejemplo, un inhibidor de mTOR descrito en el presente documento, tal como, por ejemplo, rapamicina, un análogo de rapamicina, OSI-027. El inhibidor de mTOR puede ser, por ejemplo, un inhibidor de mTORC1 y/o un inhibidor de mTORC2, por ejemplo, un inhibidor de mTORC1 y/o inhibidor de mTORC2 descrito en el presente documento. En una modalidad, el inhibidor de quinasa es un inhibidor de MNK, por ejemplo, un inhibidor de MNK descrito en el presente documento, tal como, por ejemplo, 4-amino-5-(4-fluoroanilino)-pirazolo [3,4-*d*] pirimidina. El inhibidor de MNK puede ser, por ejemplo, un MNK1a, MNK1b, MNK2a y/o MNK2b inhibidor.

En una modalidad, el inhibidor de quinasa es un inhibidor de CDK4 seleccionado de aloisina A; flavopiridol o HMR-1275, 2-(2-clorofenil)-5,7-dihidroxi-8-[(3S,4R)-3-hidroxi-1-metil-4-piperidinil]-4-cromenona; crizotinib (PF-02341066; 2-(2-clorofenil)-5,7-dihidroxi-8-[(2R,3S)-2-(hidroximetil)-1-metil-3-pirrolidinil]- 4H-1-benzopiran-4-ona, clorhidrato (P276-00); 1-metil-5-[[2-[5-(trifluorometil)-1H-imidazol-2-il]-4-piridinil]oxi]-N-[4-(trifluorometil)fenil]-1H-bencimidazol-2-amina (RAF265); indisulam (E7070); roscovitina (CYC202); palbociclib (PD0332991); dinaciclib (SCH727965); N-[5-[[(5-tert-butiloxazol-2-il)metil]tio]tiazol-2-il]piperidina-4-carboxamida (BMS 387032); ácido 4-[[9-cloro-7-(2,6-difluorofenil)-5*H*-pirimido[5,4-*d*][2]benzazepin-2-il]amino]-benzóico (MLN8054); 5-[3-(4,6-difluoro-1H-bencimidazol-2-il)-1H-indazol-5-il]-N-etil-4-metil-3-piridinametanamina (AG-024322); ácido 4-(2,6-diclorobenzoilamino)-1H-pirazol-3-carboxílico N-(piperidin-4-il)amida (AT7519); 4-[2-metil-1-(1-metiletil)-1H-imidazol-5-il]-N-[4-(metilsulfonil)fenil]-2-pirimidinamina (AZD5438); y XL281 (BMS908662).

En una modalidad, el inhibidor de quinasa es un inhibidor de CDK4, por ejemplo, palbociclib (PD0332991), y el palbociclib se administra a una dosis de aproximadamente 50 mg, 60 mg, 70 mg, 75 mg, 80 mg, 90 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg (por ejemplo, 75 mg, 100 mg o 125 mg) diariamente durante un período de tiempo, por ejemplo, diariamente durante 14-21 días de un ciclo de 28 días, o diariamente durante 7-12 días de un ciclo de 21 días. En una modalidad, se administran 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 o más ciclos de palbociclib.

En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con una quinasa dependiente de ciclina (CDK) 4 o 6 inhibidor, por ejemplo, un inhibidor de CDK4 o un inhibidor de CDK6 describe en este documento. En formas de realización, una célula que expresa CARdescrito en este documento se administra a un sujeto en combinación con un inhibidor de CDK4 /6 (por ejemplo, un inhibidor que se dirige tanto CDK4 y CDK6), por ejemplo, un inhibidor de CDK4/6 se describe aquí. En una realización, el sujeto tiene MCL. MCL es un cáncer agresivo que responde mal a las terapias disponibles en la actualidad, es decir, esencialmente incurable. En muchos casos de MCL, se expresa la ciclina D1 (un regulador de CDK4 / 6) (por ejemplo, debido a la translocación cromosómica que implica inmunoglobulina y genes de ciclina D1) en las células de LCM. Por lo tanto, sin pretender imponer ninguna teoría, se cree que las células MCL son muy sensibles a la inhibición de CDK4/6 con una alta especificidad (es decir, un efecto mínimo sobre las células inmunes normales). Inhibidores de CDK4/6 solos han tenido cierta eficacia en el tratamiento del MCL, pero sólo han logrado una remisión parcial con una alta tasa de recaídas. Un inhibidor ejemplar CDK4 / 6 es LEE011 (también llamado ribociclib), la estructura de los cuales se muestra a continuación.



Sin estar ligado por la teoría, se cree que la administración de una célula que expresa CAR descrita en este documento con un inhibidor de CDK4/6 (por ejemplo, LEE011 u otro

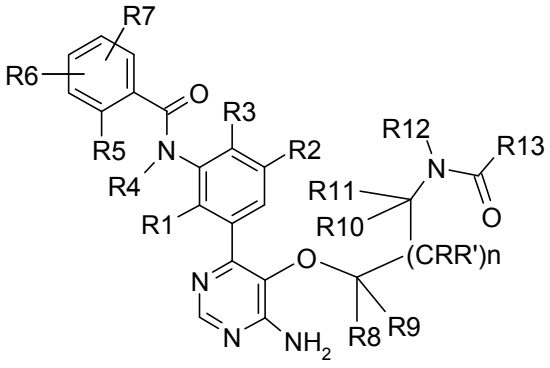
inhibidor de CDK4/6 que se describe en el presente documento) se puede lograr una mayor capacidad de respuesta, por ejemplo, con tasas de remisión más altas y / o menores tasas de recaída, por ejemplo, en comparación con un inhibidor solo de CDK4/6.

En una modalidad, el inhibidor de quinasa es un inhibidor de BTK seleccionado de ibrutinib (PCI-32765); GDC-0834; RN-486; CGI-560; CGI-1764; HM-71224; CC-292; ONO-4059; CNX-774; y LFM-A13. En una modalidad, el inhibidor de BTK no reduce ni inhibe la actividad quinasa de la quinasa inducible por interleuquina-2 (ITK), y se selecciona de GDC-0834; RN-486; CGI-560; CGI-1764; HM-71224; CC-292; ONO-4059; CNX-774 y LFM-A13.

En una modalidad, el inhibidor de quinasa es un inhibidor de BTK, por ejemplo, ibrutinib (PCI-32765).

En realizaciones, el sujeto tiene CLL, linfoma de células del manto (MCL), o linfoma linfocítico pequeño (SLL). Por ejemplo, el sujeto tiene una deleción en el brazo corto del cromosoma 17 (del (17p), por ejemplo, en una célula leucémica). En otros ejemplos, el sujeto no tiene una expresión del (17p). En realizaciones, el sujeto ha recaído CLL o SLL, por ejemplo, el sujeto ha sido previamente administrada una terapia contra el cáncer (por ejemplo, sido previamente administrada una, dos, tres, o cuatro terapias de cáncer anteriores). En las realizaciones, el sujeto tiene CLL refractaria o SLL. En otras realizaciones, el sujeto tiene linfoma folicular, por ejemplo, la recaída o linfoma folicular refractario. En una realización, el inhibidor de quinasa es un inhibidor de BTK, por ejemplo, ibrutinib (PCI-32765), y el ibrutinib se administra a una dosis de aproximadamente 250 mg, 300 mg, 350 mg, 400 mg, 420 mg, 440 mg, 460 mg, 480 mg, 500 mg, 520 mg, 540 mg, 560 mg, 580 mg, 600 mg (por ejemplo, 250 mg, 420 mg o 560 mg) diariamente durante un período de tiempo, por ejemplo, diariamente durante un ciclo de 21 días o diariamente durante un ciclo de 28 días. En una modalidad, se administran 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 o más ciclos de ibrutinib.

En algunas modalidades de los métodos, usos y composiciones del presente documento, el inhibidor de BTK es un inhibidor de BTK descrito en la Solicitud Internacional WO/2015/079417, que se incluye aquí en su totalidad como referencia. Por ejemplo, en algunas modalidades, el inhibidor de BTK es un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo;



(I)

en donde,

R1 es hidrógeno, alquilo C1-C6 opcionalmente sustituido con hidroxi;

R2 es hidrógeno o halógeno;

R3 es hidrógeno o halógeno;

R4 es hidrógeno;

R5 es hidrógeno o halógeno;

o R4 y R5 están unidos entre sí y representan un enlace, -CH2-, -CH2-CH2-, -CH = CH-, -CH=CH-CH2-; -CH2-CH=CH-; o -CH2-CH2-CH2-;

R6 y R7 representan independientemente el uno del otro H, alquilo C1-C6 opcionalmente sustituido con hidroxi, cicloalquilo C3-C6 opcionalmente sustituido con halógeno o hidroxi, o halógeno;

R8, R9, R, R', R10 y R11 independientemente los unos de los otros representan H, o alquilo C1-C6 opcionalmente sustituido con alcoxilo C1-C6; o dos cualquiera de R8, R9, R, R', R10 y R11 junto con el átomo de carbono al que están unidos pueden formar un anillo carbocíclico saturado de 3-6 miembros;

R12 es hidrógeno o alquilo C1-C6 opcionalmente sustituido con halógeno o alcoxilo C1-C6;

o R12 y uno cualquiera de R8, R9, R, R', R10 o R11 junto con los átomos a los que están unidos pueden formar un anillo azacíclico de 4, 5, 6 o 7 miembros, cuyo anillo puede estar opcionalmente sustituido con halógeno, ciano, hidroxilo, alquilo C1-C6 o alcoxilo C1-C6;

n es 0 o 1; y

R13 es alquenilo C2-C6 opcionalmente sustituido con alquilo C1-C6, alcoxilo C1-C6, o N,N-di alquilo C1-C6 amino; alquinilo C2-C6 opcionalmente sustituido con alquilo C1-C6 o alcoxilo C1-C6; u óxido de alquilenilo C2-C6 opcionalmente sustituido con alquilo C1-C6.

En algunas modalidades, el inhibidor de BTK de Fórmula I se selecciona de: N-(3-(5-((1-acriloilazetidin-3-il)oxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; (E)-N-(3-(6-amino-5-((1-(but-2-enoil)azetidin-3-il)oxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(6-amino-5-((1-propioloilazetidin-3-il)oxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(6-amino-5-((1-(but-2-inoil)azetidin-3-il)oxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(5-((1-acriloilpiperidin-4-il)oxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(6-amino-5-(2-(N-metilacrilamido)etoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; (E)-N-(3-(6-amino-5-(2-(N-metilbut-2-enamido)etoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(6-amino-5-(2-(N-metilpropiolamido)etoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; (E)-N-(3-(6-amino-5-(2-(4-metoxi-N-metilbut-2-enamido)etoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(6-amino-5-(2-(N-metilbut-2-inamido)etoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(2-((4-amino-6-(3-(4-ciclopropil-2-fluorobenzamido)-5-fluoro-2-metilfenil)pirimidin-5-il)oxi)etil)-N-metiloxirano-2-carboxamida; N-(2-((4-amino-6-(3-(6-ciclopropil-8-fluoro-1-oxoisoquinolin-2(1H)-il)fenil)pirimidin-5-il)oxi)etil)-N-metilacrilamida; N-(3-(5-(2-acrilamidoetoxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(6-amino-5-(2-(N-etilacrilamido)etoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(6-amino-5-(2-(N-(2-fluoroetil)acrilamido)etoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(5-((1-acrilamidociclopropil)metoxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; (S)-N-(3-(5-(2-acrilamidopropoxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; (S)-N-(3-(6-amino-5-(2-(but-2-inamido)propoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; (S)-N-(3-(6-amino-5-(2-(N-metilacrilamido)propoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; (S)-N-(3-(6-amino-5-(2-(N-metilbut-2-inamido)propoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(6-amino-5-(3-(N-metilacrilamido)propoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-

2-fluorobenzamida; (S)-N-(3-(5-((1-acriloilpirrolidin-2-il)metoxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; (S)-N-(3-(6-amino-5-((1-(but-2-inoil)pirrolidin-2-il)metoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; (S)-2-(3-(5-((1-acriloilpirrolidin-2-il)metoxi)-6-aminopirimidin-4-il)-5-fluoro-2-(hidroximetil)fenil)-6-ciclopropil-3,4-dihidroisoquinolin-1(2H)-one; N-(2-((4-amino-6-(3-(6-ciclopropil-1-oxo-3,4-dihidroisoquinolin-2(1H)-il)-5-fluoro-2-(hidroximetil)fenil)pirimidin-5-il)oxi)etil)-N-metilacrilamida; N-(3-(5-(((2S,4R)-1-acriloil-4-metoxipirrolidin-2-il)metoxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(6-amino-5-(((2S,4R)-1-(but-2-inoil)-4-metoxipirrolidin-2-il)metoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; 2-(3-(5-(((2S,4R)-1-acriloil-4-metoxipirrolidin-2-il)metoxi)-6-aminopirimidin-4-il)-5-fluoro-2-(hidroximetil)fenil)-6-ciclopropil-3,4-dihidroisoquinolin-1(2H)-one; N-(3-(5-(((2S,4S)-1-acriloil-4-metoxipirrolidin-2-il)metoxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(6-amino-5-(((2S,4S)-1-(but-2-inoil)-4-metoxipirrolidin-2-il)metoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(5-(((2S,4R)-1-acriloil-4-fluoropirrolidin-2-il)metoxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(6-amino-5-(((2S,4R)-1-(but-2-inoil)-4-fluoropirrolidin-2-il)metoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; (S)-N-(3-(5-((1-acriloilazetidin-2-il)metoxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; (S)-N-(3-(6-amino-5-((1-propioloilazetidin-2-il)metoxi)pirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; (S)-2-(3-(5-((1-acriloilazetidin-2-il)metoxi)-6-aminopirimidin-4-il)-5-fluoro-2-(hidroximetil)fenil)-6-ciclopropil-3,4-dihidroisoquinolin-1(2H)-one; (R)-N-(3-(5-((1-acriloilazetidin-2-il)metoxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; (R)-N-(3-(5-((1-acriloilpiperidin-3-il)metoxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(5-(((2R,3S)-1-acriloil-3-metoxipirrolidin-2-il)metoxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; N-(3-(5-(((2S,4R)-1-acriloil-4-cianopirrolidin-2-il)metoxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida; o N-(3-(5-(((2S,4S)-1-acriloil-4-cianopirrolidin-2-il)metoxi)-6-aminopirimidin-4-il)-5-fluoro-2-metilfenil)-4-ciclopropil-2-fluorobenzamida.

A menos que se indique lo contrario, los términos químicos usados anteriormente en la descripción del inhibidor de BTK de Fórmula I se usan de acuerdo con su significando según lo

establece la Solicitud Internacional WO/2015/079417, que se incorpora aquí como referencia en su totalidad.

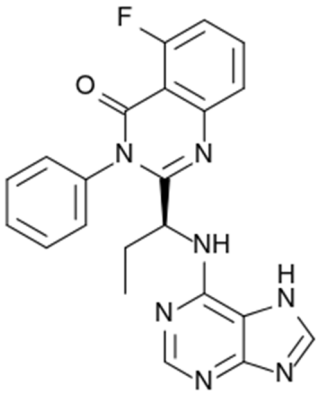
En una modalidad, el inhibidor de quinasa es un inhibidor de mTOR seleccionado *de temsirolimu*s; ridaforolimus (1*R*,2*R*,4*S*)-4-[(2*R*)-2 [(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*, 23*S*,24*E*,26*E*,28*Z*,30*S*,32^{S},35*R*)-1,18-dihidroxi-19,30-dimetoxi-15,17,21,23, 29,35-hexametil-2,3,10,14,20-pentaoxo-11,36-dioxa-4-azatriciclo[30.3.1.0*4,9*] hexatriaconta-16,24,26,28-tetraen-12-il]propil]-2-metoxiciclohexil dimetilfosfinato, también conocido como AP23573 y MK8669; everolimus (RAD001); rapamicina (AY22989); simapimod; (5-{2,4-bis[(3*S*)-3-metilmorfolin-4-il]pirido[2,3-*d*]pirimidin-7-il}-2-metoxifenil)metanol (AZD8055); 2-amino-8-[*trans*-4-(2-hidroxietoxi)ciclohexil]-6-(6-metoxi-3-piridinil)-4-metil-pirido[2,3-*d*]pirimidin-7(8H*)-ona (PF04691502); y* N2-[1,4-dioxo-4-[[4-(4-oxo-8-fenil-4H-1-benzopiran-2-il)morfolinium-4-il]metoxi]butil]-L-arginilglicil-L-α-aspartil-serina-, sal interna (SF1126) (SEQ ID NO: 1316); y XL765.

En una modalidad, el inhibidor de quinasa es un inhibidor de mTOR, por ejemplo, rapamicina, y la rapamicina se administra a una dosis de aproximadamente 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg (por ejemplo, 6 mg) al día durante un período de tiempo, por ejemplo, diariamente durante un ciclo de 21 días o diariamente durante un ciclo de 28 días. En una modalidad, se administran 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 o más ciclos de rapamicina. En una modalidad, el inhibidor de quinasa es un inhibidor de mTOR, por ejemplo, everolimus, y el everolimus se administra a una dosis de aproximadamente 2 mg, 2,5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg (por ejemplo, 10 mg) al día durante un período de tiempo, por ejemplo, diariamente durante un ciclo de 28 días. En una modalidad, se administran 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 o más ciclos de everolimus.

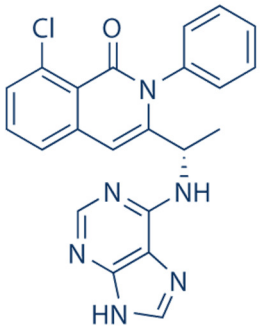
En una modalidad, el inhibidor de quinasa es un inhibidor de MNK seleccionado de CGP052088; 4-amino-3-(p-fluorofenilamino)-pirazolo [3,4-*d*] pirimidina (CGP57380); cercosporamida; ETC-1780445-2; y 4-amino-5-(4-fluoroanilino)-pirazolo [3,4-*d*] pirimidina.

En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con un inhibidor de la fosfoinosítido 3-quinasa (PI3K) (por ejemplo, un inhibidor de PI3K se describe aquí, por ejemplo, idelalisib o duvelisib) y / o rituximab. En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con idelalisib y rituximab. En formas de realización, una célula que

expresa CAR descrita en este documento se administra a un sujeto en combinación con duvelisib y rituximab. Idelalisib (también llamado GS-1101 o CAL-101; Gilead) es una pequeña molécula que bloquea la isoforma delta de PI3K. La estructura de idelalisib (5-fluoro-3-fenil-2 - [(1S) -1- (7H-purin-6-ilamino) propil] -4 (3H) -quinazolinona) se muestra a continuación.



Duvelisib (también llamado IPI-145; Infinity farmacéuticos y Abbvie) es una pequeña molécula que bloquea PI3K-δ, γ. La estructura de duvelisib (8-cloro-2-fenil-3 - [(1S) -1- (9H-purin-6-ilamino) etil] -1 (2H) isoquinolinona) se muestra a continuación.



En las realizaciones, el sujeto tiene CLL. En realizaciones, el sujeto ha recaído CLL, por ejemplo, el sujeto ha sido previamente administrada una terapia contra el cáncer (por ejemplo, sido previamente administrado un anticuerpo anti-CD20 o previamente ha administrado ibrutinib). Por ejemplo, el sujeto tiene una deleción en el brazo corto del cromosoma 17 (del (17p), por ejemplo, en una célula leucémica). En otros ejemplos, el sujeto no tiene una expresión del (17p). En realizaciones, el sujeto comprende una célula leucémica que comprende una mutación en la cadena pesada variable-región de inmunoglobulina (*IgVH*) De genes. En otras realizaciones, el sujeto no comprende una célula leucémica que comprende una mutación en el gen de inmunoglobulina de cadena pesada variable-región (IgVH). En las realizaciones, el sujeto

tiene una deleción en el brazo largo del cromosoma 11 (del (11q)). En otras realizaciones, el sujeto no tiene una del (11q). En formas de realización, idelalisib se administra a una dosis de aproximadamente 100 a 400 mg (por ejemplo, 100-125, 125-150, 150-175, 175-200, 200-225, 225-250, 250-275, 275-300, 325-350, 350-375, 375-400 mg o), por ejemplo, BID. En formas de realización, duvelisib se administra a una dosis de aproximadamente 15 a 100 mg (por ejemplo, aproximadamente 15-25, 25-50, 50-75, o 75 a 100 mg), por ejemplo, dos veces al día. En formas de realización, el rituximab se administra a una dosis de aproximadamente 350 a 550 mg / m2 (por ejemplo, 350-375, 375-400, 400-425, 425-450, 450-475, o 475 a 500 mg / m2), por ejemplo, por vía intravenosa.

En una modalidad, el inhibidor de quinasa es un fosfoinositol 3-quinasa (PI3K) y un inhibidor de mTOR seleccionado de entre 2-amino-8-[*trans*-4-(2-hidroxietoxi)ciclohexil]-6-(6-metoxi-3-piridinil)-4-metil-pirido[2,3-*d*]pirimidin-7(8*H*)-ona (PF-04691502); *N*-[4-[[4-(dimetilamino)-1-piperidinil]carbonil]fenil]-*N*'-[4-(4,6-di-4-morpholinil-1,3,5-triazin-2-il)fenil]urea (PF-05212384, PKI-587); 2-metil-2-{4-[3-metil-2-oxo-8-(quinolin-3-il)-2,3-dihidro-1*H*-imidazo[4,5-c]quinolin-1-il]fenil}propanenitrilo (BEZ-235); apitolisib (GDC-0980, RG7422); 2,4-difluoro-N-{2-(metiloxi)-5-[4-(4-piridazinil)-6-quinolinil]-3-piridinil}bencenosulfonamida (GSK2126458); 8-(6-metoxipiridin-3-il)-3-metil-1-(4-(piperazin-1-il)-3-(trifluorometil)fenil)-1H-imidazo[4,5-c]quinolin-2(3H)-ona ácido maléico (NVP-BGT226); 3-[4-(4-morfolinilpirido[3',2':4,5]furo[3,2-d]pirimidin-2-il]fenol (PI-103); 5-(9-isopropil-8-metil-2-morfolino-9H-purin-6-il)pirimidin-2-amina (VS-5584, SB2343); y N-[2-[(3,5-dimetoxifenil)amino]quinoxalin-3-il]-4-[(4-metil-3-metoxifenil)carbonil]aminofenilsulfonamida (XL765).

En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con un inhibidor de la cinasa del linfoma anaplásico (ALK). cinasas ALK a modo de ejemplo incluyen, pero no se limitan a crizotinib (Pfizer), ceritinib (Novartis), alectinib (Chugai), brigatinib (también llamado AP26113; Ariad), entrectinib (Ignyta), PF-06463922 (Pfizer), TSR-011 (Tesaro) (véase, por ejemplo, de ensayos clínicos Identificador Nº NCT02048488), CEP-37440 (Teva), y X-396 (Xcovery). En algunas realizaciones, el sujeto tiene un cáncer sólido, por ejemplo, un cáncer sólido descrito en este documento, por ejemplo, cáncer de pulmón.

El nombre químico de crizotinib es 3-[(1R) -1- (2,6-dicloro-3-fluorofenil) etoxi] -5- (1-piperidin-4-ilpirazol-4-il) piridin-2-amina. El nombre químico de ceritinib es 5-Cloro-N2-[2-isopropoxy-5-metil-4-(4-piperidinil)fenil]-N4-[2-(isopropilsulfonil)fenil]-2,4-pirimidinediamina. El nombre químico de alectinib es 9-etil-6,6-dimetil-8-(4-morfolinopiperidin-1-il)-11-oxo-6,11-dihidro-5H-benzo[b]carbazol-3-carbonitrilo. El nombre químico de brigatinib es 5-Cloro-N2-{4-[4-(dimetilamino)-1-piperidinol]-2-metoxifenil}-N4-[2-(dimetilfosforil)fenil]-2,4-pirimidinediamina. El nombre químico de entrectinib es N-(5-(3,5-difluorobencil)-1H-indazol-3-il)-4-(4-metilpiperazin-1-il)-2-((tetrahidro-2H-piran-4-il)amino)benzamida. El nombre químico del PF-06463922 es (10R)-7-Amino-12-fluoro-2,10,16-trimetil-15-oxo-10,15,16,17-tetrahidro-2H-8,4-(meteno)pirazolo[4,3-h][2,5,11]-benzoxadiazaciclotetradecin-3-carbonitrilo. La estructura química de la CEP-37440 es (S)-2-((5-chloro-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-1-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-2-il)amino)pirimidin-4-il)amino)-N-metilbenzamida. El nombre químico de la X-396 es (R)-6-amino-5-(1-(2,6-dicloro-3-fluorofeni)etoxi)-N-(4-(4-metilpiperazina-1-carbonil)fenil)piridazin-3-carboxamida.

En una modalidad, el inhibidor de quinasa es un inhibidor de ITK seleccionado de ibrutinib; N-(5-(5-(4-acetilpiperazina-1-carbonil)-4-metoxi-2-metilfeniltio)tiazol-2-il)-4-((3,3-dimetilbutan-2-ilamino)metil)benzamida (BMS-509744); 7-bencil-1-(3-(piperidin-1-il)propil)-2-(4-(piridin-4-il)fenil)-1H-imidazo[4,5-g]quinoxalin-6(5H)-ona (CTA056); *R*)-3-(1-(1-acriloilpiperidin-3-il)-4-amino-1*H*-pirazolo[3,4-d]pirimidin-3-il)-*N*-(3-metil-4-(1-metiletil))benzamida (PF-06465469).

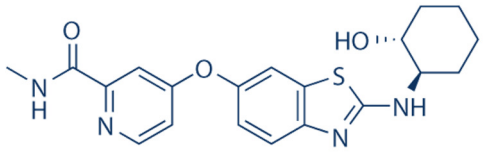
También se pueden usar fármacos que inhiben la calcineurina fosfatasa dependiente de calcio (ciclosporina y FK506) o que inhiben la quinasa p70S6, que es importante para la señalización inducida por factor de crecimiento (rapamicina). (Liu *et al*., Cell 66:807-815, 1991; Henderson *et al*., Immun. 73: 316-321, 1991; Bierer *et al*., Curr. Opin. Immun. 5: 763-773, 1993). En un aspecto adicional, las composiciones celulares de la presente invención pueden ser administradas a un paciente en combinación con (por ejemplo, antes, simultáneamente o después) un trasplante de médula ósea, terapia ablativa con células T usando agentes de quimioterapia tales como fludarabina, terapia de radiación de haz externo (XRT), ciclofosfamida y/o o anticuerpos como OKT3 o CAMPATH. En un aspecto, las composiciones celulares de la

presente invención se administran después de una terapia ablativa con células B, tal como agentes que reaccionan con CD20, por ejemplo, Rituxan. Por ejemplo, en una modalidad, sujetos pueden someterse posteriormente a tratamiento estándar con quimioterapia de alta dosis, seguida de un trasplante de células madre de sangre periférica. En ciertas modalidades, los sujetos reciben una infusión de las células inmunes expandidas de la presente invención después del trasplante. En una modalidad adicional, las células expandidas se administran antes o después de la cirugía.

En algunas realizaciones, una o más células que expresan CAR-descritos en este documento se administran en combinación con un virus oncolítico. En formas de realización, los virus oncolíticos son capaces de replicarse selectivamente en y provocando la muerte o retardando el crecimiento de una célula cancerosa. En algunos casos, los virus oncolíticos no tienen ningún efecto o un efecto mínimo sobre las células no cancerosas. Un virus oncolítico incluye pero no se limita a un adenovirus oncolítico, oncolítico Herpes Simplex Virus, retrovirus oncolítico, parvovirus oncolítico, virus vaccinia oncolítico, virus Sinbis oncolítico, virus de la gripe oncolítico, o virus de ARN oncolítico (por ejemplo, reovirus oncolítico, oncolítico virus de la enfermedad Newcastle (NDV), virus del sarampión oncolíticos, o virus de la estomatitis vesicular oncolítico (VSV)). formas de realización, una célula que expresa CAR descrito en este documento se administran a un sujeto en combinación con un inhibidor de indolamina 2,3-dioxigenasa (IDO). IDO es una enzima que cataliza la degradación de los aminoácidos, L-triptófano, a quinurenina. Muchos cánceres sobreexpresan IDO, por ejemplo, de próstata, colorrectal, pancreático, cervical, gástrico, de ovario, cabeza, y cáncer de pulmón. PDC, macrófagos y células dendríticas (DC) pueden expresar IDO. Sin estar ligado por la teoría, se cree que una disminución en (por ejemplo, catalizada por la IDO) Resultados de L-triptófano en un medio inmunosupresor mediante la inducción de anergia de células T y la apoptosis. Por lo tanto, sin pretender imponer ninguna teoría, se cree que un inhibidor de IDO puede mejorar la eficacia de una que expresa célula CAR- descrito en este documento, por ejemplo, por la disminución de la supresión o la muerte de una célula inmune que expresa CAR. En las realizaciones, el sujeto tiene un tumor sólido, por ejemplo, un tumor sólido descrito en este documento, por ejemplo, de próstata, colorrectal, pancreático, cervical, gástrico, de ovario, cabeza o cáncer de pulmón. inhibidores ejemplares de IDO incluyen, pero no se limitan a 1-metil-triptófano, indoximod (NewLink Genética) (véase, por ejemplo, Clinical Trial Identificador Nos NCT01191216;. NCT01792050), y INCB024360 (Incyte Corp.) (véase, por

ejemplo, ensayo clínico . Nos identificador NCT01604889; NCT01685255)

En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con un modulador de células supresoras de origen mieloide (MDSCs). MDSCs se acumulan en la periferia y en el sitio de tumor de muchos tumores sólidos. Estas células suprimen las respuestas de células T, lo que obstaculiza la eficacia de la terapia de células que expresan CAR. Sin estar ligado por la teoría, se cree que la administración de un modulador de MDSC mejora la eficacia de una célula que expresa CAR-descrito en este documento. En una realización, el sujeto tiene un tumor sólido, por ejemplo, un tumor sólido descrito en este documento, por ejemplo, glioblastoma. moduladores ejemplares de MDSCs incluyen, pero no se limitan a MCS110 y BLZ945. MCS110 es un anticuerpo monoclonal (mAb) contra macrófagos, factor estimulante de colonias (M-CSF). Véase, por ejemplo, de ensayos clínicos Identificador Nº NCT00757757. BLZ945 es un inhibidor de molécula pequeña de factor estimulante de colonias 1 receptor (CSF1R). Véase, por ejemplo, Pyonteck et al. Nat. Medicina. 19 (2013): 1264-1272. La estructura de BLZ945 se muestra a continuación.



En formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con una célula CD19 CART (por ejemplo, CTL019, por ejemplo, como se describe en WO2012 / 079000, incorporada aquí por referencia). En las realizaciones, el sujeto tiene leucemia mieloide aguda (AML), por ejemplo, una AML positiva CD19 o un AML CD19 negativo. En realizaciones, el sujeto tiene un linfoma CD19 +, por ejemplo, un CD19 + CD19 de una FL + LBDCG Linfoma no Hodgkin (LNH), un CD19 + o. En las realizaciones, el sujeto tiene un CD19 + linfoma en recaída o refractario. En formas de realización, una quimioterapia lymphodepleting se administra al sujeto antes de, simultáneamente con, o después de la administración (por ejemplo, infusión) de las células T

CARD CD19. En un ejemplo, la quimioterapia lymphodepleting se administra al sujeto antes de la administración de células CD19 de la compra. Por ejemplo, la quimioterapia lymphodepleting termina 1-4 días (por ejemplo,. 1, 2, 3, o 4 días) antes de la infusión de células CAR TCD19. En formas de realización, se administran múltiples dosis de células CART CD19, por ejemplo, como se describe en el presente documento. Por ejemplo, una sola dosis comprende alrededor de 5 x 108 células T CARCD19 . En formas de realización, una quimioterapia lymphodepleting se administra al sujeto antes de, simultáneamente con, o después de la administración (por ejemplo, infusión) de una célula CAR que expresan describe en este documento, por ejemplo, una célula CAR que expresan CD19 no. En formas de realización, un CAR CD19 se administra al sujeto antes de, simultáneamente con, o después de la administración (por ejemplo, infusión) de una célula no CD19 CAR que expresan, por ejemplo, una célula que no expresa CD19 CAR-descrito en este documento.

En algunas formas de realización, una célula que expresa CAR- descrito en este documento se administra a un sujeto en combinación con una célula CD19 CAR que expresan, por ejemplo, CTL019, por ejemplo, como se describe en WO2012 / 079000, incorporada aquí por referencia, para el tratamiento de una enfermedad asociada con la expresión de CLL-1, por ejemplo, un cáncer se describe en el presente documento. Sin estar ligado por la teoría, se cree que la administración de una célula que expresa CAR CD19 en combinación con una célula que expresa CAR mejora la eficacia de una célula que expresa CAR descrito en este documento por la orientación células tempranas de linaje de cáncer, por ejemplo, células madre de cáncer, modulando la respuesta inmune, agotamiento de células B de regulación, y / o mejorar el microambiente tumoral. Por ejemplo, una célula que expresa un CAR CD19 de cáncer de dianas celulares que expresan los marcadores tempranos de linaje, por ejemplo, células madre de cáncer y células que expresan CD19, mientras que la célula que expresa CAR descrito en este documento se dirige a células cancerosas que expresan los marcadores de linaje posterior, por ejemplo, CLL-1. Este enfoque de preacondicionamiento puede mejorar la eficacia de la célula que expresa CAR- descrito en este documento. En tales realizaciones, la célula CAR CD19 - expresión se administra antes de, simultáneamente con, o después de la administración (por ejemplo, infusión) de una célula CAR que expresan describe en este documento.

En formas de realización, una célula que expresa CAR que se describe en este documento también expresa un CAR de orientación CD19, por ejemplo, un CAR CD19. En una

realización, la célula que expresa un CAR descrito en este documento y un CAR de CD19 se administra a un sujeto para tratamiento de un cáncer descrito en este documento, por ejemplo, AML. En una realización, las configuraciones de una o ambas de las moléculas CAR comprenden un dominio de señalización intracelular primario y un dominio de señalización coestimuladora. En otra realización, las configuraciones de una o ambas de las moléculas CAR comprenden un dominio intracelular de señalización principal y dos o más, por ejemplo, 2, 3, 4, o 5 o más, coestimuladora dominios de señalización. En tales realizaciones, la molécula de CAR se describe en este documento y el CAR CD19 puede tener el mismo o un dominio de señalización intracelular primaria diferente, las mismas o diferentes de señalización coestimuladoras dominios, o el mismo número o un número diferente de dominios de señalización coestimuladoras. Alternativamente, el CAR que se describe en este documento y el CAR CD19 están configurados como un CAR segmentado, en el que una de las moléculas CAR comprenden un dominio de unión a antígeno y un dominio coestimuladora (por ejemplo, el 4-1BB), mientras que la otra molécula CAR comprende unirse a un antígeno dominio y un dominio de señalización intracelular primaria (por ejemplo, CD3 zeta).

En algunas formas de realización, una célula que expresa CAR descrita en este documento se administra a un sujeto en combinación con un polipéptido de interleucina-15 (IL-15), un receptor alfa de interleucina-15 (IL-15Ra) polipéptido, o una combinación de ambos una IL -15 polipéptido y un polipéptido de IL-15Ra por ejemplo, Hetil-15 (Admune Therapeutics, LLC). Hetil-15 es un complejo no covalente heterodimérico de la IL-15 e IL-15Ra. Hetil-15 se describe en, por ejemplo, EE.UU. 8.124.084, EE.UU. 2012/0177598, EE.UU. 2009/0082299, EE.UU. 2012/0141413, 2011/0081311 y EE.UU., que se incorpora aquí por referencia. En formas de realización, het-IL-15 se administra por vía subcutánea. En las realizaciones, el sujeto tiene un cáncer, por ejemplo, cáncer sólido, por ejemplo, melanoma o cáncer de colon. En las realizaciones, el sujeto tiene un cáncer metastásico.

En formas de realización, un sujeto que tiene una enfermedad descrita en el presente documento, por ejemplo, un trastorno hematológico, por ejemplo, AML o MDS, se administra una célula que expresa CAR descrita en el presente documento en combinación con un agente, por ejemplo, citotóxica o quimioterapia agente, una terapia biológica (por ejemplo, anticuerpo, por ejemplo, el anticuerpo monoclonal, o la terapia celular), o un inhibidor de (por ejemplo, inhibidor de la cinasa). En formas de realización, se administra al sujeto una célula CAR-

expresión descrito en el presente documento en combinación con un agente citotóxico, por ejemplo, CPX-351 (Celator Pharmaceuticals), citarabina, daunorubicina, vosaroxin (Sunesis Pharmaceuticals), sapacitabine (Cyclacel Pharmaceuticals), idarubicina o mitoxantrona. CPX-351 es una formulación liposomal que comprende citarabina y daunorrubicina a una proporción de 5: 1 molar. En formas de realización, se administra al sujeto una célula que expresa CAR descrita en este documento en combinación con un agente de hipometilación, por ejemplo, un inhibidor de la ADN metiltransferasa, por ejemplo, azacitidina o decitabina. En formas de realización, se administra al sujeto una célula que expresa CAR- descrita en el presente documento en combinación con una terapia biológica, por ejemplo, un anticuerpo o la terapia celular, por ejemplo, 225Ac-lintuzumab (Actimab-A; actinio Pharmaceuticals), IPH2102 (innata Pharma / Bristol Myers Squibb), SGN-CD33A (Seattle Genetics), o gemtuzumab ozogamicina (Mylotarg; Pfizer). SGN-CD33A es un conjugado anticuerpo-fármaco (ADC) que comprende un dímero pirrolobenzodiazepina que se une a un anticuerpo anti-CD33. Actimab-A es un anticuerpo anti-CD33 (lintuzumab) marcado con actinio. IPH2102 es un anticuerpo monoclonal que se dirige a los receptores de tipo inmunoglobulina asesinas (KIR). En formas de realización, se administra al sujeto una célula que expresa CAR descrito en el presente documento en combinación un inhibidor de FLT3, por ejemplo, sorafenib (Bayer), midostaurina (Novartis), quizartinib (Daiichi Sankyo), crenolanib (Arog Pharmaceuticals), PLX3397 (Daiichi Sankyo), AKN-028 (Akinion Pharmaceuticals), o ASP2215 (Astellas). En formas de realización, se administra al sujeto una célula que expresa CAR descrita en el presente documento en combinación con un inhibidor de la isocitrato deshidrogenasa (IDH), por ejemplo, AG-221 (Celgene / Agios) o AG-120 (Agios / Celgene). En formas de realización, se administra al sujeto una célula CAR-expresión descrito en este documento en combinación con un regulador del ciclo celular, por ejemplo, inhibidor de quinasa polo-como 1 (Plk1), por ejemplo, volasertib (Boehringer Ingelheim); o un inhibidor de la quinasa dependiente de ciclina 9 (Cdk9), por ejemplo, alvocidib (Tolero Farmacéutica / Sanofi Aventis). En formas de realización, se administra al sujeto una célula que expresa CAR descrita en el presente documento en combinación con un receptor inhibidor de células B de señalización de red, por ejemplo, un inihibitor de linfoma de células B 2 (Bcl-2), por ejemplo, venetoclax (Abbvie / Roche); o un inhibidor de la tirosina quinasa de Bruton (Btk), por ejemplo, ibrutinib (Pharmacyclics / Johnson & Johnson Janssen Pharmaceutical). En formas de realización, se administra al sujeto una célula CAR-expresión descrito en el presente documento en combinación con un inhibidor de la

aminopeptidasa M1, por ejemplo, tosedostat (CTI BioPharma / Vernalis); un inhibidor de la histona deacetilasa (HDAC), por ejemplo, pracinostat (MEI Pharma); un inhibidor de la multi-quinasa, por ejemplo, rigosertib (Onconova Terapéutica / Baxter / Symbio); o una peptídico CXCR4 agonista inverso, por ejemplo, BL-8040 (BioLineRx).

En otra realización, los sujetos reciben una infusión de la célula que expresa CAR, célula por ejemplo, expresión de CAR CD19 -, las composiciones de la presente invención antes del trasplante, por ejemplo, el trasplante alogénico de células madre, de células. En una realización preferida, las células CAR expresar expresan transitoriamente el CAR, por ejemplo, por electroporación de un CAR ARNm, por lo que la expresión del antígeno dirigido por el CAR, por ejemplo, CD19 se termina antes de la infusión de células madre del donante para evitar el fracaso del injerto.

En algunas modalidades, el virus oncolítico es un virus, por ejemplo, un virus oncolítico recombinante, descrito en US2010/0178684 A1, el cual se incluye en el presente documento en su totalidad a manera de referencia. En algunas modalidades, un virus oncolítico recombinante comprende una secuencia de ácido nucleico (por ejemplo, una secuencia de ácido nucleico heteróloga) que codifica a un inhibidor de una respuesta inmune o inflamatoria, por ejemplo, tal como se describe en US2010/0178684 A1, que se incluye en el presente documento en su totalidad a manera de referencia. En algunas modalidades, el virus oncolítico recombinante, por ejemplo, el NDV oncolítico, se compone de una proteína pro-apoptótica (por ejemplo, apoptina), una citoquina (por ejemplo, GM-CSF, interferón-gamma, interleucina-2 (IL-2), factor de necrosis tumoral alfa), una inmunoglobulina (por ejemplo, un anticuerpo contra firbonectina ED-B), un antígeno asociado a tumor, una proteína adaptadora biespecífica (por ejemplo, anticuerpo biespecífico o fragmento de anticuerpo dirigido contra la proteína NDV HN y un receptor co-estimulador de células T, tal como CD3 o CD28, o proteína de fusión entre IL-2 humana y anticuerpo de cadena sencilla dirigido contra la proteína NDV HN). Véase, por ejemplo, Zamarin et al. Future Microbiol. 7.3 (2012): 347-67, que se incluye en su totalidad en el presente documento como referencia. En algunas modalidades, el virus oncolítico es un NDV oncolítico quimérico, como el que se describe en los documentos US 8591881 B2, US 2012/0122185 A1 o US 2014/0271677 A1, cada uno de los cuales se incluye en su totalidad en el presente documento a manera de referencia.

En algunas modalidades, el virus oncolítico comprende un adenovirus de replicación

condicionada (CRAd), el cual está diseñado para replicarse exclusivamente en células cancerosas. Véase, por ejemplo, Alemany et al. Nature Biotechnol. 18 (2000): 723-27. En algunas modalidades, un adenovirus oncolítico comprende uno de los adenovirus descritos en la Tabla 1, página 725, de Alemany et al., que se incluye en su totalidad en el presente documento a manera de referencia.

Ejemplos de virus oncolíticos incluyen, de manera enunciativa más no limitativa, los siguientes:

Adenovirus oncolítico grupo B (ColoAd1) (PsiOxus Terapéutica Ltd.) (Véase, por ejemplo, el Identificador de Ensayo Clínico No.: NCT02053220);

ONCOS-102 (previamente llamado CGTG-102), que es un adenovirus que comprende factor estimulador de colonias de granulocitos y macrófagos (GM-CSF) (Oncos Therapeutics) (véase, por ejemplo, el Identificador de Ensayo Clínico No. NCT01598129);

VCN-01, que es un adenovirus humano oncolítico modificado genéticamente que codifica a la hialuronidasa humana PH20 (VCN Biosciences, SL) (Véase, por ejemplo, el Identificador de Ensayo Clínico No.: NCT02045602 y NCT02045589);

Adenovirus de replicación condicional ICOVIR-5, el cual es un virus derivado de adenovirus humano de tipo silvestre serotipo 5 (hAd5) que ha sido modificado para replicarse selectivamente en células cancerosas con una vía de retinoblastoma/E2F no regulada (Institut Català d'Oncologia) (véase, por ejemplo, el Identificador de Ensayo Clínico: NCT01864759);

Celyvir, el cual comprende células madre mesenquimales (MSC) autólogas derivadas de médula ósea infectada con ICOVIR5, un adenovirus oncolítico (Hospital Infantil Universitario Niño Jesús, Madrid, España/Ramón Alemany) (véase, por ejemplo, el Identificador de Ensayo Clínico No.: NCT01844661);

CG0070, el cual es un adenovirus oncolítico de replicación condicional serotipo 5 (Ad5), en el que el promotor E2F-1 humano genera la expresión de los genes virales esenciales E1a, restringiendo así la replicación viral y la citotoxicidad en las células tumorales defectuosas de la vía del retinoblastoma (Rb) (Cold Genesys, Inc.) (Véase, por ejemplo, el Identificador de Ensayo Clínico No.: NCT02143804); o

DNX-2401 (previamente llamado Delta-24-RGD), el cual es un adenovirus diseñado para replicarse selectivamente en células defectuosas de la vía del retinoblastoma (Rb) y para

infectar células que expresan ciertas integrinas de unión RGD de manera más eficiente (Clínica Universidad de Navarra, Universidad de Navarra/DNAtrix, Inc.) (Véase, por ejemplo, el Identificador de Ensayo Clínico No.: NCT01956734).

En algunas modalidades, un virus oncolítico descrito en este documento se administra mediante inyección, por ejemplo, inyección subcutánea, intra-arterial, intravenosa, intramuscular, intratecal o intraperitoneal. En algunas modalidades, un virus oncolítico descrito en el presente documento se administra por vía intratumoral, transdérmica, transmucosa, oral, intranasal o mediante administración pulmonar.

En una modalidad, se puede administrar al sujeto un agente que reduce o mejora un efecto secundario asociado a la administración de una célula que expresa CAR. Los efectos secundarios asociados a la administración de una célula que expresa un CAR incluyen, de manera enunciativa mas no limitativa, CRS y linfohistiocitosis hemofagocítica (HLH), también denominada síndrome de activación de macrófagos (MAS). Los síntomas de CRS incluyen fiebre alta, náuseas, hipotensión transitoria, hipoxia y similares. En consecuencia, los métodos descritos en el presente documento pueden comprenden la administración de una célula que expresa un CAR descrita en el presente documento a un sujeto y la administración además de un agente para controlar los niveles elevados de un factor soluble que resultan del tratamiento con una célula que expresa CAR. En una modalidad, el factor soluble elevado en el sujeto es uno o más de entre IFN-γ, TNFα, IL-2 y IL-6. Por lo tanto, un agente administrado para tratar este efecto secundario puede ser un agente que neutralice uno o más de estos factores solubles. Ejemplos de estos agentes incluyen, de manera enunciativa mas no limitativa, un esteroide (por ejemplo, corticosteroides), un inhibidor de TNF y un inhibidor de IL-6. Un ejemplo de un inhibidor de TNFα es una molécula de anticuerpo anti-TNFα, infliximab, adalimumab, certolizumab pegol y golimumab. Otro ejemplo de un inhibidor de TNFα es una proteína de fusión tal como entanercept. Inhibidores de TNFα de moléculas pequeñas incluyen, de manera enunciativa mas no limitativa, derivados de la xantina (por ejemplo, pentoxifilina) y bupropión. Un ejemplo de un inhibidor de IL-6 es una molécula de anticuerpo anti-IL-6 tal como tocilizumab (toc), sarilumab, elsilimomab, CNTO 328, ALD518/BMS-945429, CNTO 136, CPSI-2364, CDP6038, VX30, ARGX-109, FE301 y FM101. En una modalidad, la molécula de anticuerpo anti-IL-6 es tocilizumab. Un ejemplo de un inhibidor basado en IL-1R es anakinra.

En algunas modalidades, se realiza reducción de linfocitos en un sujeto, por ejemplo,

antes de administrar una o más células que expresan una CAR descritas en el presente documento. En algunas modalidades, la reducción de linfocitos comprende la administración de uno o más de melfalán, cytoxan, ciclofosfamida y fludarabina.

En algunas modalidades, una quimioterapia reductora de linfocitos se administra al sujeto antes de, simultáneamente con o después de la administración (por ejemplo, infusión) de células CAR, por ejemplo, células descritas en el presente documento. En un ejemplo, la quimioterapia reductora de linfocitos se administra al sujeto antes de la administración de células CAR. Por ejemplo, la quimioterapia reductora de linfocitos termina 1-4 días (por ejemplo, 1, 2, 3, o 4 días) antes de la infusión de células CAR. En algunas modalidades, las dosis múltiples de células CAR se administran, por ejemplo, tal como se describe en el presente documento. Por ejemplo, una sola dosis comprende aproximadamente 5 x 10^8 células CAR. En algunas modalidades, una quimioterapia reductora de linfocitos se administra al sujeto antes de, simultáneamente con o después de la administración (por ejemplo, infusión) de una célula que expresa un CAR descrita en el presente documento.

En algunas modalidades, las células que expresan CAR en el presente documento se administran a un sujeto en combinación con una célula que expresa un CAR de CD19, por ejemplo, CTL019, por ejemplo, tal como se describe en WO2012/079000, el cual se incluye en el presente documento a manera de referencia, para el tratamiento de una enfermedad asociada a la expresión de antígeno de cáncer, por ejemplo, un cáncer descrito el presente documento. Al margen de las limitaciones que impone la teoría, se cree que la administración de una célula que expresa un CAR de CD19 en combinación con otra célula que expresa un CAR mejora la eficacia de una célula que expresa un CAR descrita en el presente documento dirigiéndose a células cancerosas de linaje temprano, por ejemplo, células madre cancerosas, modulando la respuesta inmunitaria, agotando las células B regulatorias y/o mejorando el microambiente tumoral. Por ejemplo, una célula que expresa un CAR de CD19 se dirige a células cancerosas que expresan marcadores de linaje temprano, por ejemplo, células madre cancerosas y células que expresan CD19, mientras que algunas otras células que expresan CAR descritas en el presente documento se dirigen a células cancerosas que expresan marcadores de linaje posterior. Este enfoque de preacondicionamiento puede incrementar la eficacia de la célula que expresa un CAR descrita en el presente documento. En dichas modalidades, la célula que expresa un CAR de CD19 se administra antes de, simultáneamente con o después de la administración (por

ejemplo, infusión) de la segunda célula que expresa CAR.

En algunas modalidades, una célula que expresa un CAR que expresa un CAR que se dirige a un antígeno de cáncer diferente a CD19 también expresa un CAR que se dirige a CD19, por ejemplo, un CAR de CD19. En una modalidad, la célula que expresa un CAR no CD19 y un CAR de CD19 se administra a un sujeto para tratamiento de un cáncer descrito en el presente documento, por ejemplo, LMA. En una modalidad, las configuraciones de una o ambas de las moléculas de CAR comprenden un dominio primario de señalización intracelular y un dominio coestimulador de señalización. En otra modalidad, las configuraciones de una o ambas de las moléculas de CAR comprenden un dominio primario de señalización intracelular y dos o más, por ejemplo, 2, 3, 4, o 5 o más, dominios coestimuladores de señalización. En dichas modalidades, la molécula de CAR no CD19 y el CAR de CD19 pueden tener el mismo dominio primario de señalización intracelular o dominios primarios de señalización intracelular diferentes, el mismo dominio coestimulador de señalización o dominios coestimuladores de señalización diferentes, o la misma cantidad de dominios coestimuladores de señalización o una cantidad diferente de dominios coestimuladores de señalización. Alternativamente, el CAR no de CD19 y el CAR de CD19 están configurados como un CAR dividido, en el que una de las moléculas de CAR comprende un dominio de unión a antígeno y un dominio coestimulador (por ejemplo, 4-1BB), mientras que la otra molécula de CAR comprende un dominio de unión a antígeno y un dominio primario de señalización intracelular (por ejemplo, CD3 zeta).

Inhibidores de molecula inhibitoria /inhibidores del punto de comprobación.

En una modalidad, se puede administrar al sujeto un agente que incrementa la actividad de una célula que expresa CAR. Por ejemplo, en una modalidad, el agente puede ser un agente que inhibe una molécula inhibidora, por ejemplo, el agente es un inhibidor de punto de control. Las moléculas inhibidoras o de coprobación, por ejemplo, de muerte programada 1 (PD1), pueden, en algunas modalidades, disminuir la capacidad de una célula que expresa un CAR para montar una respuesta efectora inmune. Ejemplos de moléculas inhibidoras incluyen PD1, PD-L1, PD-L2, CTLA4, TIM3, CEACAM (por ejemplo, CEACAM-1, CEACAM-3 y/o CEACAM-5), LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, CD160, 2B4, CD80, CD86, B7-H3 (CD276), CMH de clase B7-H4 (VTCN1), HVEM (TNFRSF14 o CD270), KIR, A2AR, CMH de clase I, II, GAL9, adenosina y TGFR (TGFR beta).

En modalidades, la célula que expresa CAR que se describe en el presente documento

comprende un receptor interruptor coestimulatoiior, por ejemplo, como se describe en WO 2013/019615, la cual se incorpora como referencia en su totalidad.

Los métodos aquí descritos pueden incluir la administración de una célula que expresa CAR en combinación con un inhibidor de punto de control. En una realización, el sujeto es un respondedor completo. En otra realización, el sujeto es un respondedor parcial o no respondedor, y, por ejemplo, en algunas realizaciones, el inhibidor de punto de control se administra antes de la célula CAR que expresan, por ejemplo, dos semanas, 12 días, 10 días, 8 días, una semana, 6 días, 5 días, 4 días, 3 días, 2 días o 1 día antes de la administración de la célula CAR-expresión. En algunas realizaciones, el inhibidor de punto de control se administra simultáneamente con la célula que expresa CAR.

La inhibición de una molécula inhibidora, por ejemplo, mediante inhibición a nivel del ADN, ARN o proteína, puede optimizar el desempeño de una célula que expresa CAR. En algunas modalidades, un ácido nucleico inhibidor, por ejemplo, un ácido nucleico inhibidor, por ejemplo, un ARNds, por ejemplo, un ARNsi o ARNsh, o una repetición palindrómica corta agrupada y regularmente interespaciada (CRISPR), una nucleasa efectora de tipo activador de transcripción (TALEN) o una endonucleasa de dedo de zinc (ZFN) se puede usar para inhibir la expresión de una molécula inhibidora en la célula que expresa CAR. En una modalidad, el inhibidor es un ARNsh. En una modalidad, la molécula inhibidora se inhibe dentro de una célula que expresa CAR. En estas modalidades, una molécula de ARNds que inhibe la expresión de la molécula inhibidora está enlazada al ácido nucleico que codifica un componente, por ejemplo, todos los componentes, del CAR.

En una modalidad, una molécula de ácido nucleico que codifica una molécula de ARNds que inhibe la expresión de la molécula que modula o regula, por ejemplo, inhibe, la función de las células T está enlazada operativamente a un promotor, por ejemplo, un promotor derivado de H1 o U6, de tal manera que la molécula de ARNds que inhibe la expresión de la molécula que modula o regula, por ejemplo, inhibe, la función de las células T se expresa, por ejemplo, se expresa dentro de una célula que expresa CAR. Véase, por ejemplo, Tiscornia G., "Development of Lentiviral Vectors Expressing siRNA", Capítulo 3, en Gene Transfer: Delivery and Expression of DNA and RNA (Eds. Friedmann y Rossi). Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, Estados Unidos, 2007; Brummelkamp TR, et al. (2002) Science 296: 550-553; Miyagishi M, et al. (2002) Nat. Biotechnol. 19: 497–500. En una modalidad, la

molécula de ácido nucleico que codifica una molécula de ARNds que inhibe la expresión de la molécula que modula o regula, por ejemplo, inhibe, la función de las células T está presente en el mismo vector, por ejemplo, un vector lentiviral, que comprende una molécula de ácido nucleico que codifica un componente, por ejemplo, todos los componentes, del CAR. En dicha modalidad, la molécula de ácido nucleico que codifica una molécula de ARNds que inhibe la expresión de la molécula que modula o regula, por ejemplo, inhibe, la función de las células T está localizada en el vector, por ejemplo, el vector lentiviral, 5'- o 3'- con respecto al ácido nucleico que codifica un componente, por ejemplo, todos los componentes, del CAR. La molécula de ácido nucleico que codifica una molécula de ARNds que inhibe la expresión de la molécula que modula o regula, por ejemplo, inhibe, la función de las células T se puede transcribir en la misma dirección o en una dirección diferente a la del ácido nucleico que codifica un componente, por ejemplo, todos los componentes, del CAR. En una modalidad, la molécula de ácido nucleico que codifica una molécula de ARNds que inhibe la expresión de la molécula que modula o regula, por ejemplo, inhibe, la función de las células T está presente en un vector diferente al vector que comprende una molécula de ácido nucleico que codifica un componente, por ejemplo, todos los componentes, del CAR. En una modalidad, la molécula de ácido nucleico que codifica una molécula de ARNds que inhibe la expresión de la molécula que modula o regula, por ejemplo, inhibe, la función de las células T se expresa transitoriamente dentro de una célula que expresa CAR. En una modalidad, la molécula de ácido nucleico que codifica una molécula de ARNds que inhibe la expresión de la molécula que modula o regula, por ejemplo, inhibe, la función de las células T se integra de manera estable en el genoma de una célula que expresa CAR. En una modalidad, la molécula de la que modula o regula, por ejemplo, inhibe, la función de las células T es PD-1.

En una realización, el inhibidor de una señal inhibidora puede ser, por ejemplo, un anticuerpo o fragmento de anticuerpo que se une a una molécula inhibidora. Por ejemplo, el agente puede ser un anticuerpo o fragmento de anticuerpo que se une a PD1, PD-L1, PD-L2 o CTLA4 (por ejemplo, ipilimumab (también referido como MDX-010 y MDX-101, y comercializados como Yervoy®; Bristol -Myers Squibb;. tremelimumab (IgG2 anticuerpo monoclonal disponible de Pfizer, anteriormente conocido como ticilimumab, CP-675206)) En una forma de realización, el agente es un anticuerpo o fragmento de anticuerpo que se une a TIM3 En una realización, el agente es un anticuerpo. o fragmento de anticuerpo que se une a LAG3. En una realización, el agente es un anticuerpo o fragmento de anticuerpo que se une a

CEACAM (por ejemplo, CEACAM-1, CEACAM-3 y / o CEACAM-5). En formas de realización, el agente que mejora la actividad de una célula CAR que expresan, por ejemplo, inhibidor de una molécula inhibidora, se administra en combinación con un CAR alogénico, por ejemplo, un CAR alogénico describe en este documento (por ejemplo, descrito en la sección CAR alogénico en el presente documento).

PD1 es un miembro inhibidor de la familia de receptores CD28, que también incluye CD28, CTLA-4, ICOS y BTLA. PD1 se expresa en células B activadas, células T y células mieloides (Agata et al. 1996 Int. Immunol 8: 765-75). Se ha demostrado que dos ligandos para PD1, PD-L1 y PD-L2 regulan a la baja la activación de células T tras unirse a PD1 (Freeman et al. 2000 J Exp Med 192: 1027-34; Latchman et al. 2001 Nat Immunol 2: 261-8; TCARer et al. 2002 Eur J Immunol 32: 634-43). PD-L1 es abundante en cánceres humanos (Dong et al. 2003 J Mol Med 81: 281-7; Blank et al. 2005 Cancer Immunol. Immunother 54: 307-314; Konishi et al. 2004 Clin Cancer Res 10: 5094). La supresión inmune puede ser revertida inhibiendo la interacción local de PD1 con PD-L1. Anticuerpos, fragmentos de anticuerpos y otros inhibidores de PD1, PD-L1 y PD-L2 están disponibles en la técnica y se pueden usar en combinación con un CAR de CD19 descrito en el presente documento. Por ejemplo, nivolumab (también conocido como BMS-936558 o MDX1106; Bristol-Myers Squibb) es un anticuerpo monoclonal totalmente humano de IgG4 que bloquea PD1 específicamente. Nivolumab (clon 5C4) y otros anticuerpos monoclonales humanos que se unen específicamente a PD1 se divulgan en US 8,008,449 y WO2006/121168. Pidilizumab (CT-011; Cure Tech) es un anticuerpo monoclonal humanizado de IgG1k que se une a PD1. Pidilizumab y otros anticuerpos monoclonales humanizados anti-PD1 se divulgan en WO2009/101611. Pembrolizumab (anteriormente conocido como lambrolizumab, y también denominado Keytruda, MK03475; Merck) es un anticuerpo monoclonal humanizado de IgG4 que se une a PD1. Pembrolizumab y otros anticuerpos humanizados anti-PD-1 se divulgan en US 8,354,509 y WO2009/114335. MEDI4736 (Medimmune) es un anticuerpo monoclonal humano que se une a PDL1, e inhibe la interacción del ligando con PD1. MDPL3280A (Genentech/Roche) es un anticuerpo monoclonal de IgG1 optimizado para Fc humano que se une a PD-L1. MDPL3280A y otros anticuerpos monoclonales humanos que se unen a PD-L1 se divulgan en la Patente de Estados Unidos No.: 7,943,743 y la Publicación de Estados Unidos No.: 20120039906. Otros agentes de unión anti-

PD-L1 incluyen YW243.55.S70 (las regiones variables de cadena pesada y ligera se muestran en SEQ ID NO. 20 y 21 en WO2010/077634) y MDX-1 105 (también conocido como BMS-936559, y, por ejemplo, agentes de unión anti-PD-L1 divulgados en WO2007/005874). AMP-224 (B7-DCIg; Amplimmune; por ejemplo, divulgado en WO2010/027827 y WO2011/066342), es un receptor soluble de PD-L2 de fusión a Fc que bloquea la interacción entre PD-1 y B7-H1. Otros anticuerpos anti-PD-1 incluyen AMP 514 (Amplimmune), entre otros, por ejemplo, anticuerpos anti-PD-1 divulgados en US 8,609,089, US 2010028330 y/o US 20120114649.

En algunas modalidades, un inhibidor de PD1 descrito en el presente documento (por ejemplo, un anticuerpo PD1, por ejemplo, un anticuerpo PD1 descrito en el presente documento) se usa junto con un CAR de CD19 descrito en el presente documento para el tratamiento de una enfermedad asociada a la expresión de CD19. En algunas modalidades, un inhibidor de PD-L1 descrito en el presente documento (por ejemplo, un anticuerpo PD-L1, por ejemplo, un anticuerpo PD-L1 descrito en el presente documento) se usa junto con un CAR de CD19 descrito en el presente documento para el tratamiento de una enfermedad asociada a la expresión de CD19. La enfermedad puede ser, por ejemplo, un linfoma tal como DLBCL, incluyendo DLBCL primario o DLBCL secundario. En algunas modalidades, el sujeto tiene, o se identifica por tener, al menos 5 %, 6 %, 7 %, 8 %, 9 %, 10 %, 20 %, 30 %, 40 %, 50 %, 60 %, 70 %, 80 % o 90 % de células cancerosas, por ejemplo, células DLBCL, que son CD3+/PD1+. En algunas modalidades, el sujeto tiene, o se identifica por tener, poblaciones de células CD19+ y células PD-L1+ sustancialmente no superpuestas en un cáncer, por ejemplo, microambiente canceroso. Por ejemplo, en algunas modalidades, menos de 20 %, 10 %, 9 %, 8 %, 7 %, 6 %, 5 %, 4 %, 3 %, 2 % o 1 % de las células en el cáncer, por ejemplo, microambiente canceroso, son doble positivas para CD19 y PD-L1.

En algunas modalidades, el sujeto se trata con una combinación de un CAR de CD19, un inhibidor de PD1 y un inhibidor de PD-L1. En algunas modalidades, el sujeto se trata con una combinación de un CAR de CD19, un inhibidor de PD1 y un inhibidor de CD3. En algunas modalidades, el sujeto se trata con una combinación de un CAR de CD19, un inhibidor de PD1, un inhibidor de PD-L1 y un inhibidor de CD3.

En algunas modalidades, los métodos de la presente invención incluyen un paso de ensayo de células en una muestra biológica, por ejemplo, una muestra que comprende células

DLBCL, para CD3 y/o PD-1 (por ejemplo, expresión de CD3 y/o PD-1). En algunas modalidades, los métodos incluyen un paso de ensayo de células en una muestra biológica, por ejemplo, una muestra que comprende células DLBCL, para CD19 y/o PD-L1 (por ejemplo, expresión de CD19 y/o PD-L1). En algunas modalidades, los métodos incluyen, por ejemplo, proporcionar una muestra que comprende células cancerosas y llevar a cabo un paso de detección, por ejemplo, mediante técnicas de inmunohistoquímica, para una o más de CD3, PD-1, CD19 o PD-L1. Los procedimientos pueden comprender un paso adicional de recomendar o administrar un tratamiento, por ejemplo, un tratamiento que comprende un CAR de CD19.

En una modalidad, el anticuerpo anti-PD-1 o fragmento del mismo es una molécula de anticuerpo anti-PD-1 tal como se describe en US 2015/0210769, llamado "Antibody Molecules to PD-1 and Uses Thereof", el cual se incluye en su totalidad en el presente documento a manera de referencia. En una modalidad, la molécula de anticuerpo anti-PD-1 incluye al menos una, dos, tres, cuatro, cinco o seis CDR(o colectivamente todas las CDR) de una regiones variables de cadena pesada y ligera de un anticuerpo seleccionado de cualquiera de BAP049-hum01, BAP049-hum02, BAP049-hum03, BAP049-hum04, BAP049-hum05, BAP049-hum06, BAP049-hum07, BAP049-hum08, BAP049-hum09, BAP049-hum10, BAP049-hum11, BAP049-hum12, BAP049-hum13, BAP049-hum14, BAP049-hum15, BAP049-hum16, BAP049-Clon-A, BAP049-Clon-B, BAP049-Clon-C, BAP049-Clon-D o BAP049-Clon-E; o tal como se describe en la Tabla 1 de US 2015/0210769, o codificada por la secuencia de nucleótidos en la Tabla 1; o una secuencia sustancialmente idéntica (por ejemplo, al menos 80 %, 85 %, 90 %, 92 %, 95 %, 97 %, 98 %, 99 % o más idéntica) a cualquiera de las secuencias mencionadas anteriormente; o CDR estrechamente relacionadas, por ejemplo, CDR que son idénticas o que tienen al menos una alteración de aminoácidos, pero no más de dos, tres o cuatro alteraciones (por ejemplo, sustituciones, deleciones, o inserciones, por ejemplo, sustituciones conservadoras).

En aún otra modalidad, la molécula de anticuerpo anti-PD-1 comprende al menos una, dos, tres o cuatro variables de un anticuerpo descrito en el presente documento, por ejemplo, un anticuerpo seleccionado entre cualquiera de BAP049-hum01, BAP049-hum02, BAP049-hum03, BAP049-hum04, BAP049-hum05, BAP049-hum06, BAP049-hum07, BAP049-hum08, BAP049-hum09, BAP049-hum10, BAP049-hum11, BAP049-hum12, BAP049-hum13, BAP049-hum14, BAP049-hum15, BAP049-hum16, BAP049-Clon-A, BAP049-Clon-B,

BAP049-Clon-C, BAP049-Clon-D o BAP049-Clon-E; o como se describe en la Tabla 1 de US 2015/0210769, o codificada por la secuencia de nucleótidos en la Tabla 1; o una secuencia sustancialmente idéntica (por ejemplo, al menos 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% o más idéntica) a cualquiera de las secuencias anteriormente mencionadas.

TIM3 (inmunoglobulina-3 de células T) también regula negativamente la función de las células T, en células T CD4+ 1 colaboradoras secretoras de IFN-gamma y células T CD8+ 1 citotóxicas, y juega un papel crítico en el agotamiento de las células T. La inhibición de la interacción entre TIM3 y sus ligandos, por ejemplo, galectina-9 (Gal9), fosfatidilserina (PS) y HMGB1, puede aumentar la respuesta inmune. Anticuerpos, fragmentos de anticuerpos y otros inhibidores de TMI 3 y sus ligandos están disponibles en la técnica y se pueden usar en combinación con un CAR de CD19 descrito en el presente documento. Por ejemplo, anticuerpos, fragmentos de anticuerpos, moléculas pequeñas o inhibidores de péptido que se dirigen a TIM3 se unen al dominio IgV de TIM3 para inhibir la interacción con sus ligandos. Los anticuerpos y péptidos que inhiben TIM3 se divulgan en WO2013/006490 y US20100247521. Otros anticuerpos anti-TIM3 incluyen versiones humanizadas de RMT3-23 (divulgado en Ngiow et al., 2011, Cancer Res., 71: 3540-3.551), y el clon 8B.2C12 (divulgado en Monney et al, 2002, Naturaleza, 415: 536-541). Anticuerpos bi-específicos que inhiben TIM3 y PD-1 se divulgan en US20130156774.

En una modalidad, el anticuerpo anti-TIM-3 o fragmento del mismo es una molécula de anticuerpo anti-TIM-3 tal como se describe en US 2015/0218274, llamado “Antibody Molecules to TIM-3 and Uses Thereof”, el cual se incluye en su totalidad en el presente documento a manera de referencia. En una modalidad, la molécula de anticuerpo anti-TIM3 incluye al menos una, dos, tres, cuatro, cinco o seis CDR (o colectivamente todas las CDR) de una región variable de cadena pesada y ligera de un anticuerpo seleccionado de entre cualquiera de ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-huM10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3- hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; o tal como se describe en las Tablas 1-4 de US 2015/0218274; o codificada por la secuencia de nucleótidos en las Tablas 1-4; o una secuencia sustancialmente idéntica (por ejemplo,, al menos 80 %, 85 %, 90 %, 92 %, 95 %, 97

%, 98 %, 99 % o más idéntica) a cualquiera de las secuencias antes mencionadas, o CDR estrechamente relacionadas, por ejemplo, CDR que son idénticas o que tienen al menos una alteración de aminoácidos, pero no más de dos, tres o cuatro alteraciones (por ejemplo, sustituciones, deleciones o inserciones, por ejemplo, sustituciones conservadoras).

En aún otra modalidad, la molécula de anticuerpo anti-TIM-3 comprende al menos una, dos, tres o cuatro regiones variables de un anticuerpo descrito en el presente documento, por ejemplo, un anticuerpo seleccionado entre cualquiera de ABTIM3, ABTIM3-hum01, ABTIM3-hum02, ABTIM3-hum03, ABTIM3-hum04, ABTIM3-hum05, ABTIM3-hum06, ABTIM3-hum07, ABTIM3-hum08, ABTIM3-hum09, ABTIM3-hum10, ABTIM3-hum11, ABTIM3-hum12, ABTIM3-hum13, ABTIM3-hum14, ABTIM3-hum15, ABTIM3-hum16, ABTIM3-hum17, ABTIM3-hum18, ABTIM3-hum19, ABTIM3-hum20, ABTIM3-hum21, ABTIM3-hum22, ABTIM3-hum23; o como se describe en las Tablas 1-4 de US 2015/0218274; o codificada por la secuencia de nucleótidos en las Tablas 1-4; o una secuencia sustancialmente idéntica (por ejemplo, al menos 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% o más idéntica) a cualquiera de las secuencias anteriormente mencionadas.

En otras modalidades, el agente que potencia la actividad de una célula que expresa un CAR es un inhibidor de CEACAM (por ejemplo, inhibidor de CEACAM-1, CEACAM-3 y/o CEACAM-5). En una modalidad, el inhibidor de CEACAM es una molécula de anticuerpo anti-CEACAM. Ejemplos de anticuerpos anti-CEACAM-1 se describen en WO 2010/125571, WO 2013/082366 WO 2014/059251 y WO 2014/022332, por ejemplo, un anticuerpo monoclonal 34B1, 26H7 y 5F4; o una forma recombinante de los mismos, tal como se describe en, por ejemplo, US 2004/0047858, US 7,132,255 y WO 99/052552. En otras modalidades, el anticuerpo anti-CEACAM se une a CEACAM-5 tal como se describe en, por ejemplo, Zheng et al. PLoS One. 2010 Sep 2; 5(9). pii: e12529 (DOI:10:1371/journal.pone.0021146), o reacciona de manera cruzada con CEACAM-1 y CEACAM-5 tal como se describe en, por ejemplo, WO 2013/054331 y US 2014/0271618.

Al margen de las limitaciones que impone la teoría, se cree que las moléculas de adhesión celular relacionadas con antígeno carcinoembrionario (CEACAM), tales como CEACAM-1 y CEACAM-5, median, al menos en parte, la inhibición de una respuesta inmune anti-tumoral (véase, por ejemplo, Markel et al. J Immunol. 2002 Mar. 15; 168(6): 2803-10; Markel et al. J Immunol. 2006 nov. 1; 177(9): 6062-71; Markel et al. Immunology. 2009 Feb.; 126(2): 186-

200; Markel et al. Cancer Immunol Immunother. 2010 Feb.; 59(2): 215-30; Ortenberg et al. Mol Cancer Ther. 2012 jun.; 11(6): 1300-10; Stern et al. J Immunol. 2005 jun. 1; 174(11): 6692-701; Zheng et al. PLoS One. 2010 Sep 2; 5(9). pii: e12529). Por ejemplo, CEACAM-1 se ha descrito como un ligando heterofílico para TIM-3 y se ha dicho que juega un papel en la tolerancia y el agotamiento de células T mediados por TIM-3 (véase, por ejemplo, WO 2014/022332; Huang, et al. (2014) Nature doi:10.1038/nature13848). En algunas modalidades, se ha demostrado que el co-bloqueo de CEACAM-1 y TIM-3 potencia una respuesta inmunitaria anti-tumoral en modelos de xenoinjerto de cáncer colorrectal (véase, por ejemplo, WO 2014/022332; Huang, et al. (2014), supra). En otras modalidades, el co-bloqueo de CEACAM-1 y PD-1 reduce la tolerancia de las células T tal como se describe, por ejemplo, en WO 2014/059251. Por lo tanto, los inhibidores de CEACAM se pueden usar con los otros inmunomoduladores descritos en el presente documento (por ejemplo, inhibidores anti-PD-1 y/o anti-TIM-3) para potenciar una respuesta inmunitaria contra un cáncer, por ejemplo, un melanoma, un cáncer de pulmón (por ejemplo, CPNM), un cáncer de vejiga, un cáncer de colon u ovario, y otros cánceres tal como se describe en el presente documento.

LAG3 (gen-3 de activación de linfocitos o CD223) es una molécula de superficie celular expresada en células T y células B activadas sobre la cual se ha demostrado que desempeña un papel en el agotamiento de células T CD8+. Anticuerpos, fragmentos de anticuerpos y otros inhibidores de LAG3 y sus ligandos están disponibles en la técnica y se pueden usar en combinación con un CAR de CD19 descrito en el presente documento. Por ejemplo, BMS-986016 (Bristol-Myers Squib) es un anticuerpo monoclonal que se dirige a LAG3. IMP701 (Immutep) es un anticuerpo antagonista de LAG3 e IMP731 (Immutep y GlaxoSmithKline) es un anticuerpo reductor de LAG3. Otros inhibidores de LAG3 incluyen IMP321 (Immutep), que es una proteína de fusión recombinante de una porción soluble de LAG3 e Ig que se une a moléculas de CMH de clase II y activa las células presentadoras de antígeno (CPA). Otros anticuerpos se divulgan, por ejemplo, en WO2010/019570.

En una modalidad, el anticuerpo anti-LAG3 o fragmento del mismo es una molécula de anticuerpo anti-LAG3 tal como se describe en US 2015/0259420, llamado “Antibody Molecules to LAG3 and Uses Thereof”, el cual se incluye en su totalidad en el presente documento a manera de referencia. En una modalidad, la molécula de anticuerpo anti-LAG-3 incluye al menos una, dos, tres, cuatro, cinco o seis CDR (o colectivamente todas las CDR) de una región

variable de cadena pesada y ligera de un anticuerpo seleccionado de cualquiera de BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (por ejemplo, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser o BAP050-hum20-Ser), BAP050-Clon-F, BAP050-Clon-G, BAP050-Clon-H, BAP050-Clon-I o BAP050-Clon-J; o como se describe en la Tabla 1 de US 2015/0259420, o codificada por la secuencia de nucleótidos en la Tabla 1; o una secuencia substancialmente idéntica (por ejemplo, al menos 80 %, 85 %, 90 %, 92 %, 95 %, 97 %, 98 %, 99 % o más idéntica) a las secuencias anteriormente mencionadas, o CDR estrechamente relacionadas; por ejemplo, CDR que son idénticas o que tienen al menos una alteración de aminoácidos, pero no más de dos, tres o cuatro alteraciones (por ejemplo, sustituciones, deleciones, o inserciones, por ejemplo, sustituciones conservadoras).

En aún otra modalidad, la molécula de anticuerpo anti-LAG-3 comprende al menos una, dos, tres o cuatro regiones variables de un anticuerpo descrito en el presente documento, por ejemplo, un anticuerpo seleccionado de cualquiera de BAP050-hum01, BAP050-hum02, BAP050-hum03, BAP050-hum04, BAP050-hum05, BAP050-hum06, BAP050-hum07, BAP050-hum08, BAP050-hum09, BAP050-hum10, BAP050-hum11, BAP050-hum12, BAP050-hum13, BAP050-hum14, BAP050-hum15, BAP050-hum16, BAP050-hum17, BAP050-hum18, BAP050-hum19, BAP050-hum20, huBAP050(Ser) (por ejemplo, BAP050-hum01-Ser, BAP050-hum02-Ser, BAP050-hum03-Ser, BAP050-hum04-Ser, BAP050-hum05-Ser, BAP050-hum06-Ser, BAP050-hum07-Ser, BAP050-hum08-Ser, BAP050-hum09-Ser, BAP050-hum10-Ser, BAP050-hum11-Ser, BAP050-hum12-Ser, BAP050-hum13-Ser, BAP050-hum14-Ser, BAP050-hum15-Ser, BAP050-hum18-Ser, BAP050-hum19-Ser o BAP050-hum20-Ser), BAP050-Clon-F, BAP050-Clon-G, BAP050-Clon-H, BAP050-Clon-I o BAP050-Clon-J; o como se describe en la Tabla 1 de US 2015/0259420, o codificada por la secuencia de nucleótidos en la Tabla 1; o una secuencia substancialmente idéntica (por ejemplo, al menos 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% o más idéntica) a cualquiera de las secuencias

anteriormente mencionadas

Si bien no se desea estar ligado por la teoría, en algunas realizaciones, un microambiente tumoral no es propicio para células efectoras inmunes que atacan las células de cáncer porque las células T + PD-L1 atacan a las células efectoras inmunes PD1+. Más específicamente, un microambiente tumoral puede comprender células tumorales (que generalmente son CD19 +), células efectoras inmunes (que pueden ser células T CD3 + y pueden ser PD1 + o PD1-, y que pueden ser células endógenas o células que expresan CAR), y células T reguladoras (que son generalmente PD-L1+). Las células T reguladoras pueden crear una "barrera" alrededor del microambiente del tumor al atacar las células efectoras inmunes que comienzan a infiltrarse en el tumor. De acuerdo con la no limitativo teoría en la presente memoria, pre-administración de un inhibidor de PD1 y/o un inhibidor de PD-L1 hace que el microambiente tumoral más favorable a las células efectoras inmunes mediante la prevención de las células PD-L1 + Treg de atacar a las células efectoras inmunes PD1+, permitiendo así la las células efectoras inmunes para atacar las células tumorales. Los datos que apoyan este modelo se ofrece en este documento, por ejemplo, en los Ejemplos 20 y 21.

Por consiguiente, en ciertos aspectos, la presente descripción proporciona métodos de terapia de combinación que comprende administrar a un sujeto una célula que expresa una molécula de CAR que se une a CD19, por ejemplo, un CAR de CD19, en combinación con un inhibidor de PD1, un inhibidor de PD-L1, o ambos. En algunas realizaciones, el inhibidor de PD1 y / o inhibidor de PD-L1 se administra antes de la terapia CAR. En otras realizaciones, el inhibidor de PD1 y / o inhibidor de PD-L1 se administra simultáneamente con o después de la terapia CAR. En algunos aspectos, el sujeto es un sujeto que tiene una enfermedad asociada con la expresión de CD19, por ejemplo, una malignidad hematológica, por ejemplo, una leucemia o linfoma, por ejemplo, DLBCL, por ejemplo DLBCL primaria. En algunas formas de realización, el paciente tiene, o se identifica por tener, niveles elevados de PD1, PDL1, o CD3, o cualquier combinación de los mismos. En algunas formas de realización, el paciente tiene, o se identifica por tener, o al menos 5%, 6%, 7%, 8%, 9%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, o 90% de las células DLBCL que son positivas para CD3 y PD1.

También se proporcionan en este documento métodos para el seguimiento de la eficacia de una terapia CAR, por ejemplo, una terapia CAR CD19. las células que expresan CAR pueden administrarse a la corriente sanguínea de un paciente con la intención de que las células de origen a una célula tumoral, por ejemplo, infiltrarse en un tumor. Por consiguiente, en algunas formas de

realización, el procedimiento comprende someter a ensayo una muestra de tumor para la presencia de células CAR que expresan. En las realizaciones, el método comprende la detección de un marcador tumoral, por ejemplo, CD19. En formas de realización, el método comprende detectar un marcador de una célula CAR que expresan, por ejemplo, un CAR o la construcción de ácido nucleico que codifica el constructo de CAR. En las realizaciones, el método comprende además la detección de un marcador de células T, por ejemplo, CD3. En algunos aspectos, el sujeto es un sujeto que tiene una enfermedad asociada con la expresión de CD19, por ejemplo, una malignidad hematológica, por ejemplo, una leucemia o linfoma, por ejemplo, DLBCL, por ejemplo DLBCL primaria. En algunas realizaciones, si las células CAR que expresan muestran pobre infiltración del tumor, el sujeto se identifica como un riesgo elevado de recaída en comparación con un sujeto con buena infiltración del tumor. En algunas realizaciones, si las células CAR que expresan muestran pobre infiltración del tumor, se administra al sujeto un inhibidor de PD1 y/o un inhibidor de PD-L1, por ejemplo, en combinación con una segunda dosis de células CAR que expresan.

En algunas modalidades, el agente que incrementa la actividad de una célula que expresa un CAR puede ser, por ejemplo, una proteína de fusión que comprende un primer dominio y un segundo dominio, donde el primer dominio es una molécula inhibidora, o un fragmento de la misma, y el segundo dominio es un polipéptido que se asocia a una señal positiva, por ejemplo, un polipéptido que comprende un dominio de señalización intracelular como se describe en el presente documento. En algunas modalidades, el polipéptido que se asocia a una señal positiva puede incluir un dominio coestimulador de CD28, CD27, ICOS, por ejemplo, un dominio de señalización intracelular de CD28, CD27y o ICOS, y o un dominio primario de señalización, por ejemplo, de CD3 zeta, por ejemplo, descrito en el presente documento. En una modalidad, la proteína de fusión es expresada por la misma célula que expresa el CAR. En otra modalidad, la proteína de fusión es expresada por una célula, por ejemplo, una célula T que no expresa un CAR anti-CD19.

En una modalidad, el agente que aumenta la actividad de una célula que expresa un CAR que se describe en el presente documento es miR-17-92.

En una modalidad, el agente que potencia la actividad de un CAR descrito en el presente documento es una citoquina. Las citoquinas tienen importantes funciones relacionadas con la expansión, la diferenciación, la supervivencia y la homeostasis de las células T. Las citoquinas

que se pueden administrar al sujeto que recibe una célula que expresa un CAR descrita en el presente documento incluyen: IL-2, IL-4, IL-7, IL-9, IL-15, IL-18 e IL-21, o una combinación de las mismas. En modalidades, la citoquina administrada es IL-7, IL-15 o IL-21, o una combinación de las mismas. La citoquina se puede administrar una vez al día o más de una vez al día, por ejemplo, dos veces al día, tres veces al día, o cuatro veces al día. La citoquina se puede administrar durante más de un día, por ejemplo, la citoquina se administra durante 2 días, 3 días, 4 días, 5 días, 6 días, 1 semana, 2 semanas, 3 semanas o 4 semanas. Por ejemplo, la citoquina se administra una vez al día durante 7 días.

En algunas modalidades, la citoquina se administra en combinación con células que expresan CAR. La citoquina se puede administrar simultáneamente o de forma concurrente con las células que expresan CAR, por ejemplo, se pueden administrar durante el mismo día. La citoquina se puede preparar en la misma composición farmacéutica que las células que expresan CAR o se puede preparar en una composición farmacéutica diferente. Alternativamente, la citoquina se puede administrar poco después de la administración de las células T que expresan CAR, por ejemplo, 1 día, 2 días, 3 días, 4 días, 5 días, 6 días o 7 días después de la administración de las células que expresan CAR. En modalidades en las que se administra la citoquina en un régimen de dosificación que ocurre durante más de un día, el primer día del régimen de dosificación de la citoquina puede ser el mismo día de la administración de las células que expresan CAR, o el primer día del régimen de dosificación de la citoquina puede ser 1 día, 2 días, 3 días, 4 días, 5 días, 6 días o 7 días después de la administración de las células T que expresan CAR. En una modalidad, en el primer día, se administran las células que expresan CAR al sujeto, y en el segundo día, se administra una citoquina una vez al día durante los siguientes 7 días. En una modalidad preferida, la citoquina que se administra en combinación con las células que expresan CAR es IL-7, IL-15 y/o IL-21.

En otras modalidades, la citoquina se administra un período de tiempo suficiente después de la administración de las células que expresan CAR, por ejemplo, al menos 2 semanas, 3 semanas, 4 semanas, 6 semanas, 8 semanas, 10 semanas, 12 semanas, 4 meses, 5 meses, 6 meses, 7 meses, 8 meses, 9 meses, 10 meses, 11 meses o 1 año o más después de la administración de las células que expresan CAR. En una modalidad, la citoquina se administra después de la evaluación de la respuesta del sujeto a las células que expresan CAR. Por ejemplo, se administran células que expresan CAR al sujeto de acuerdo con la dosis y regímenes descritos

en el presente documento. La respuesta del sujeto a la terapia con TCAR se evalúa a las 2 semanas, 3 semanas, 4 semanas, 6 semanas, 8 semanas, 10 semanas, 12 semanas, 4 meses, 5 meses, 6 meses, 7 meses, 8 meses, 9 meses, 10 meses, 11 meses o 1 año o más después de la administración de las células que expresan CAR, usando cualquiera de los métodos descritos en el presente documento, incluyendo la inhibición del crecimiento del tumor, la reducción de las células tumorales circulantes, o la regresión del tumor. Se puede administrar una citoquina a los sujetos que no muestran una respuesta suficiente a la terapia con TCAR. La administración de la citoquina al sujeto que tiene una respuesta sub-óptima a la terapia con TCAR mejora la eficacia y/o la actividad anti-tumoral del TCAR. En una modalidad, la citoquina que se administra después de la administración de las células que expresan CAR es IL-7.

Otras terapias de combinación pueden incluir agentes anti-alergénicos, anti-eméticos, analgésicos, terapias adjuntas.

Algunos pacientes pueden experimentar reacciones alérgicas a los agentes terapéuticos descritos en el presente documento y/u otro(s) agente(s) anti-cancerosos(s) durante o después de la administración; por lo tanto, a menudo se administran agentes anti-alérgicos para minimizar el riesgo de que ocurra una reacción alérgica. Agentes anti-alérgicos adecuados incluyen corticosteroides, tales como dexametasona (por ejemplo, Decadron®), beclometasona (por ejemplo, Beclovent®), hidrocortisona (también conocida como cortisona, succinato sódico de hidrocortisona, fosfato sódico de hidrocortisona, y vendida bajo los nombres comerciales Ala-Cort®, fosfato de hidrocortisona, Solu-Cortef®, Hydrocort Acetate® y Lanacort®), prednisolona (vendida bajo los nombres comerciales Delta-Cortel®, Orapred®, Pediapred® y Prelone®), prednisona (vendida bajo los nombres comerciales Deltasone®, Liquid Red®, Meticorten® y Orasone®), metilprednisolona (también conocida como 6-metilprednisolona, acetato de metilprednisolona, succinato sódico de metilprednisolona, y vendida bajo los nombres comerciales Duralone®, Medralone®, Medrol®, M-Prednisol® y Solu-Medrol®); antihistamínicos, como la difenhidramina (por ejemplo, Benadryl®), hidroxizina y ciproheptadina; y broncodilatadores, como los agonistas de los receptores beta-adrenérgicos, albuterol (por ejemplo, Proventil®) y terbutalina (Brethine®).

Algunos pacientes pueden experimentar náuseas durante y después de la administración de los agentes terapéuticos descritos en el presente documento y/u otro(s) agente(s) anti-canceroso(s); por lo tanto, se usan anti-eméticos para prevenir las náuseas (parte

superior del estómago) y el vómito. Anti-eméticos adecuados incluyen aprepitant (Emend®), ondansetron (Zofran®), granisetrón HCl (Kytril®), lorazepam (Ativan®), Dexametasona (Decadron®), proclorperazina (Compazine®), casopitant (Rezonic® y Zunrisa®), y sus combinaciones.

A menudo se prescriben medicamentos para aliviar el dolor experimentado durante el período de tratamiento con el fin de que el paciente se sienta más cómodo. Con frecuencia se usan analgésicos comunes de venta sin receta, como Tylenol. Sin embargo, fármacos analgésicos opioides como hidrocodona/paracetamol o hidrocodona/acetaminofén (por ejemplo, Vicodin®), morfina (por ejemplo, Astramorph® o Avinza®), oxicodona (por ejemplo, OxyContin® o Percocet®), clorhidrato de oximorfona (Opana®) y fentanilo (por ejemplo, Duragesic®) también son útiles para el dolor moderado o grave.

En un esfuerzo por proteger las células normales de la toxicidad del tratamiento y por limitar la toxicidad de órganos, se pueden usar como terapia adjunta agentes citoprotectores (tales como neuroprotectores, eliminadores de radicales libres, cardioprotectores, neutralizadores de la extravasación de antraciclinas, nutrientes y similares). Agentes citoprotectores adecuados incluyen amifostina (Ethyol®), glutamina, dimesna (Tavocept®), mesna (Mesnex®), dexrazoxano (Zinecard® o Totect®), xaliproden (Xaprila®) y leucovorina (también conocida como leucovorina de calcio, factor citrovorum y ácido folínico).

La estructura de los compuestos activos identificados por números de código, nombres genéricos o comerciales se pueden consultar en la edición actual del compendio estándar "The Merck Index" o en bases de datos, por ejemplo, Patents International (por ejemplo, IMS World Publications).

Los compuestos anteriormente mencionados, que pueden utilizarse en combinación con un compuesto de la presente invención, se pueden preparar y administrar como se describe en la técnica, tal como en los documentos citados anteriormente.

En una realización, la presente invención proporciona composiciones farmacéuticas que comprenden al menos un compuesto de la presente invención (por ejemplo, un compuesto de la presente invención) o una sal farmacéuticamente aceptable del mismo junto con un vehículo farmacéuticamente aceptable adecuado para la administración a un sujeto humano o animal , ya sea solo o junto con otros agentes anti-cáncer.

En una realización, la presente invención proporciona métodos de tratamiento de sujetos humanos o animales que sufren de una enfermedad proliferativa celular, tal como el cáncer. La presente invención proporciona métodos de tratamiento de un sujeto humano o animal en necesidad de tal tratamiento, que comprende administrar al sujeto una cantidad terapéuticamente eficaz de un compuesto de la presente invención (por ejemplo, un compuesto de la presente invención) o una sal farmacéuticamente aceptable de los mismos , ya sea solo o en combinación con otros agentes anti-cáncer.

En particular, las composiciones o bien serán formulados juntos como una combinación terapéutica o se administran por separado.

En la terapia de combinación, el compuesto de la presente invención y otro agente (s) anti-cáncer se puede administrar ya sea simultáneamente, concurrentemente o secuencialmente sin límites de tiempo específicos, en donde tal administración proporciona niveles terapéuticamente eficaces de los dos compuestos en el cuerpo del paciente.

En una realización preferida, el compuesto de la presente invención y el otro agente (s) anti-cáncer se administran generalmente de forma secuencial en cualquier orden por infusión o por vía oral. El régimen de dosificación puede variar dependiendo de la etapa de la enfermedad, la condición física del paciente, perfiles de seguridad de los fármacos individuales, y la tolerancia de los fármacos individuales, así como otros criterios bien conocidos por el médico tratante y médico (s) administrar la combinación. El compuesto de la presente invención y otro agente (s) contra el cáncer se puede administrar en cuestión de minutos el uno del otro, horas, días o incluso semanas de diferencia, dependiendo del ciclo particular que se usa para el tratamiento. Además, el ciclo podría incluir la administración de un fármaco con más frecuencia de la otra durante el ciclo de tratamiento y en diferentes dosis por la administración de la droga.

En otro aspecto de la presente invención, se proporcionan kits que incluyen uno o más compuestos de la presente invención y un socio de combinación como se describe en el presente documento. kits representativos incluyen (a) un compuesto de la presente invención o una sal farmacéuticamente aceptable del mismo, (b) al menos un socio de combinación, por ejemplo, como se indicó anteriormente, en el que tal kit puede comprender un inserto de paquete u otro etiquetado incluyendo instrucciones para la administración.

Un compuesto de la presente invención también se puede usar ventajosamente en combinación con procesos terapéuticos conocidos, por ejemplo, la administración de hormonas o especialmente la radiación. Un compuesto de la presente invención puede en particular ser utilizado como un radiosensibilizador, especialmente para el tratamiento de tumores que exhiben pobre sensibilidad a la radioterapia.

Combinación con una dosis potenciadora inmune baja de un inhibidor de mTOR

En una modalidad, las células que expresan una molécula de CAR, por ejemplo, una molécula de CAR descrita en el presente documento, se administran en combinación con una dosis potenciadora inmune baja de un inhibidor de mTOR. Por ejemplo, en una modalidad, la terapia de combinación incluye: Células que expresan CAR de CD19, un inhibidor de células B (inhibidor de una o más de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1, por ejemplo, una célula que expresa un CAR que se dirige a una o más de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1), y un inhibidor de mTOR. Los métodos descritos en el presente documento usan dosis potenciadoras inmunes bajas de inhibidores de mTOR, por ejemplo, inhibidores de mTOR alostéricos, incluyendo rapálogos como RAD001. La administración de una dosis potenciadora inmune baja de un inhibidor de mTOR (por ejemplo, una dosis que no es suficiente para suprimir completamente el sistema inmunitario, pero es suficiente para mejorar la función inmunitaria) puede optimizar el desempeño de las células efectoras inmunes, por ejemplo, células T o células que expresan CAR, en el sujeto. Los métodos para medir la inhibición de mTOR, las dosis, los regímenes de tratamiento y las composiciones farmacéuticas adecuadas se describen en la Solicitud de Patente de Estados Unidos No. 2015/01240036, la cual se incluye a manera de referencia.

En una modalidad, la administración de una dosis potenciadora inmune baja de un inhibidor de mTOR puede producir uno o más de los siguientes resultados:

i) una disminución en el número de células efectoras inmunes PD-1 positivas;

ii) un aumento en el número de células efectoras inmunes PD-1 negativas;

iii) un aumento en la relación de células efectoras inmunes PD-1 negativas / células efectoras inmunes PD-1 positivas;

iv) un aumento en el número de células T inalteradas;

v) un aumento en la expresión de uno o más de los siguientes marcadores: $CD62L^{high}$,

$CD127^{high}$, $CD27^{+}$ y BCL2, por ejemplo, en células T de memoria, por ejemplo, precursores de células T de memoria;

vi) una disminución en la expresión de KLRG1, por ejemplo, en células T de memoria, por ejemplo, precursores de células T de memoria; o

vii) un aumento en el número de precursores de células T de memoria, por ejemplo, células con cualquiera o una combinación de las siguientes características: aumento de $CD62L^{alto}$, aumento de $CD127^{alto}$, aumento de $CD27^{+}$, disminución de KLRG1 y aumento de BCL2;

y donde cualquiera de los anteriores, por ejemplo, i), ii), iii), iv), v), vi), o vii), se produce, por ejemplo, al menos transitoriamente, por ejemplo, en comparación con un sujeto no tratado.

En otra modalidad, la administración de una dosis potenciadora inmune baja de un inhibidor de mTOR produce una mayor o prolongada proliferación o persistencia de células que expresan CAR, por ejemplo, en cultivo o en un sujeto, por ejemplo, en comparación con células que expresan CAR no tratadas o sujetos no tratados. En algunas modalidades, el aumento de la proliferación o la persistencia está asociado a un aumento en la cantidad de células que expresan CAR. Los métodos para medir la proliferación mayor o prolongada se describen en los Ejemplos 18 y 19. En otra modalidad, la administración de una dosis potenciadora inmune baja de un inhibidor de mTOR produce una mayor destrucción de células cancerosas por células que expresan CAR, por ejemplo, en cultivo o en un sujeto, por ejemplo, en comparación con células que expresan CAR no tratadas o sujetos no tratados. En algunas modalidades, el aumento de la destrucción de células cancerosas se asocia a una disminución en el volumen del tumor.

En una modalidad, las células que expresan una molécula de CAR, por ejemplo, una molécula de CAR descrita en el presente documento, se administran en combinación con una dosis potenciadora inmune baja de un inhibidor de mTOR, por ejemplo, un inhibidor de mTOR alostérico, por ejemplo, RAD001, o un inhibidor de mTOR catalítico. Por ejemplo, la administración de una dosis potenciadora inmune baja del inhibidor de mTOR se puede iniciar antes de la administración de una célula que expresa un CAR descrita en el presente documento; finalizar antes de la administración de una célula que expresa un CAR descrita en el presente documento; iniciar al mismo tiempo que la administración de una célula que expresa un CAR descrita en el presente documento; ocurrir simultáneamente con la administración de una célula que expresa un CAR descrita en el presente documento; o continuar después de la

administración de una célula que expresa un CAR descrita en el presente documento.

Alternativamente, o adicionalmente, la administración de una dosis potenciadora inmune baja de un inhibidor de mTOR puede optimizar las células efectoras inmunes que serán modificadas para expresar una molécula de CAR descrita en el presente documento. En dichas modalidades, la administración de una dosis potenciadora inmune baja de un inhibidor de mTOR, por ejemplo, un inhibidor alostérico, por ejemplo, RAD001, o un inhibidor catalítico, se inicia o se completa antes de la recolección de las células efectoras inmunes, por ejemplo, células T o células NK, que serán modificadas para expresar una molécula de CAR descrita en el presente documento, de un sujeto.

En otra modalidad, las células efectoras inmunes, por ejemplo, células T o células NK, que serán modificadas para expresar una molécula de CAR descrita en el presente documento, por ejemplo, después de recolectar de un sujeto, o las células efectoras inmunes que expresan CAR, por ejemplo, células T o células NK, por ejemplo, antes de la administración a un sujeto, pueden ser cultivadas en presencia de una dosis potenciadora inmune baja de un inhibidor de mTOR.

En una modalidad, la administración al sujeto de una dosis potenciadora inmune baja de un inhibidor de mTOR comprende la administración, por ejemplo, una vez por semana, por ejemplo, en una forma de dosificación de liberación inmediata, de entre 0,1 y 20, entre 0,5 y 10, entre 2,5 y 7,5, entre 3 y 6, o aproximadamente 5 mg de RAD001, o una dosis bioequivalente de los mismos. En una modalidad, la administración al sujeto de una dosis potenciadora inmune baja de un inhibidor de mTOR comprende la administración, por ejemplo, una vez por semana, por ejemplo, en una forma de dosificación de liberación sostenida, de entre 0,3 y 60, entre 1,5 y 30, entre 7,5 y 22,5, entre 9 y 18, o aproximadamente 15 mg de RAD001, o una dosis bioequivalente de los mismos.

En una modalidad, una dosis de un inhibidor de mTOR se asocia con, o proporciona, la inhibición de mTOR de al menos 5 % pero no más de 90 %, al menos 10 % pero no más de 90 %, al menos 15 % pero no más de 90 %, al menos 20 % pero no más de 90 %, al menos 30 % pero no más de 90 %, al menos 40 % pero no más de 90 %, al menos 50 % pero no más de 90 %, al menos 60 % pero no más de 90 %, al menos 70 % pero no más de 90 %, al menos 5 % pero no más de 80 %, al menos 10 % pero no más de 80 %, al menos 15 % pero no más de 80 %, al menos 20 % pero no más de 80 %, al menos 30 % pero no más de 80 %, al menos 40 %

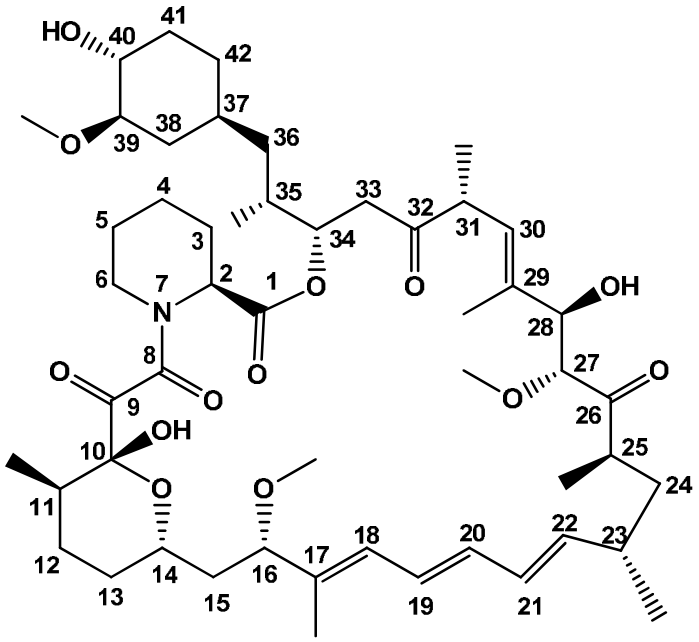
pero no más de 80 %, al menos 50 % pero no más de 80 %, al menos 60 % pero no más de 80 %, al menos 5 % pero no más de 70 %, al menos 10 % pero no más de 70 %, al menos 15 % pero no más de 70 %, al menos 20, pero no más de 70 %, al menos 30 % pero no más de 70 %, al menos 40 % pero no más de 70 %, al menos 50 % pero no más de 70 %, al menos 5 % pero no más de 60 %, al menos 10 % pero no más de 60 %, al menos 15 % pero no más de 60 %, al menos 20 % pero no más de 60 %, al menos 30 % pero no más de 60 %, al menos 40% pero no más de 60 %, al menos 5 % pero no más de 50 %, al menos 10 % pero no más de 50 %, al menos 15 % pero no más de 50 %, al menos 20 % pero no más de 50 %, al menos 30 % pero no más de 50 %, al menos 40 % pero no más de 50 %, al menos 5 % pero no más de 40 %, al menos 10 % pero no más de 40 %, al menos 15 % pero no más de 40 %, al menos 20 % pero no más de 40 %, al menos 30 % pero no más de 40 %, al menos 35 % pero no más de 40 %, al menos 5 % pero no más de 30 %, al menos 10 % pero no más de 30 %, al menos 15 % pero no más de 30 %, al menos 20 % pero no más de 30 %, o al menos 25 % pero no más de 30 %.

El grado de inhibición de mTOR se puede expresar como, o corresponde a, el grado de inhibición de quinasa S6 P70, por ejemplo, el grado de inhibición de mTOR se puede determinar por el nivel de disminución de la actividad de la quinasa p70 S6, por ejemplo, por la disminución en la fosforilación de un sustrato de quinasa P70 S6. El nivel de inhibición de mTOR puede ser evaluado usando diversos métodos, tales como la medición de la actividad de quinasa P70 S6 mediante el ensayo de Boulay, tal como se describe en la Solicitud de Patente de Estados Unidos No. 2015/01240036, que se incluye en el presente documento a manera de referencia, o tal como se describe en la Patente de Estados Unidos No. 7,727,950, que se incluye en el presente documento a manera de referencia; la medición del nivel de S6 fosforilado mediante Western blot; o la evaluación de un cambio en la relación de células efectoras inmunes PD1 negativas y células efectoras inmunes PD1 positivas.

Tal como se usa en el presente documento, el término "inhibidor de mTOR" se refiere a un compuesto o ligando, o a una sal farmacéuticamente aceptable del mismo, que inhibe la quinasa mTOR en una célula. En una modalidad, un inhibidor de mTOR es un inhibidor alostérico. Los inhibidores de mTOR alostéricos incluyen compuesto tricíclico neutral de rapamicina (sirolimus), compuestos relacionados con la rapamicina, es decir, compuestos estructural y funcionalmente similares a la rapamicina incluyendo, por ejemplo, derivados de rapamicina, análogos de rapamicina (también conocidos como rapálogos) y otros compuestos

macrólidos que inhiben actividad de mTOR. En una modalidad, un inhibidor de mTOR es un inhibidor catalítico.

La rapamicina es un antibiótico macrólido conocido producido por Streptomyces hygroscopicus, que tiene la estructura presentada en la Fórmula A.



(A)

Véase, por ejemplo, McAlpine, J.B. et al., J. Antibiotics (1991) 44: 688; Schreiber, S.L. et al., J. Am. Chem. Soc. (1991) 113: 7433, Patente de Estados Unidos No. 3,929,992. Existen varios esquemas de numeración propuestos para la rapamicina. Para evitar confusiones, cuando se nombran análogos de rapamicina específicos en el presente documento, los nombres se dan con referencia a la rapamicina usando el esquema de numeración de fórmula A.

Análogos de rapamicina útiles en la invención incluyen, por ejemplo, análogos con sustitución de O en los que el grupo hidroxilo en el anillo de ciclohexilo se reemplaza con OR_1, donde R_1 es hidroxialquilo, hidroxialcoxialquilo, acilaminoalquilo o aminoalquilo; por ejemplo, RAD001, también conocido como, everolimus, tal como se describe en US 5,665,772 y WO94/09010, cuyos contenidos se incluyen a manera de referencia.

Otros análogos de rapamicina adecuados incluyen aquellos sustituidos en la posición 26 o 28. El análogo de rapamicina puede ser un epímero de un análogo mencionado anteriormente, particularmente un epímero de un análogo sustituido en la posición 40, 28 o 26, y puede además estar opcionalmente hidrogenado, por ejemplo, tal como se describe en US 6,015,815, WO95/14023 y WO99/15530, cuyos contenidos se incluyen a manera de referencia**,** por

ejemplo, ABT578, también conocido como zotarolimus o un análogo de rapamicina descrito en US 7,091,213, WO98/02441 y WO01/14387, cuyos contenidos se incluyen a manera de referencia, por ejemplo, AP23573, también conocido como ridaforolimus.

Ejemplos de análogos de rapamicina útiles en la presente invención del documento US 5,665,772 incluyen, de manera enunciativa mas no limitativa, 40-O-bencil-rapamicina, 40-O-(4'-hidroximetil)bencil-rapamicina, 40-O-[4'-(1,2-dihidroxietil)]bencil-rapamicina, 40-O-allil-rapamicina, 40-O-[3'-(2,2-dimetil-1,3-dioxolan-4(S)-il)-prop-2'-en-1'-il]-rapamicina, (2'E,4'S)-40-O-(4',5'-dihidroxipent-2'-an-1'-il)-rapamicina, 40-O-(2-hidroxi)etoxicarbonilmetil-rapamicina, 40-O-(2-hidroxi)etil-rapamicina, 40-O-(3-hidroxi)propil-rapamicina, 40-O-(6-hidroxi)hexil-rapamicina, 40-O-[2-(2-hidroxi)etoxi]etil-rapamicina, 40-O-[(3S)-2,2-dimetildioxolan-3-il]metil-rapamicina, 40-O-[(2S)-2,3-dihidroxiprop-1-il]-rapamicina, 40-O-(2-acetoxi)etil-rapamicina, 40-O-(2-nicotinoiloxi)etil-rapamicina, 40-O-[2-(N-morfolino)acetoxi]etil-rapamicina, 40-O-(2-N-imidazolilacetoxi)etil-rapamicina, 40-O-[2-(N-metil-N'-piperazinil)acetoxi]etil-rapamicina, 39-O-desmetil-39,40-O,O-etileno-rapamicina, (26R)-26-dihidro-40-O-(2-hidroxi)etil-rapamicina, 40-O-(2-aminoetil)-rapamicina, 40-O-(2-acetaminoetil)-rapamicina, 40-O-(2-nicotinamidoetil)-rapamicina, 40-O-(2-(N-metil-imidazo-2'-ilcarbetoxamido)etil)-rapamicina, 40-O-(2-etoxicarbonilaminoetil)-rapamicina, 40-O-(2-tolilsulfonamidoetil)-rapamicina y 40-O-[2-(4',5'-dicarboetoxi-1',2',3'-triazol-1'-il)-etil]-rapamicina.

Otros análogos de rapamicina útiles en la presente invención son análogos donde el grupo hidroxilo en el anillo de ciclohexilo de la rapamicina y/o el grupo hidroxi en la posición 28 se sustituye con un grupo hidroxiéster, por ejemplo, análogos de rapamicina divulgados en la Patente de Estados Unidos RE44,768, por ejemplo, temsirolimus.

Otros análogos de rapamicina útiles en la presente invención incluyen aquellos en los que el grupo metoxi en la posición 16 se sustituye con otro sustituyente, preferiblemente alquiniloxi, bencilo, ortometoxibencilo o clorobencilo (opcionalmente sustituido con hidroxi) y/o en los que el grupo metoxi en la posición 39 es eliminado junto con el carbono 39 de modo que el anillo de ciclohexilo de la rapamicina se convierte en un anillo de ciclopentilo que carece del grupo metoxi en la posición 39; por ejemplo, como se describe en WO95/16691 y WO96/41807, cuyos contenidos se incluyen como referencia. Los análogos pueden ser modificados adicionalmente de tal manera que el hidroxi en la posición 40 de la rapamicina es alquilado y/o el carbonilo 32 es reducido.

Los análogos de rapamicina de WO95/16691 incluyen, de manera enunciativa mas no limitativa, 16-demtoxi-16-(pent-2-inil)oxi-rapamicina, 16-demtoxi-16-(but-2-inil)oxi-rapamicina, 16-demtoxi-16-(propargil)oxi-rapamicina, 16-demetoxi-16-(4-hidroxi-but-2-inil)oxi-rapamicina, 16-demetoxi-16-benciloxi-40-O-(2-hidroxietil)-rapamicina, 16-demetoxi-16-benciloxi-rapamicina, 16-demetoxi-16-orto-metoxibencil-rapamicina, 16-demetoxi-40-O-(2-metoxietil)-16-pent-2-inil)oxi-rapamicina, 39-demetoxi-40-desoxi-39-formil-42-nor-rapamicina, 39-demetoxi-40-desoxi-39-hidroximetil-42-nor-rapamicina, 39-demetoxi-40-desoxi-39-carboxi-42-nor-rapamicina, 39-demetoxi-40-desoxi-39-(4-metil-piperazin-1-il)carbonil-42-nor-rapamicina, 39-demetoxi-40-desoxi-39-(morfolin-4-il)carbonil-42-nor-rapamicina, 39-demetoxi-40-desoxi-39-[N-metil, N-(2-piridin-2-il-etil)]carbamoil-42-nor-rapamicina y 39-demetoxi-40-desoxi-39-(p-toluenesulfonilhidrazonometil)-42-nor-rapamicina.

Los análogos de rapamicina de WO96/41807 incluyen, de manera enunciativa mas no limitativa, 32-deoxo-rapamicina, 16-O-pent-2-inil-32-deoxo-rapamicina, 16-O-pent-2-inil-32-deoxo-40-O-(2-hidroxi-etil)-rapamicina, 16-O-pent-2-inil-32-(S)-dihidro-40-O-(2-hidroxietil)-rapamicina, 32(S)-dihidro-40-O-(2-metoxi)etil-rapamicina y 32(S)-dihidro-40-O-(2-hidroxietil)-rapamicina.

Otro análogo de rapamicina adecuado es umirolimus, tal como se describe en el documento US2005/0101624, cuyo contenido se incluye en el presente documento por referencia.

RAD001, también conocido como everolimus (Afinitor®), tiene el nombre químico (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihidroxi-12-{(1R)-2-[(1S,3R,4R)-4-(2-hidroxietoxi)-3-metoxiciclohexil]-1-metiletil}-19,30-dimetoxi-15,17,21,23,29,35-hexametil-11,36-dioxa-4-aza-triciclo[30.3.1.04,9]hexatriaconta-16,24,26,28-tetraeno-2,3,10,14,20-pentaona, tal como se describe en US 5,665,772 y WO94/09010, cuyo contenido se incluye a manera de referencia.

Otros ejemplos de inhibidores de mTOR alostéricos incluyen sirolimus (rapamicina, AY-22989), 40-[3-hidroxi-2-(hidroximetil)-2-metilpropanoato]-rapamicina (también llamado temsirolimus o CCI-779) y ridaforolimus (AP-23573/MK-8669). Otros ejemplos de inhibidores de mTOR alostéricos incluyen zotarolimus (ABT578) y umirolimus.

Alternativamente o adicionalmente, se ha encontrado que inhibidores de mTOR catalíticos, competitivos con ATP se dirigen al dominio de la quinasa mTOR directamente y se dirigen tanto a mTORC1 como a mTORC2. Estos también son inhibidores de mTORC1 más

eficaces que inhibidores de mTOR alostéricos tales como la rapamicina, ya que modulan productos de mTORC1 resistentes a la rapamicina tales como la fosforilación de 4EBP1-T37/46 y la traducción dependiente de cap.

Los inhibidores catalíticos incluyen: BEZ235 o 2-metil-2-[4-(3-metil-2-oxo-8-quinolin-3-il-2,3-dihidro-imidazo[4,5-c]quinolin-1-il)-fenil]-propionitrilo, o la forma de sal monotosilato (la síntesis de BEZ235 se describe en WO2006/122806); CCG168 (también conocido como AZD-8055, Chresta, C.M., et al., Cancer Res, 2010, 70(1), 288-298), que tiene el nombre químico {5-[2,4-bis-((S)-3-metil-morfolin-4-il)-pirido[2,3d]pirimidin-7-il]-2-metoxi-fenil}-metanol; 3-[2,4-bis[(3S)-3-metilmorfolin-4-il]pirido[2,3-d]pirimidin-7-il]-N-metilbenzamida (WO09104019); 3-(2-aminobenzo[d]oxazol-5-il)-1-isopropil-1H-pirazolo[3,4-d]pirimidin-4-amina (WO10051043 y WO2013023184); A N-(3-(N-(3-((3,5-dimetoxifenil)amino)quinoxalina-2-il)sulfamoil)fenil)-3-metoxi-4-metilbenzamida (WO07044729 y WO12006552); PKI-587 (Venkatesan, A.M., J. Med.Chem., 2010, 53, 2636-2645), que tiene el nombre químico 1-[4-[4-(dimetilamino)piperidina-1-carbonil]fenil]-3-[4-(4,6-dimorfolino-1,3,5-triazin-2-il)fenil]urea; GSK-2126458 (ACS Med. Chem. Lett., 2010, 1, 39-43) que tiene el nombre químico 2,4-difluoro-N-{2-metoxi-5-[4-(4-piridazinil)-6-quinolinil]-3-piridinil}bencenosulfonamida; 5-(9-isopropil-8-metil-2-morfolino-9H-purin-6-il)pirimidin-2-amina (WO10114484); y (E)-N-(8-(6-amino-5-(trifluorometilpiridin-3-il)-1-(6-(2-cianopropan-2-il)piridin-3-il)-3-metil-1H-imidazo[4,5-c]quinolin-2(3H)-ilideno)cianamida (WO12007926).

Otros ejemplos de inhibidores de mTOR catalíticos incluyen 8-(6-metoxi-piridin-3-il)-3-metil-1-(4-piperazin-1-il-3-trifluorometil-fenil)-1,3-dihidro-imidazo[4,5-c]quinolin-2-ona (WO2006/122806) y Ku-0063794 (Garcia-Martinez JM, et al., Biochem J., 2009, 421(1), 29-42. Ku-0063794 es un inhibidor específico del blanco de la rapamicina en mamíferos (MTOR). WYE-354 es otro ejemplo de un inhibidor de mTOR catalítico (Yu K, et al. (2009). Biochemical, Cellular, and In vivo Activity of Novel ATP-Competitive and Selective Inhibitors of the Mammalian Target of Rapamycin. Cancer Res. 69(15): 6232-6240).

Los inhibidores de mTOR útiles según la presente invención también incluyen pro-fármacos, derivados, sales farmacéuticamente aceptables o análogos de cualquiera de los anteriores.

Los inhibidores de mTOR, tal como RAD001, se pueden formular para entrega con base en métodos bien establecidos en la técnica de acuerdo con las dosis específicas descritas en el presente documento. En particular, la Patente de Estados Unidos No. 6,004,973 (que se incluye

en el presente documento a manera de referencia) proporciona ejemplos de formulaciones que se pueden usar con los inhibidores de mTOR descritos en el presente documento.

Métodos y biomarcadores para evaluar la eficacia de CAR y la idoneidad de una muestra

La presente divulgación proporciona, entre otras cosas, firmas genéticas que indican si un paciente con cáncer tratado con una terapia con CAR es propenso a caer o ha recaído. Al margen de las limitaciones que impone la teoría, el Ejemplo 12 establece una base experimental para esta firma genética.

En una modalidad, firmas de genes de transcripción nuevas descritas el presente documento (por ejemplo, en la **Tabla 29** en el Ejemplo 12) se usan para permitir mejoras en productos fabricados, lo que reduce la probabilidad de recaída del paciente. En una modalidad, las firmas de genes descritas en este documento se usan para modificar la aplicación terapéutica del producto fabricado, lo que reduce la probabilidad de recaída del paciente.

En una modalidad, las firmas de genes descritas en el presente documento (por ejemplo, en la **Tabla 29** en el Ejemplo 12) se identifican en un sujeto antes del tratamiento con una célula que expresa CAR, por ejemplo, tratamiento con TCAR (por ejemplo, un tratamiento con TCAR19, por ejemplo, terapia con CTL019) que predicen la recaída frente al tratamiento con CAR. En una modalidad, las firmas de genes descritas en el presente documento se identifican en una muestra de aféresis. En una modalidad, las firmas de genes descritas en el presente documento se identifican en una muestra de médula espinal. En una modalidad, las firmas de genes descritas en el presente documento se identifican en un producto de células que expresan CAR fabricado, por ejemplo, producto de TCAR (por ejemplo, un producto de TCAR19, por ejemplo, CTL019) antes de la infusión.

Esta divulgación también proporciona evidencia, por ejemplo, en el Ejemplo 12, de que (al margen de los límites que impone la teoría) disminuir la firma de T_{REG} en el paciente antes de la aféresis o durante la fabricación del producto de TCAR reduce el riesgo de recaída del paciente.

En una modalidad, un paciente recibe tratamiento previo con una o más terapias que reducen las células T_{REG} antes de recolectar las células para la fabricación del producto de CAR, por ejemplo, fabricación del producto de TCAR, lo que reduce el riesgo de recaída del paciente

frente al tratamiento con células que expresan CAR (por ejemplo, tratamiento con CTL019). Los métodos para reducir las células T_{REG} son conocidos en la técnica. Los métodos para reducir las células T_{REG} incluyen, de manera enunciativa más no limitativa, ciclofosfamida, anticuerpo anti-GITR, reducción de CD25, y combinaciones de los mismos.

En una modalidad, un paciente recibe tratamiento con ciclofosfamida o un anticuerpo anti-GITR antes de recolectar las células para la fabricación del producto de células que expresan CAR, lo que reduce el riesgo de recaída del paciente frente al tratamiento con células que expresan CAR (por ejemplo, tratamiento con CTL019).

En una modalidad, un paciente recibe tratamiento con un anticuerpo anti-GITR antes de recolectar las células para la fabricación del producto de células que expresan CAR, lo que reduce el riesgo de recaída del paciente frente al tratamiento con células que expresan CAR (por ejemplo, tratamiento con CTL019).

En una modalidad, el proceso de fabricación de células que expresan CAR se modifica para reducir las células T_{REG} antes de fabricar el producto de células que expresa un CAR (por ejemplo, un producto de CTL019). En una modalidad, la reducción de CD25 se usa para reducir las células T_{REG} antes de la fabricación del producto de células que expresan CAR (por ejemplo, un producto de CTL019).

En una modalidad, después de tratar a un paciente o un producto de células que expresan CAR con un tratamiento que reduce las células T_{REG}, el paciente se trata con una terapia de combinación. La terapia de combinación puede comprender, por ejemplo, un inhibidor de CD19, tal como una célula que expresa un CAR de CD19, y uno o más inhibidores de células B, por ejemplo, inhibidores de células B tal como se describen en el presente documento.

En una modalidad, un paciente se somete a ensayo para identificar el nivel de células T_{REG} en una muestra del paciente, por ejemplo, una muestra que comprende células cancerosas y/o una muestra que representa un microambiente tumoral. En una modalidad, esta información se usa para determinar un curso de tratamiento para el paciente. Por ejemplo, en una modalidad, si se identifica que el paciente tiene niveles altos de células T_{REG} en comparación con un control, la terapia comprende la administración de un tratamiento diferente a una célula que expresa CAR. Por ejemplo, la terapia puede comprender la administración de una molécula de anticuerpo, la administración de una molécula pequeña terapéutica, cirugía o terapia de

radiación, o cualquier combinación de las mismas. Esta terapia puede dirigirse a uno o más antígenos de células B.

En una modalidad, un paciente recidivante es un paciente que tiene, o que se identifica por tener, un mayor nivel de expresión (por ejemplo, aumento en los niveles de ARN) de uno o más de (por ejemplo, 2, 3, 4 o todos) los siguientes genes, en comparación con los no pacientes no recidivantes: MIR199A1, MIR1203, uc021ovp, ITM2C y HLA-DQB1 y/o menores niveles de expresión (por ejemplo, disminución en los niveles de ARN) de uno o más de (por ejemplo, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 todos) los siguientes genes, en comparación con pacientes no recidivantes: PPIAL4D, TTTY10, TXLNG2P, MIR4650-1, KDM5D, USP9Y, PRKY, RPS4Y2, RPS4Y1, NCRNA00185, SULT1E1 y EIF1AY.

En otro aspecto, la invención presenta un método para evaluar o monitorear la eficacia de una terapia con células que expresan CAR, en un sujeto (por ejemplo, un sujeto que tiene un cáncer), o la idoneidad de una muestra (por ejemplo, una muestra de aféresis) para una terapia con CAR, por ejemplo, una terapia que incluye la administración de una dosis potenciadora inmune baja de un inhibidor de mTOR. El método incluye adquirir un valor de eficacia para la terapia con CAR, o de idoneidad de la muestra, donde dicho valor es indicativo de la eficacia o la idoneidad de la terapia con células que expresan CAR.

En algunas modalidades, el valor de la eficacia a la terapia CAR, o la idoneidad de la muestra, comprende una medida de uno, dos, tres, cuatro, cinco, seis o más (todos) de los siguientes:

(i) el nivel o actividad de una, dos, tres, o más (por ejemplo, todas) células T_{EFF} en reposo, células T_{REG} en reposo, células T más jóvenes (por ejemplo, células CD4 o CD8 más jóvenes, o células T gama/delta), o células T de memoria tempranas, o una combinación de las mismas, de una muestra (por ejemplo, una muestra de aféresis o una muestra de producto de células que expresan CAR fabricado);

(ii) el nivel o actividad de una, dos, tres, o más (por ejemplo, todas) células T_{EFF} activadas, células T_{REG} activadas, células T más viejas (por ejemplo, células CD4 o CD8 más viejas), o células T de memoria tardías, o una combinación de las mismas, de una muestra (por ejemplo, una muestra de aféresis o una muestra de producto de células que expresan CAR fabricado);

(iii) el nivel o actividad de un marcador de agotamiento de células inmunes, por ejemplo,

uno, dos o más inhibidores de puntos de control inmunitario (por ejemplo, PD-1, PD-L1, TIM-3 y/o LAG-3) de una muestra (por ejemplo, una muestra de aféresis o una muestra de producto de células que expresan CAR fabricado). En una modalidad, una célula inmunitaria tiene un fenotipo agotado, por ejemplo, co-expresa al menos dos marcadores de agotamiento, por ejemplo, co-expresa PD-1 y TIM-3. En otras modalidades, una célula inmunitaria tiene un fenotipo agotado, por ejemplo, co-expresa al menos dos marcadores de agotamiento, por ejemplo, co-expresa PD-1 y LAG-3;

(iv) el nivel o actividad de células efectoras inmunes CD27 y/o CD45RO- (por ejemplo, CD27 + CD45RO-), por ejemplo, en una población de células T CD4+ o células T CD8+, de una muestra (por ejemplo, una muestra de aféresis o una muestra de producto de células que expresan CAR fabricado);

(v) el nivel o actividad de uno, dos, tres, cuatro, cinco, diez, doce o más de los biomarcadores seleccionados de entre CCL20, IL-17a y/o IL-6, PD-1, PD-L1, LAG-3, TIM-3, CD57, CD27, CD122, CD62L, KLRG1;

(vi) el nivel o actividad de una citoquina (por ejemplo, la calidad de una citoquina reportera) de una muestra de producto de células que expresan CAR; o

(vii) la eficiencia de transducción de una célula que expresa un CAR de una muestra de producto de células que expresan CAR fabricado.

En algunas modalidades de cualquiera de los métodos divulgados en el presente documento, la terapia con células que expresan CAR comprende una pluralidad (por ejemplo, una población) de células efectoras inmunes que expresan CAR, por ejemplo, una pluralidad (por ejemplo, una población) de células T o células NK, o una combinación de las mismas. En una modalidad, la terapia con células que expresan CAR incluye la administración de una dosis potenciadora inmune baja de un inhibidor de mTOR.

En algunas modalidades de cualquiera de los métodos divulgados en el presente documento, la medida de uno o más de (i) - (vii) se obtiene a partir de una muestra de aféresis adquirida del sujeto. La muestra de aféresis se puede evaluar antes de la infusión o la re-infusión.

En algunas modalidades de cualquiera de los métodos divulgados en el presente documento, la medida de uno o más de (i) - (vii) se obtiene a partir de una muestra de producto de células que expresan CAR fabricado. El producto de células que expresan CAR fabricado puede ser evaluado antes de la infusión o la re-infusión.

En algunas modalidades de cualquiera de los métodos divulgados en el presente documento, el sujeto se evalúa antes de recibir, durante o después de recibir la terapia con células que expresan CAR.

En algunas modalidades de cualquiera de los métodos divulgados en el presente documento, la medida de uno o más de (i) - (vii) evalúa un perfil para una o más de la expresión génica, la citometría de flujo o la expresión de proteínas.

En algunas modalidades de cualquiera de los métodos descritos en el presente documento, el método comprende además la identificación del sujeto como un sujeto con respuesta, sin respuesta, recidivante o no recidivante, con base en una medida de una o más de (i) - (vii).

En algunas modalidades de cualquiera de los métodos descritos en el presente documento, un sujeto con respuesta (por ejemplo, un sujeto con respuesta completa) tiene, o se identifica por tener, un nivel mayor o actividad de una, dos, o más (todas) de células T inalteradas, GZMK o PPF1BP2 en comparación con un sujeto sin respuesta.

En algunas modalidades de cualquiera de los métodos descritos en el presente documento, un sujeto sin respuesta tiene, o se identifica por tener, un mayor nivel o actividad de una, dos, tres, cuatro, cinco, seis, siete, o más (por ejemplo, todas) de IL22, IL-2RA, IL-21, IRF8, IL8, CCL17, CCL22, células T efectoras o células T reguladoras en comparación con un sujeto con respuesta.

En una modalidad, un paciente recidivante es un paciente que tiene, o que se identifica por tener, un mayor nivel de expresión de uno o más de (por ejemplo, 2, 3, 4 o todos) los siguientes genes, en comparación con los no pacientes no recidivantes: MIR199A1, MIR1203, uc021ovp, ITM2C y HLA-DQB1 y/o menores niveles de expresión de uno o más de (por ejemplo, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 todos) los siguientes genes, en comparación con pacientes no recidivantes: PPIAL4D, TTTY10, TXLNG2P, MIR4650-1, KDM5D, USP9Y, PRKY, RPS4Y2, RPS4Y1, NCRNA00185, SULT1E1 y EIF1AY.

En algunas modalidades de cualquiera de los métodos descritos en el presente documento, un sujeto con respuesta completa tiene, o se identifica por tener, un porcentaje mayor, por ejemplo, un porcentaje mayor estadísticamente significativo de células T CD8+ en comparación con un valor de referencia, por ejemplo, el porcentaje de células T CD8+ de un sujeto sin respuesta.

En algunas modalidades de cualquiera de los métodos descritos en el presente

documento, un sujeto con respuesta completa tiene, o se identifica por tener, un porcentaje mayor, por ejemplo, un porcentaje mayor estadísticamente significativo de células efectoras inmunes CD27+ CD45RO-, por ejemplo, en la publicación de CD8+, en comparación con un valor de referencia, por ejemplo, la cantidad de células efectoras inmunes CD27+ CD45RO- de un sujeto sin respuesta.

En algunas modalidades de cualquiera de los métodos descritos en el presente documento, un sujeto con respuesta completa o respuesta parcial tiene, o se identifica por tener, un porcentaje mayor, por ejemplo, un porcentaje mayor estadísticamente significativo de células T CD4+ en comparación con un valor de referencia, por ejemplo, el porcentaje de células T CD4+ de un sujeto sin respuesta.

En algunas modalidades de cualquiera de los métodos descritos en el presente documento, un sujeto con respuesta completa tiene, o se identifica por tener, un porcentaje mayor de una, dos, tres o más (por ejemplo, todas) células T_{EFF} en reposo, células T_{REG} en reposo, células T más jóvenes (por ejemplo, células CD4 o CD8 más jóvenes, o células T gama/delta), o células T de memoria tempranas, o una combinación de las mismas, en comparación con un valor de referencia, por ejemplo, la cantidad de células T_{EFF} en reposo, células T_{REG} en reposo, células T más jóvenes (por ejemplo, células CD4 o CD8 más jóvenes), o células T de memoria tempranas de un sujeto sin respuesta.

En algunas modalidades de cualquiera de los métodos descritos en el presente documento, un sujeto sin respuesta tiene, o se identifica por tener, un porcentaje mayor de una, dos, tres o más (por ejemplo, todas) células T_{EFF} activadas, células T_{REG} activadas, células T más viejas (por ejemplo, células CD4 o CD8 más viejas), o células T de memoria tardías, o una combinación de las mismas, en comparación con un valor de referencia, por ejemplo, la cantidad de células T_{EFF} activadas, células T_{REG} activadas, células T más viejas (por ejemplo, células CD4 o CD8 más viejas), o células T de memoria tardías de un sujeto con respuesta.

En algunas modalidades de cualquiera de los métodos descritos en el presente documento, un sujeto sin respuesta tiene, o se identifica por tener, un porcentaje mayor de un marcador de agotamiento de las células inmunitarias, por ejemplo, uno, dos o más inhibidores de puntos de control inmunitario (por ejemplo, PD-1, PD-L1, TIM-3 y/o LAG-3). En una modalidad, un sujeto sin respuesta tiene, o se identifica por tener, un mayor porcentaje de células efectoras inmunes que expresan PD-1, PD-L1 o LAG-3 (por ejemplo, células T CD4+ y/o células T CD8+) (por ejemplo, células que expresan CAR de CD4+ y/o células T CD8+) en

comparación con el porcentaje de células efectoras inmunes que expresan PD-1 o LAG-3 de un sujeto con respuesta.

En una modalidad, un sujeto sin respuesta tiene, o se identifica por tener, un mayor porcentaje de células inmunitarias que tienen un fenotipo agotado, por ejemplo, células inmunitarias que co-expresan al menos dos marcadores de agotamiento, por ejemplo, co-expresan PD-1, PD-L1 y/o TIM-3. En otras modalidades, un sujeto sin respuesta tiene, o se identifica por tener, un mayor porcentaje de células inmunitarias que tienen un fenotipo agotado, por ejemplo, células inmunitarias que co-expresan al menos dos marcadores de agotamiento, por ejemplo, co-expresan PD-1 y LAG-3.

En algunas modalidades de cualquiera de los métodos divulgados en el presente documento, un sujeto sin respuesta tiene, o se identifica por tener, un mayor porcentaje células PD-1/ PD-L1+/LAG-3+ en la población de células que expresan CAR en comparación con un sujeto con respuesta (por ejemplo, un sujeto con respuesta completa) a la terapia con células que expresan CAR.

En algunas modalidades de cualquiera de los métodos divulgados en el presente documento, un sujeto con respuesta parcial tiene, o se identifica por tener, un porcentaje más alto de células PD-1/ PD-L1+/LAG-3+, que los sujetos con respuesta, en la población de células que expresan CAR.

En algunas modalidades de cualquiera de los métodos descritos en el presente documento, un sujeto sin respuesta tiene, o se identifica por tener, un fenotipo agotado de PD1/PD-L1+ CAR+ y co-expresión de LAG3 en la población de células que expresan CAR.

En algunas modalidades de cualquiera de los métodos divulgados en el presente documento, un sujeto sin respuesta tiene, o se identifica por tener, un mayor porcentaje células PD-1/ PD-L1+/TIM-3+ en la población de células que expresan CAR en comparación con un sujeto con respuesta (por ejemplo, un sujeto con respuesta completa).

En algunas modalidades de cualquiera de los métodos divulgados en el presente documento, un sujeto con respuesta parcial tiene, o se identifica por tener, un porcentaje más alto de células PD-1/ PD-L1+/TIM-3+, que los sujetos con respuesta, en la población de células que expresan CAR.

En algunas modalidades de cualquiera de los métodos divulgados en el presente documento, la presencia de células T CD8+ CD27+ CD45RO- en una muestra de aféresis es un predictor positivo de la respuesta del sujeto a una terapia con células que expresan CAR.

En algunas modalidades de cualquiera de los métodos divulgados en el presente documento, un alto porcentaje de células T PD1+ CAR+ y LAG3+ o TIM3+ en una muestra de aféresis es un predictor de pronóstico negativo de la respuesta de un sujeto a una terapia con células que expresan CAR.

En algunas modalidades de cualquiera de los métodos divulgados en el presente documento, el sujeto con respuesta (por ejemplo, el sujeto con respuesta completa o parcial) tiene uno, dos, tres o más (o todos) de los siguientes perfiles:

(i) tiene una mayor cantidad células efectoras inmunes CD27+ en comparación con un valor de referencia, por ejemplo, una mayor cantidad de células efectoras inmunes CD27+ que un sujeto sin respuesta;

(i) tiene una mayor cantidad células T CD8+ en comparación con un valor de referencia, por ejemplo, una mayor cantidad de células T CD8+ que un sujeto sin respuesta;

(iii) tiene una menor cantidad de células inmunitarias que expresan uno o más inhibidores de punto de control, por ejemplo, un inhibidor de punto de control seleccionado de entre PD-1, PD-L1, LAG-3, TIM-3 y KLRG-1, o una combinación, en comparación con un valor de referencia, por ejemplo, la cantidad de células que expresan uno o más inhibidores de punto de control que un sujeto sin respuesta; o

(iv) tiene una mayor cantidad de una, dos, tres, cuatro o más (todas) de células TEFF en reposo, células T_{REG} en reposo, células CD4 inalteradas, células T de memoria no estimuladas o células T de memoria tempranas, o una combinación de las mismas, en comparación con un valor de referencia, por ejemplo, la cantidad de células T_{EFF} en reposo, células T_{REG} en reposo, células CD4 inalteradas, células T de memoria no estimuladas o células T de memoria tempranas que un sujeto sin respuesta.

En algunas modalidades de cualquiera de los métodos divulgados en el presente documento, el nivel o la actividad de citoquinas (vi) se selecciona de entre una, dos, tres, cuatro, cinco, seis, siete, ocho, o más (o todas) de las citoquinas CCL20/MIP3a, IL17A, IL6, GM-CSF, IFNγ, IL10, IL13, IL2, IL21, IL4, IL5, IL9 o TNFα, o una combinación de las mismas. La citoquina se puede elegir entre una, dos, tres, cuatro o más (todas) de IL-17A, CCL20, IL2, IL6 o TNFa. En una modalidad, un nivel o actividad mayor de una citoquina seleccionada de entre una o ambas de IL-17A y CCL20, es indicativo de una mayor capacidad de respuesta o una disminución de las recaídas.

En algunas modalidades de cualquiera de los métodos divulgados en el presente

documento, una eficacia de transducción de 15 % o superior en (vii) es indicativa de una mayor capacidad de respuesta o una disminución de las recaídas.

En algunas modalidades de cualquiera de los métodos divulgados en el presente documento, una eficacia de transducción de menos de 15 % (vii) es indicativa de una menor capacidad de respuesta o un aumento de las recaídas.

En algunas modalidades, el sujeto con respuesta, un sujeto sin respuesta, un sujeto con recaída o un sujeto sin recaída identificado mediante los métodos en el presente documento puede ser evaluado adicionalmente de acuerdo con criterios clínicos. Por ejemplo, un sujeto con respuesta completa tiene, o se identifica por tener, una enfermedad, por ejemplo, un cáncer, que exhibe una respuesta completa, por ejemplo, una remisión completa, a un tratamiento. Una respuesta completa se puede identificar, por ejemplo, usando las directrices NCCN Guidelines® (las cuales se incluyen en su totalidad en el presente documento a manera de referencia), tal como se describe en el presente documento. Un sujeto con respuesta parcial tiene, o se identifica por tener, una enfermedad, por ejemplo, un cáncer, que exhibe una respuesta parcial, por ejemplo, una remisión parcial, a un tratamiento. Un sujeto con respuesta parcial se puede identificar, por ejemplo, usando las directrices NCCN Guidelines®, tal como se describe en el presente documento. A sujeto sin respuesta tiene, o se identifica por tener, una enfermedad, por ejemplo, un cáncer, que no muestra una respuesta a un tratamiento, por ejemplo, el paciente tiene una enfermedad estable o una enfermedad progresiva. Un sujeto sin respuesta se puede identificar, por ejemplo, usando las directrices NCCN Guidelines®, tal como se describe en el presente documento.

Alternativamente, o en combinación con los métodos divulgados en el presente documento, con respuesta a dicho valor, realizando uno, dos, tres, cuatro o más de:

administrar, por ejemplo, a un sujeto con respuesta o un sujeto sin recaída, una terapia con células que expresan CAR;

administrar una dosificación alterada de una terapia con células que expresan CAR;

alterar el esquema o la programación de una terapia con células que expresan CAR;

administrar, por ejemplo, a un sujeto sin respuesta o un sujeto con respuesta parcial, un agente adicional en combinación con una terapia con células que expresan CAR, por ejemplo, un inhibidor de punto de control, por ejemplo, un inhibidor de punto de control descrito en el presente documento;

administrar a un sujeto sin respuesta o con respuesta parcial una terapia que aumenta la

cantidad de células T más jóvenes en el sujeto antes del tratamiento con una terapia con células que expresan CAR;

modificar un proceso de fabricación de una terapia con células que expresan CAR, por ejemplo, aumentando para células T más jóvenes antes de introducir un ácido nucleico que codifica un CAR, o incrementando la eficacia de transducción, por ejemplo, para un sujeto identificado como sin respuesta o con respuesta parcial;

administrar una terapia alternativa, por ejemplo, para un sujeto sin respuesta, con respuesta parcial o recidivante; o

si el sujeto es, o se identifica por ser, un sujeto sin respuesta o recidivante, disminuir la población de células T_{REG} y/o firma genética T_{REG}, por ejemplo, mediante uno o más de agotamiento de CD25, administración de ciclofosfamida, anticuerpo anti-GITR, o una combinación de los mismos.

En ciertas modalidades, el sujeto recibe un tratamiento previo con un anticuerpo anti-GITR. En cierta modalidad, el sujeto se trata con un anticuerpo anti-GITR antes de la infusión o re-infusión.

Medicina personalizada (teranósticos)

CARACTERÍSTICAS DE CD19, POR EJEMPLO, MUTACIONES

Sin desear estar limitado por la teoría, algunos pacientes con cáncer muestran una respuesta inicial a un inhibidor de CD19 tal como una célula que expresa CAR CD19, y luego recaída. En algunas realizaciones, se produce la recaída (al menos en parte) por un desplazamiento del marco y / o prematuro codón de parada en CD19 en las células cancerosas, o cualquier otro cambio en la expresión (incluyendo los niveles de expresión) de CD19 que reduce la capacidad de una célula que expresa CAR CD19 para dirigirse a las células cancerosas. Una mutación de este tipo puede reducir la eficacia de la terapia de CD19 y contribuir a una recaída del paciente. Por consiguiente, en algunas realizaciones, puede ser beneficioso cuando una terapia CD19 se complementa o reemplaza con una terapia dirigida a un segundo, de destino diferente, por ejemplo, un objetivo expresado en células B, por ejemplo, uno o más de CD10, CD20, CD22 , CD34, CD123, FLT-3, o ROR1. Varias terapias de combinación de ejemplo de este tipo se describen en el presente documento.

Esta solicitud divulga, entre otras cosas, métodos para tratar un sujeto que tiene cáncer,

que comprende uno o más de: (1) determinar si un sujeto tiene una diferencia, por ejemplo, una diferencia estadísticamente significativa, en una característica de CD19 en relación con una característica de referencia, y (2) si hay una diferencia entre la característica determinada y la característica de referencia, administrar al sujeto una dosis terapéuticamente eficaz de una terapia con CAR, por ejemplo, TCAR, tratando de este modo al sujeto. El paciente puede ser, por ejemplo, un paciente que ha recaído después de recibir tratamiento con un inhibidor de CD19, por ejemplo, una célula que expresa un CAR de CD19. El paciente puede ser un paciente que ha recibido o está recibiendo una terapia con CAR de CD19 y está en riesgo de sufrir una recaída. El paciente puede ser un sujeto que no responde a una terapia con CAR de CD19.

La característica puede ser, por ejemplo, la secuencia de CD19, por ejemplo, secuencia de ácido nucleico o proteína. La secuencia se puede determinar, por ejemplo, tal como se describe en los Ejemplos, mediante secuenciación de ácidos nucleicos de alto desempeño, o mediante espectrometría de masas de proteínas. Tal como se describe en el Ejemplo del presente documento, un paciente puede recaer después de una terapia con TCAR de CD19 debido a mutaciones en CD19, por ejemplo, en el exón 2 de CD19, por ejemplo, una mutación que causa un desplazamiento del marco y un codón de terminación prematuro en CD19. En algunas modalidades, la inserción o deleción no causa uno o ambos de un desplazamiento del marco y un codón de terminación prematuro. La mutación puede ser, por ejemplo, una inserción, una deleción, una sustitución, una translocación o una combinación de cualquiera de las anteriores. La inserción, deleción o sustitución puede involucrar, por ejemplo, al menos 1, 2, 3, 4, 5, 10, 15, 20, 20 o 50 nucleótidos. La inserción, deleción o sustitución puede involucrar, por ejemplo, como máximo 2, 3, 4, 5, 10, 15, 20, 20, 50 o 100 nucleótidos. En algunos casos, una población de células comprenderá más de una mutación. En dichos casos, las mutaciones pueden estar en sub-poblaciones de células que se superponen o que no se superponen.

En algunos casos, un paciente se identifica por tener una característica de CD19 que reduce la capacidad de CD19 para interactuar con un inhibidor de CD19 tal como una célula que expresa un CAR de CD19. Dicha característica puede ser, por ejemplo, una mutación del marco de lectura, un codón de terminación prematuro, una alteración en la secuencia de ácido nucleico o una alteración en la estructura del transcrito de ARNm primario. La característica puede ser, por ejemplo, una desviación de la producción normal de CD19 que se produce antes del corte y empalme. La característica puede ser, por ejemplo, una característica diferente a la omisión de

exón. Estos pacientes pueden ser tratados con un inhibidor de otro blanco, por ejemplo, un inhibidor de células B, por ejemplo, una célula que expresa un CAR dirigida contra otro epítopo, por ejemplo, un epítopo dentro de una o más de CD10, CD20, CD22, CD34, CD123, FLT-3 o ROR1.

En algunos casos, un paciente se identifica por tener una característica de CD19 que reduce la capacidad de CD19 para interactuar con un inhibidor de CD19, tal como una célula que expresa un CAR de CD19, pero no reduce ni elimina la capacidad de CD19 para interactuar con un segundo inhibidor de CD19, tal como un inhibidor de CD19 que se une a una región diferente en CD19. Dicha característica puede ser, por ejemplo, una mutación que no causa una o ambas de una mutación de desplazamiento de marco o un codón de terminación prematuro. Dicha característica puede ser, por ejemplo, una alteración en la secuencia de ácido nucleico o una alteración en la estructura del transcrito de ARNm primario, una desviación de la producción normal de CD19 que se produce antes del corte y empalme, o cualquier otra característica diferente a la omisión de exón. Estos pacientes pueden ser tratados con un inhibidor de CD19, por ejemplo, un inhibidor de células B dirigido contra una región intacta de CD19, por ejemplo, una porción de tipo silvestre de CD19. Por ejemplo, si hay una mutación presente en el exón 2, el segundo inhibidor de CD19 puede unirse a un exón diferente al exón 2, o una parte del exón 2 que carece de la mutación. El segundo inhibidor de CD19 puede ser, por ejemplo, un inhibidor de CD19 descrito en el presente documento.

FIRMAS T_{EFF} Y T_{REG}

Los métodos de la presente invención pueden incluir pasos para determinar una firma T_{REG} o para determinar los niveles de células T_{EFF} o células T_{REG}, por ejemplo, en un paciente o en una población de células, por ejemplo, células inmunitarias. Los métodos de la presente invención también pueden incluir pasos para reducir el nivel de células T_{REG}, o disminuir una firma T_{REG}, en un paciente o en una población de células. En algunas modalidades, una T_{EEF} es una célula con expresión regulada hacia arriba de uno o más (por ejemplo, al menos 10, 20, 30, 40, 50, 60, 70, 80 o todos) de los siguientes genes: AIM2, ALAS1, B4GALT5, BATF, C3orf26, C4orf43, CCL3, CCL4, CCT3, CCT7, CD40LG, CHAC2, CSF2, CTNNA1, EBNA1BP2, EDARADD, EEF1E1, EIF2B3, EIF2S1, FABP5, FAM40B, FKBP4, FOSL1, GFOD1, GLRX2, HSPD1, HSPE1, IFNG, IL15RA, IL21, IL2RA, IL3, KCNK5, KIAA0020, LARP4, LRP8, LTA,

MANF, MIR1182, MIR155, MIR155HG, MTCH2, MYOF, NDUFAF1, NLN, NME1, NME1-NME2, OTUD7B, PAM, PDIA6, PEA15, PFKM, PGAM1, PGAM4, PPIL1, PRDX4, PRSS23, PSMD1, PSMD11, PSMD14, PTRH2, PUS7, RBBP8, RPF2, RPP25, SFXN1, SLC27A2, SLC39A14, SLC43A3, SORD, SPR, SRXN1, STIP1, STT3A, TBX21, TMCC2, TMEM165, TNFRSF9, TXN, TXNDC5, UCK2, VDR, WDR12, YWHAG y ZDHHC16. En algunas modalidades, una T_{REG} es una célula con expresión regulada hacia arriba de uno o más (por ejemplo, al menos 10, 20, 30, 40, 50, 60, 70 o todos) de los siguientes genes: AIM2, ALAS1, BATF, C5orf32, CCL17, CD40LG, CHAC2, CSF1, CTSL1, EBNA1BP2, EDARADD, EMP1, EPAS1, FABP5, FAM40B, FKBP4, FOSL1, GCLM, GK, GPR56, HMOX1, HSPD1, HSPE1, IKBIP, IL10, IL13, IL15RA, IL1RN, IL2RA, IL3, IL4, IL5, IL9, KCNK5, LTA, MANF, MIR1182, MIR155, MIR155HG, MYOF, NDUFAF1, NLN, NME1, NME1-NME2, PANX2, PDIA6, PGAM4, PPIL1, PPPDE2, PRDX4, PRKAR1B, PSMD1, PSMD11, PUS7, RBBP8, SLC27A2, SLC39A14, SLC43A3, SRXN1, STIP1, STT3A, TBX21, TNFRSF11A, TNFRSF1B, TNFRSF8, TNFRSF9, TXN, UCK2, VDR, VTRNA1-3, WDR12, YWHAG, ZDHHC16 y ZNF282. La expresión regulada hacia arriba puede ser, por ejemplo, medida 16 horas después de la estimulación. La expresión regulada hacia arriba se puede determinar, por ejemplo, midiendo los niveles de ARN de los genes indicados.

Composiciones y tratamientos farmacéuticos

Las composiciones farmacéuticas de la presente invención pueden comprender, en algunos aspectos, una célula que expresa CAR, por ejemplo, una pluralidad de células que expresan CAR, tal como se describe en el presente documento, en combinación con uno o más vehículos, diluyentes o excipientes farmacéuticamente o fisiológicamente aceptables. Dichas composiciones pueden comprender tampones tales como solución salina tamponada neutra, solución salina tamponada con fosfato y similares; carbohidratos tales como glucosa, manosa, sacarosa o dextranos, manitol; proteínas; polipéptidos o aminoácidos tales como glicina; antioxidantes; agentes quelantes tales como EDTA o glutatión; adyuvantes (por ejemplo, hidróxido de aluminio); y conservantes. Las composiciones de la presente invención son, en un aspecto, formuladas para administración por vía intravenosa.

Las composiciones farmacéuticas de la presente invención se pueden administrar de una manera apropiada para la enfermedad a ser tratada (o prevenida). La cantidad y la frecuencia de

administración serán determinadas por factores tales como la condición del paciente y el tipo y la gravedad de la enfermedad del paciente, aunque las dosis apropiadas pueden ser determinadas por ensayos clínicos.

En una modalidad, la composición farmacéutica está sustancialmente libre de, por ejemplo, no hay niveles detectables de un contaminante, por ejemplo, seleccionado del grupo que consiste en endotoxina, micoplasma, lentivirus con capacidad de replicación (RCL), p24, ácido nucleico VSV-G, gag de VIH, esferas revestidas anti-CD3/anti-CD28 residuales, anticuerpos de ratón, suero humano mezclado, albúmina de suero bovino, suero bovino, componentes de medios de cultivo, componentes celulares o plásmidos de encapsidación de vectores, una bacteria y un hongo. En una modalidad, la bacteria es al menos una seleccionada del grupo que consiste en Alcaligenes faecalis, Candida albicans, Escherichia coli, Haemophilus influenza, Neisseria meningitidis, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae y Streptococcus pyogenes grupo A.

Cuando se indica "una cantidad inmunológicamente eficaz", "una cantidad eficaz antitumoral", "una cantidad eficaz inhibidora de tumores," o "cantidad terapéutica", la cantidad exacta de las composiciones de la presente invención a ser administrada puede ser determinada por un médico considerando las diferencias individuales en cuanto a la edad, el peso, el tamaño del tumor, el grado de infección o metástasis, y la condición del paciente (sujeto). En algunas modalidades, se puede afirmar que una composición farmacéutica que comprende las células, por ejemplo, células T descritas en el presente documento, se puede administrar a una dosis entre 10^4 y 10^9 células/kg de peso corporal, en algunos casos entre 10^5 y 10^6 células/kg de peso corporal, incluyendo todos los valores enteros dentro de estos rangos. En algunas modalidades, las células, por ejemplo, células T descritas en el presente documento, se pueden administrar a $3x10^4$, $1x10^6$, $3x10^6$ o $1x10^7$ células/kg de peso corporal. Las composiciones de células T también se pueden administrar varias veces usando estas dosis. Las células se pueden administrar usando técnicas de infusión conocidas comúnmente en la inmunoterapia (véase, por ejemplo, Rosenberg et al., New Eng. J. of Med. 319: 1676, 1988).

En algunas modalidades, una dosis de células CAR (por ejemplo, células CAR de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3 o ROR1) comprende aproximadamente 1×10^5, 2×10^5, 5×10^5, 1×10^6, $1{,}1 \times 10^6$, 2×10^6, $3{,}6 \times 10^6$, 5×10^6, 1×10^7, $1{,}8 \times 10^7$, 2×10^7, 5×10^7, 1×10^8, 2×10^8 o 5×10^8 células/kg. En algunas modalidades, una dosis de células CAR (por

ejemplo, células de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3 o ROR1) comprende al menos aproximadamente 1 x 10^5, 2 x 10^5, 5 x 10^5, 1 x 10^6, 1,1 x 10^6, 2 x 10^6, 3,6 x 10^6, 5 x 10^6, 1 x 10^7, 1,8 x 107, 2 x 10^7, 5 x 107, 1 x 10^8, 2 x 10^8 o 5 x 10^8 células/kg. En algunas modalidades, una dosis de células CAR (por ejemplo, células CAR de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3 o ROR1) comprende al menos aproximadamente 1 x 10^5, 2 x 10^5, 5 x 10^5, 1 x 10^6, 1,1 x 10^6, 2 x 10^6, 3,6 x 10^6, 5 x 10^6, 1 x 10^7, 1,8 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8 o 5 x 10^8 células/kg. En algunas modalidades, una dosis de células CAR (por ejemplo, células CAR de CD10, CD19, CD20, CD22, CD34, CD123, ROR1 o FLT-3) comprende de aproximadamente 1,1 x 10^6 – 1,8 x 10^7 células/kg o aproximadamente 8 x 10^5 - 1.5 x 10^6 células/kg. En algunas modalidades, una dosis de células CAR (por ejemplo, células CAR de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3 o ROR1) comprende aproximadamente 1 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9 o 5 x 10^9 células. En algunas modalidades, una dosis de células CAR (por ejemplo, células CAR de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3 o ROR1) comprende al menos aproximadamente 1 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9 o 5 x 10^9 células. En algunas modalidades, una dosis de células CAR (por ejemplo, células CAR de CD10, CD19, CD20, CD22, CD34, CD123, FLT-3 o ROR1) comprende hasta aproximadamente 1 x 10^7, 2 x 10^7, 5 x 10^7, 1 x 10^8, 2 x 10^8, 5 x 10^8, 1 x 10^9, 2 x 10^9 o 5 x 10^9 células.

En ciertos aspectos, puede ser deseable administrar células activadas, por ejemplo, células T o células NK, a un sujeto y, posteriormente, extraer sangre nuevamente (o llevar a cabo una aféresis), activar las células de allí provenientes de acuerdo con la presente invención y reinfundir al paciente con estas células activadas y ampliadas. Este proceso se puede llevar a cabo varias veces cada tantas semanas. En ciertos aspectos, las células, por ejemplo, células T o células NK, pueden ser activadas a partir de extracciones de sangre entre 10 cc y 400 cc. En ciertos aspectos, las células, por ejemplo, células T o células NK, se activan a partir de extracciones de sangre de 20cc, 30cc, 40cc, 50cc, 60cc, 70cc, 80cc, 90cc o 100cc.

La administración de las composiciones al sujeto se puede llevar a cabo de cualquier manera conveniente, incluyendo mediante inhalación de aerosol, inyección, ingestión, transfusión, implante o trasplante. Las composiciones descritas en el presente documento se pueden administrar a un paciente por vía transarterial, subcutánea, intradérmica, intratumoral,

intranodal, intramedular, intramuscular, mediante inyección intravenosa (i.v.) o por vía intraperitoneal. En un aspecto, las composiciones de células, por ejemplo, composiciones de células T o células NK, de la presente invención se administran mediante inyección intradermal o subcutánea. En un aspecto, las composiciones de células, por ejemplo, composiciones de células T o células NK, de la presente invención se administran mediante inyección intravenosa. Las composiciones de células, por ejemplo, composiciones de células T o células NK, se pueden inyectar directamente en un tumor, nódulo linfático o sitio de la infección.

En un aspecto ejemplar en particular, los sujetos pueden ser sometidos a leucaféresis, donde se recolectan, se enriquecen o se agotan leucocitos ex vivo para seleccionar y/o aislar las células de interés, por ejemplo, células T. Estos aislados de células, por ejemplo, aislados de células T o células NK, se pueden expandir mediante métodos conocidos en la técnica y ser tratados de tal manera que sea posible introducir uno o más constructos de CAR de la invención, para crear así una célula que expresa CAR, por ejemplo, TCAR de la invención. Los sujetos que lo requieran pueden someterse posteriormente a tratamiento estándar con quimioterapia de alta dosis, seguida de un trasplante de células madre de sangre periférica. En ciertos aspectos, los sujetos reciben una infusión de las células que expresan CAR expandidas de la presente invención posterior o simultáneamente con el trasplante. En un aspecto adicional, las células expandidas se administran antes o después de la cirugía.

Las dosis de los tratamientos anteriores a ser administradas a un paciente variarán de acuerdo con la naturaleza precisa de la condición a tratar y el receptor del tratamiento. El escalamiento de las dosis para administración humana puede realizarse de acuerdo con las prácticas aceptadas en la técnica. La dosis de un agente terapéutico, por ejemplo, un anticuerpo, por ejemplo, CAMPATH, por ejemplo, puede ser, por ejemplo, entre 1 y aproximadamente 100 mg para un paciente adulto, por ejemplo, administrada diariamente durante un periodo entre 1 y 30 días. Una dosis diaria adecuada es de 1 a 10 mg por día, aunque en algunos casos se pueden usar dosis más grandes de hasta 40 mg por día (descritas en la Patente de Estados Unidos No. 6,120,766).

En una modalidad, el CAR se introduce en células, por ejemplo, células T o células NK, por ejemplo, usando transcripción in vitro, y el sujeto (por ejemplo, un humano) recibe una administración inicial de células que expresan CAR, por ejemplo, células TCAR de la invención, y una o más administraciones posteriores de células que expresan CAR, por ejemplo,

células TCAR de la invención, donde una o más administraciones posteriores se suministran menos de 15 días, por ejemplo, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3 o 2 días después de la última administración. En una modalidad, se suministra al sujeto (por ejemplo, un humano) más de una administración de células que expresan CAR, por ejemplo, células TCAR de la invención por semana, por ejemplo, se suministran 2, 3 o 4 administraciones de células que expresan CAR, por ejemplo, células TCAR de la invención por semana. En una modalidad, el sujeto (por ejemplo, un sujeto humano) recibe más de una administración de células que expresan CAR, por ejemplo, células TCAR, por semana (por ejemplo, 2, 3 o 4 administraciones por semana) (también denominado aquí como un ciclo), seguida de una semana de ausencia de células que expresan CAR, por ejemplo, administraciones de células TCAR, y luego una o más administraciones adicionales de las células que expresan CAR, por ejemplo, células TCAR (por ejemplo, más de una administración de las células que expresan CAR, por ejemplo, células TCAR por semana) administradas al sujeto. En otra modalidad, el sujeto (por ejemplo, un sujeto humano) recibe más de un ciclo de células que expresan CAR, por ejemplo, células TCAR, y el tiempo entre cada ciclo es menor de 10, 9, 8, 7, 6, 5, 4 o 3 días. En una modalidad, las células que expresan CAR, por ejemplo, célula TCAR se administran cada día de por medio para 3 administraciones por semana. En una modalidad, las células que expresan CAR, por ejemplo, células TCAR de la invención se administran durante al menos dos, tres, cuatro, cinco, seis, siete, ocho o más semanas.

En algunas modalidades, los sujetos pueden ser sujetos adultos (es decir, tener 18 años de edad o más). En ciertas modalidades, los sujetos pueden tener entre 1 y 30 años de edad. En algunas modalidades, los sujetos tienen 16 años de edad o más. En ciertas modalidades, los sujetos pueden tener entre 16 y 30 años de edad. En algunas modalidades, los sujetos son niños (es decir, tienen entre 1 y 18 años de edad).

En un aspecto, las células que expresan CAR, por ejemplo, células TCARs, se generan usando vectores virales lentivirales, tales como lentivirus. Las células que expresan CAR, por ejemplo, TCAR generadas de esta manera, tendrán expresión de CAR estable.

En un aspecto, las células que expresan CAR, por ejemplo, TCAR, se generan usando un vector viral tal como un vector gammaretroviral, por ejemplo, un vector gammaretroviral descrito en el presente documento. Las TCARs generadas usando estos vectores pueden tener expresión de CAR estable.

En un aspecto, las células que expresan CAR, por ejemplo, TCAR, expresan vectores de CAR de manera transitoria durante 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 días después de la transducción. La expresión transitoria de los CAR se puede realizar mediante la entrega de vectores de ARN de CAR. En un aspecto, el ARN de CAR se transduce en la célula, por ejemplo, célula NK o célula T, mediante electroporación.

Un problema potencial que puede surgir en pacientes que están siendo tratados con células T que expresan CAR de manera transitoria (particularmente TCAR con scFv murino) es la anafilaxia después de múltiples tratamientos.

Al margen de las limitaciones que impone la teoría, se cree que dicha respuesta anafiláctica podría ser causada porque el paciente desarrolla una respuesta anti-CAR humoral, es decir, los anticuerpos anti-CAR que tienen un isotipo anti-IgE. Se cree que las células productoras de anticuerpos de un paciente sufren un cambio de clase de isotipo IgG (que no causa anafilaxia) a isotipo IgE cuando hay un descanso de diez a catorce días en la exposición al antígeno.

Si un paciente tiene un alto riesgo de generar una respuesta a anticuerpos anti-CAR durante el curso de terapia con CAR transitoria (tales como aquellos generados mediante transducciones de ARN), las pausas de infusión de TCAR no deben durar más de diez a catorce días.

CARs y anticuerpos de CD19

Humanización de anticuerpo anti-CD19 murino

La humanización del anticuerpo CD19 murino es deseable para el entorno clínico, donde los residuos específicos de ratón pueden inducir una respuesta al antígeno humano anti-murino (HAMA) en pacientes que reciben tratamiento con TCAR19, por ejemplo, tratamiento con células T transducidas con el constructo de CAR19. La producción, caracterización y eficacia de las secuencias de CAR de CD19 humanizadas se describe en la Solicitud Internacional WO2014/153270, la cual se incluye en el presente documento en su totalidad a manera de referencia, incluyendo los Ejemplos 1-5 (p. 115-159), por ejemplo, las Tablas 3, 4 y 5 (p. 125-147).

Constructos de CAR por ejemplo Constructos de CAR CD19

De los constructos de CAR CD19 descritos en la solicitud internacional WO2014/153270, se reproducen ciertas secuencias en el presente documento. Se entiende que las secuencias en esta sección también pueden ser usadas en el context de otros CARs, por ejemplo, CD10 CARs, CD20 CARs, CD22 CARs, CD34 CARs, CD123 CARs, FLT-3 CARs, ROR1 CARs, CD79b CARs, CD179b CARs, o CD79a CARs.

Las secuencias d elos fragmentos scFv humanizados (SEQ ID NOS: 1-12) se proporcionan a continuación en la **Tabla 2**. Los constructos completos de CAR fueron generados usando las secuencias SEQ ID NOs: 1-12 cons secuencias adicionales, SEQ ID NOs: 13-17, mostradas a continuación, para generar los constructos completos de CAR con las SEQ ID NOs: 31-42.

- líder (secuencia de aminoácidos) (SEQ ID NO: 13)

MALPVTALLLPLALLLHAARP

- **líder (secuencia de ácido nucleíco) (SEQ ID NO: 54)**

ATGGCCCTGCCTGTGACAGCCCTGCTGCTGCCTCTGGCTCTGCTGCTGCATGCCGCT AGACCC

- bisagra CD8 (secuencia de aminoácidos) (SEQ ID NO: 14)

TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD

- **bisagra CD8 (secuencia de ácido nucleíco) (SEQ ID NO: 55)**

ACCACGACGCCAGCGCCGCGACCACCAACACCGGCGCCCACCATCGCGTCGCAGCC CCTGTCCCTGCGCCCAGAGGCGTGCCGGCCAGCGGCGGGGGGCGCAGTGCACACGA GGGGGCTGGACTTCGCCTGTGAT

- CD8 transmembrana (secuencia de aminoácidos) (SEQ ID NO: 15)

IYIWAPLAGTCGVLLLSLVITLYC

- **transmembrana (secuencia de ácido nucleíco) (SEQ ID NO: 56)**

ATCTACATCTGGGCGCCCTTGGCCGGGACTTGTGGGGTCCTTCTCCTGTCACTGGTT ATCACCCTTTACTGC

- dominio intracelular 4-1BB (secuencia de aminoácidos) (SEQ ID NO: 16)

KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL

- **dominio intracelular 4-1BB (secuencia de ácido nucleíco) (SEQ ID NO: 60)**

AAACGGGGCAGAAAGAAACTCCTGTATATATTCAAACAACCATTTATGAGACCAGT
ACAAACTACTCAAGAGGAAGATGGCTGTAGCTGCCGATTTCCAGAAGAAGAAGAA
GGAGGATGTGAACTG

- dominio CD3 zeta (secuencia de aminoácidos) (SEQ ID NO: 17)

RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG
LYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

- **CD3 zeta (secuencia de ácido nucleíco) (SEQ ID NO: 101)**

AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACAAGCAGGGCCAGAACC
AGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAG
AGACGTGGCCGGGACCCTGAGATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGG
AAGGCCTGTACAATGAACTGCAGAAAGATAAGATGGCGGAGGCCTACAGTGAGAT
TGGGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTACCAGGGT
CTCAGTACAGCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCC
TCGC

- **Dominio CD3 zeta (secuencia de aminoácidos; secuencia de referencia NCBI NM_000734.3) (SEQ ID NO:43)**

RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEG
LYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

- **CD3 zeta (secuencia de ácido nucleíco; secuencia de referencia NCBI NM_000734.3); (SEQ ID NO:44)**

AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACCAGCAGGGCCAG
AACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTT
TGGACAAGAGACGTGGCCGGGACCCTGAGATGGGGGGAAAGCCGAGAAGGA
AGAACCCTCAGGAAGGCCTGTACAATGAACTGCAGAAAGATAAGATGGCGG
AGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGC
ACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACACCTACGACGC

CCTTCACATGCAGGCCCTGCCCCCTCGC

Dominio CD28 (secuencia de aminoácidos, SEQ ID NO: 1317)

RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS

Dominio CD28 (secuencia de nucleótidos, SEQ ID NO: 1318)

AGGAGTAAGAGGAGCAGGCTCCTGCACAGTGACTACATGAACATGACTCCCCGCCG
CCCCGGGCCCACCCGCAAGCATTACCAGCCCTATGCCCCACCACGCGACTTCGCAG
CCTATCGCTCC

Dominio ICOS de tipo silvestre (secuencia de aminoácidos, SEQ ID NO: 1319)

TKKKYSSSVHDPNGEYMFMRAVNTAKKSRLTDVTL

Dominio ICOS de tipo silvestre (secuencia de nucleótidos, SEQ ID NO: 1320)

ACAAAAAAGAAGTATTCATCCAGTGTGCACGACCCTAACGGTGAATACATGTTCAT
GAGAGCAGTGAACACAGCCAAAAAATCCAGACTCACAGATGTGACCCTA

Dominio ICOS Y a F mutante (secuencia de aminoácidos, SEQ ID NO: 1321)

TKKKYSSSVHDPNGEFMFMRAVNTAKKSRLTDVTL

Bisagra IgG4 (secuencia de aminoácidos) (SEQ ID NO:102)

ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI
SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP
PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGKM

Bisagra IgG4 (nucleotide sequence) (SEQ ID NO:103)

GAGAGCAAGTACGGCCCTCCCTGCCCCCCTTGCCCTGCCCCCGAGTTCCTGGGCGGA
CCCAGCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCCGGACC
CCCGAGGTGACCTGTGTGGTGGTGGACGTGTCCCAGGAGGACCCCGAGGTCCAGTT
CAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCCCGGGAG

GAGCAGTTCAATAGCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGA
CTGGCTGAACGGCAAGGAATACAAGTGTAAGGTGTCCAACAAGGGCCTGCCCAGCA
GCATCGAGAAAACCATCAGCAAGGCCAAGGGCCAGCCTCGGGAGCCCCAGGTGTA
CACCCTGCCCCCTAGCCAAGAGGAGATGACCAAGAACCAGGTGTCCCTGACCTGCC
TGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAG
CCCGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACAGCGACGGCAGCTTCTT
CCTGTACAGCCGGCTGACCGTGGACAAGAGCCGGTGGCAGGAGGGCAACGTCTTTA
GCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAGC
CTGTCCCTGGGCAAGATG

Todos estos clones contenían un cambio de residuo Q/K en el dominio señal del dominio co-estimulador derivado de 4-1BB.

Tabla 2: Constructos CD19 CAR Humanizados

Nombre	**SEQ ID**	**Secuencia**
CAR 1		
Dominio CAR1 scFv	1	EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPGQAPRLL IYHTSRLHSGIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTL PYTFGQGTKLEIKGGGGSGGGGSGGGGSQVQLQESGPGLVKPSETLS LTCTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYSSSLKSR VTISKDNSKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYAMDYWGQG TLVTVSS
103101 CAR1 scFv - nt Soluble	61	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggcccgaaattgtgatgacccagtcacccgccactc ttagcctttcacccggtgagcgcgcaaccctgtcttgcagagcctcc caagacatctcaaaataccttaattggtatcaacagaagcccggaca ggctcctcgccttctgatctaccacaccagccggctccattctggaa tccctgccaggttcagcggtagcggatctgggaccgactacaccctc actatcagctcactgcagccagaggacttcgctgtctatttctgtca gcaagggaacaccctgccctacacctttggacagggcaccaagctcg agattaaaggtggaggtggcagcggaggaggtgggtccggcggtgga ggaagccaggtccaactccaagaaagcggaccgggtcttgtgaagcc

		atcagaaactctttcactgacttgtactgtgagcggagtgtctctcc ccgattacggggtgtcttggatcagacagccaccggggaagggtctg gaatggattggagtgatttggggctctgagactacttactactcttc atccctcaagtcacgcgtcaccatctcaaaggacaactctaagaatc aggtgtcactgaaactgtcatctgtgaccgcagccgacaccgccgtg tactattgcgctaagcattactattatggcgggagctacgcaatgga ttactggggacagggtactctggtcaccgtgtccagccaccaccatc atcaccatcaccat
103101 CAR1 scFv - aa Soluble	73	**MALPVTALLLPLALLLHAARP**eivmtqspatlslspgeratlscras qdiskylnwyqqkpgqaprlliyhtsrlhsgiparfsgsgsgtdytl tisslqpedfavyfcqqgntlpytfgqgtkleikggggsggggsggg gsqvqlqesgpglvkpsetlsltctvsgvslpdygvswirqppgkgl ewigviwgsettyyssslksrvtiskdnsknqvslklssvtaadtav yycakhyyyggsyamdywgqgtlvtvss**hhhhhhhh**
104875 CAR 1 – completo - nt	85	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggcccgaaattgtgatgacccagtcacccgccactc ttagcctttcacccggtgagcgcgcaaccctgtcttgcagagcctcc caagacatctcaaaataccttaattggtatcaacagaagcccggaca ggctcctcgccttctgatctaccacaccagccggctccattctggaa tccctgccaggttcagcggtagcggatctgggaccgactacaccctc actatcagctcactgcagccagaggacttcgctgtctatttctgtca gcaagggaacaccctgccctacacctttggacagggcaccaagctcg agattaaaggtggaggtggcagcggaggaggtgggtccggcggtgga ggaagccaggtccaactccaagaaagcggaccgggtcttgtgaagcc atcagaaactctttcactgacttgtactgtgagcggagtgtctctcc ccgattacggggtgtcttggatcagacagccaccggggaagggtctg gaatggattggagtgatttggggctctgagactacttactactcttc atccctcaagtcacgcgtcaccatctcaaaggacaactctaagaatc aggtgtcactgaaactgtcatctgtgaccgcagccgacaccgccgtg tactattgcgctaagcattactattatggcgggagctacgcaatgga ttactggggacagggtactctggtcaccgtgtccagcaccactaccc cagcaccgaggccacccaccccggctcctaccatcgcctcccagcct

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104875 CAR 1 – completo - aa	31	MALPVTALLLPLALLLHAARPeivmtqspatlslspgeratlsc**rasqdiskyln**wyqqkpgqaprlliy**htsrlhs**giparfsgsgsgtdytl tisslqpedfavyfc**qqgntlpyt**fgqgtkleikggggsggggsggg gsqvqlqesgpglvkpsetlsltctvsgvslp**dygvs**wirqppgkgl ewig**viwgsettyyssslks**rvtiskdnsknqvslklssvtaadtav yycak**hyyyggsyamdy**wgqgtlvtvsstttpaprpptpaptiasqp lslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvit lyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrv kfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkp rrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglsta tkdtydalhmqalppr
CAR 2		
Dominio CAR2 scFv	2	eivmtqspatlslspgeratlscrasqdiskylnwyqqkpgqaprll iyhtsrlhsgiparfsgsgsgtdytltisslqpedfavyfcqqgntl pytfgqgtkleikggggsggggsggggsqvqlqesgpglvkpsetls ltctvsgvslpdygvswirqppgkglewigviwgsettyyqsslksr vtiskdnsknqvslklssvtaadtavyycakhyyyggsyamdywgqg tlvtvss

103102 CAR2 - scFv - nt Soluble	62	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggcccgaaattgtgatgacccagtcacccgccactc ttagcctttcacccggtgagcgcgcaaccctgtcttgcagagcctcc caagacatctcaaaataccttaattggtatcaacagaagcccggaca ggctcctcgccttctgatctaccacaccagccggctccattctggaa tccctgccaggttcagcggtagcggatctgggaccgactacaccctc actatcagctcactgcagccagaggacttcgctgtctatttctgtca gcaagggaacaccctgccctacacctttggacagggcaccaagctcg agattaaaggtggaggtggcagcggaggaggtgggtccggcggtgga ggaagccaggtccaactccaagaaagcggaccgggtcttgtgaagcc atcagaaactctttcactgacttgtactgtgagcggagtgtctctcc ccgattacggggtgtcttggatcagacagccaccggggaagggtctg gaatggattggagtgatttggggctctgagactacttactaccaatc atccctcaagtcacgcgtcaccatctcaaaggacaactctaagaatc aggtgtcactgaaactgtcatctgtgaccgcagccgacaccgccgtg tactattgcgctaagcattactattatggcgggagctacgcaatgga ttactggggacagggtactctggtcaccgtgtccagccaccaccatc atcaccatcaccat
103102 CAR2 - scFv - aa Soluble	74	**MALPVTALLLPLALLLHAARP**eivmtqspatlslspgeratlscras qdiskylnwyqqkpgqaprlliyhtsrlhsgiparfsgsgsgtdytl tisslqpedfavyfcqqgntlpytfgqgtkleikggggsggggsggg gsqvqlqesgpglvkpsetlsltctvsgvslpdygvswirqppgkgl ewigviwgsettyyqsslksrvtiskdnsknqvslklssvtaadtav yycakhyyyggsyamdywgqgtlvtvss**hhhhhhhh**
104876 CAR 2 - completo - nt	86	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggcccgaaattgtgatgacccagtcacccgccactc ttagcctttcacccggtgagcgcgcaaccctgtcttgcagagcctcc caagacatctcaaaataccttaattggtatcaacagaagcccggaca ggctcctcgccttctgatctaccacaccagccggctccattctggaa tccctgccaggttcagcggtagcggatctgggaccgactacaccctc actatcagctcactgcagccagaggacttcgctgtctatttctgtca gcaagggaacaccctgccctacacctttggacagggcaccaagctcg

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104876 CAR 2 - completo - aa	32	MALPVTALLLPLALLLHAARPeivmtqspatlslspgeratlsc**ras qdiskyln**wyqqkpgqaprlliy**htsrlhs**giparfsgsgsgtdytl tisslqpedfavyfc**qqgntlpyt**fgqgtkleikggggsggggsggg gsqvqlqesgpglvkpsetlsltctvsgvslp**dygvs**wirqppgkgl ewig**viwgsettyyqsslks**rvtiskdnsknqvslklssvtaadtav yycak**hyyyggsyamdy**wgqgtlvtvsstttpaprpptpaptiasqp lslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvit lyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrv

		kfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkp rrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglsta tkdtydalhmqalppr
CAR 3		
Dominio CAR3 scFv	3	qvqlqesgpglvkpsetlsltctvsgvslpdygvswirqppgkglew igviwgsettyyssslksrvtiskdnsknqvslklssvtaadtavyy cakhyyyggsyamdywgqgtlvtvssggggsggggsggggseivmtq spatlslspgeratlscrasqdiskylnwyqqkpgqaprlliyhtsr lhsgiparfsgsgsgtdytltisslqpedfavyfcqqgntlpytfgq gtkleik
103104 CAR 3 - scFv - nt Soluble	63	atggctctgcccgtgaccgcactcctcctgccactggctctgctgct tcacgccgctcgcccacaagtccagcttcaagaatcagggcctggtc tggtgaagccatctgagactctgtccctcacttgcaccgtgagcgga gtgtccctcccagactacggagtgagctggattagacagcctcccgg aaagggactggagtggatcggagtgatttggggtagcgaaaccactt actattcatcttccctgaagtcacgggtcaccatttcaaaggataac tcaaagaatcaagtgagcctcaagctctcatcagtcaccgccgctga caccgccgtgtattactgtgccaagcattactactatggagggtcct acgccatggactactggggccagggaactctggtcactgtgtcatct ggtggaggaggtagcggaggaggcgggagcggtggaggtggctccga aatcgtgatgacccagagccctgcaaccctgtccctttctcccgggg aacgggctacccttttcttgtcgggcatcacaagatatctcaaaatac ctcaattggtatcaacagaagccgggacaggcccctaggcttcttat ctaccacacctctcgcctgcatagcgggattcccgcacgctttagcg ggtctggaagcgggaccgactacactctgaccatctcatctctccag cccgaggacttcgccgtctacttctgccagcagggtaacaccctgcc gtacaccttcggccagggcaccaagcttgagatcaaacatcaccacc atcatcaccatcac
103104 CAR 3 - scFv - aa Soluble	75	**MALPVTALLLPLALLLHAARP**qvqlqesgpglvkpsetlsltctvsg vslpdygvswirqppgkglewigviwgsettyyssslksrvtiskdn sknqvslklssvtaadtavyycakhyyyggsyamdywgqgtlvtvss ggggsggggsggggseivmtqspatlslspgeratlscrasqdisky

		lnwyqqkpgqaprlliyhtsrlhsgiparfsgsgsgtdytltisslq pedfavyfcqqgntlpytfgqgtkleik**<u>hhhhhhhh</u>**
104877 CAR 3 – completo - nt	87	atggctctgcccgtgaccgcactcctcctgccactggctctgctgct tcacgccgctcgcccacaagtccagcttcaagaatcagggcctggtc tggtgaagccatctgagactctgtccctcacttgcaccgtgagcgga gtgtccctcccagactacggagtgagctggattagacagcctcccgg aaagggactggagtggatcggagtgatttggggtagcgaaaccactt actattcatcttccctgaagtcacgggtcaccatttcaaaggataac tcaaagaatcaagtgagcctcaagctctcatcagtcaccgccgctga caccgccgtgtattactgtgccaagcattactactatggagggtcct acgccatggactactggggccagggaactctggtcactgtgtcatct ggtggaggaggtagcggaggaggcgggagcggtggaggtggctccga aatcgtgatgacccagagccctgcaaccctgtccctttctcccgggg aacgggctacccttttcttgtcgggcatcacaagatatctcaaaatac ctcaattggtatcaacagaagccgggacaggcccctaggcttcttat ctaccacacctctcgcctgcatagcgggattcccgcacgctttagcg ggtctggaagcgggaccgactacactctgaccatctcatctctccag cccgaggacttcgccgtctacttctgccagcagggtaacaccctgcc gtacaccttcggccagggcaccaagcttgagatcaaaaccactactc ccgctccaaggccacccacccctgccccgaccatcgcctctcagccg ctttccctgcgtccggaggcatgtagacccgcagctggtggggccgt gcatacccggggtcttgacttcgcctgcgatatctacatttgggccc ctctggctggtacttgcggggtcctgctgctttcactcgtgatcact ctttactgtaagcgcggtcggaagaagctgctgtacatctttaagca acccttcatgaggcctgtgcagactactcaagaggaggacggctgtt catgccggttcccagaggaggaggaaggcggctgcgaactgcgcgtg aaattcagccgcagcgcagatgctccagcctacaagcaggggcagaa ccagctctacaacgaactcaatcttggtcggagagaggagtacgacg tgctggacaagcggagaggacgggacccagaaatgggcgggaagccg cgcagaaagaatccccaagagggcctgtacaacgagctccaaaagga taagatggcagaagcctatagcgagattggtatgaaaggggaacgca gaagaggcaaaggccacgacggactgtaccagggactcagcaccgcc

		accaaggacacctatgacgctcttcacatgcaggccctgccgcctcg g
104877 CAR 3 – completo - aa	33	MALPVTALLLPLALLLHAARPqvqlqesgpglvkpsetlsltctvsg vslp**dygvs**wirqppgkglewig**viwgsettyyssslks**rvtiskdn sknqvslklssvtaadtavyycak**hyyyggsyamdy**wgqgtlvtvss ggggsggggsggggseivmtqspatlslspgeratlsc**rasqdisky ln**wyqqkpgqaprlliy**htsrlhs**giparfsgsgsgtdytltisslq pedfavyfc**qqgntlpyt**fgqgtkleiktttpaprpptpaptiasqp lslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvit lyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrv kfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkp rrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglsta tkdtydalhmqalppr
CAR 4		
Dominio CAR4 scFv	4	qvqlqesgpglvkpsetlsltctvsgvslpdygvswirqppgkglew igviwgsettyyqsslksrvtiskdnsknqvslklssvtaadtavyy cakhyyyggsyamdywgqgtlvtvssggggsggggsggggseivmtq spatlslspgeratlscrasqdiskylnwyqqkpgqaprlliyhtsr lhsgiparfsgsgsgtdytltisslqpedfavyfcqqgntlpytfgq gtkleik
103106 CAR4 – scFv - nt Soluble	64	atggctctgcccgtgaccgcactcctcctgccactggctctgctgct tcacgccgctcgcccacaagtccagcttcaagaatcagggcctggtc tggtgaagccatctgagactctgtccctcacttgcaccgtgagcgga gtgtccctcccagactacggagtgagctggattagacagcctcccgg aaagggactggagtggatcggagtgatttggggtagcgaaaccactt actatcaatcttccctgaagtcacgggtcaccatttcaaaggataac tcaaagaatcaagtgagcctcaagctctcatcagtcaccgccgctga caccgccgtgtattactgtgccaagcattactactatggagggtcct acgccatggactactggggccagggaactctggtcactgtgtcatct ggtggaggaggtagcggaggaggcgggagcggtggaggtggctccga aatcgtgatgacccagagccctgcaaccctgtccctttctcccgggg aacgggctacccttttcttgtcgggcatcacaagatatctcaaaatac

		ctcaattggtatcaacagaagccgggacaggcccctaggcttcttat ctaccacacctctcgcctgcatagcgggattcccgcacgctttagcg ggtctggaagcgggaccgactacactctgaccatctcatctctccag cccgaggacttcgccgtctacttctgccagcagggtaacaccctgcc gtacaccttcggccagggcaccaagcttgagatcaaacatcaccacc atcatcaccatcac
103106 CAR4 – scFv -aa Soluble	76	**MALPVTALLLPLALLLHAARP**qvqlqesgpglvkpsetlsltctvsg vslpdygvswirqppgkglewigviwgsettyyqsslksrvtiskdn sknqvslklssvtaadtavyycakhyyyggsyamdywgqgtlvtvss ggggsggggsggggseivmtqspatlslspgeratlscrasqdisky lnwyqqkpgqaprlliyhtsrlhsgiparfsgsgsgtdytltisslq pedfavyfcqqgntlpytfgqgtkleik**hhhhhhhh**
104878 CAR 4 – completo - nt	88	atggctctgcccgtgaccgcactcctcctgccactggctctgctgct tcacgccgctcgcccacaagtccagcttcaagaatcagggcctggtc tggtgaagccatctgagactctgtccctcacttgcaccgtgagcgga gtgtccctcccagactacggagtgagctggattagacagcctcccgg aaagggactggagtggatcggagtgatttggggtagcgaaaccactt actatcaatcttccctgaagtcacgggtcaccatttcaaaggataac tcaaagaatcaagtgagcctcaagctctcatcagtcaccgccgctga caccgccgtgtattactgtgccaagcattactactatggagggtcct acgccatggactactggggccagggaactctggtcactgtgtcatct ggtggaggaggtagcggaggaggcgggagcggtggaggtggctccga aatcgtgatgacccagagccctgcaaccctgtccctttctcccgggg aacgggctacccttttcttgtcgggcatcacaagatatctcaaaatac ctcaattggtatcaacagaagccgggacaggcccctaggcttcttat ctaccacacctctcgcctgcatagcgggattcccgcacgctttagcg ggtctggaagcgggaccgactacactctgaccatctcatctctccag cccgaggacttcgccgtctacttctgccagcagggtaacaccctgcc gtacaccttcggccagggcaccaagcttgagatcaaaaccactactc ccgctccaaggccacccacccctgccccgaccatcgcctctcagccg ctttccctgcgtccggaggcatgtagacccgcagctggtggggccgt gcatacccggggtcttgacttcgcctgcgatatctacatttgggccc

		ctctggctggtacttgcggggtcctgctgctttcactcgtgatcact ctttactgtaagcgcggtcggaagaagctgctgtacatctttaagca acccttcatgaggcctgtgcagactactcaagaggaggacggctgtt catgccggttcccagaggaggaggaaggcggctgcgaactgcgcgtg aaattcagccgcagcgcagatgctccagcctacaagcaggggcagaa ccagctctacaacgaactcaatcttggtcggagagaggagtacgacg tgctggacaagcggagaggacgggacccagaaatgggcgggaagccg cgcagaaagaatccccaagagggcctgtacaacgagctccaaaagga taagatggcagaagcctatagcgagattggtatgaaaggggaacgca gaagaggcaaaggccacgacggactgtaccagggactcagcaccgcc accaaggacacctatgacgctcttcacatgcaggccctgccgcctcg g
104878 CAR 4 – completo - aa	34	MALPVTALLLPLALLLHAARPqvqlqesgpglvkpsetlsltctvsg vslp**dygvs**wirqppgkglewig**viwgsettyyqsslks**rvtiskdn sknqvslklssvtaadtavyycak**hyyyggsyamdy**wgqgtlvtvss ggggsggggsggggseivmtqspatlslspgeratlsc**rasqdisky ln**wyqqkpgqaprlliy**htsrlhs**giparfsgsgsgtdytltisslq pedfavyfc**qqgntlpyt**fgqgtkleiktttpaprpptpaptiasqp lslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvit lyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrv kfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkp rrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglsta tkdtydalhmqalppr
CAR 5		
Dominio CAR5 scFv	5	eivmtqspatlslspgeratlscrasqdiskylnwyqqkpgqaprll iyhtsrlhsgiparfsgsgsgtdytltisslqpedfavyfcqqgntl pytfgqgtkleikggggsggggsggggsggggsqvqlqesgpglvkp setlsltctvsgvslpdygvswirqppgkglewigviwgsettyyss slksrvtiskdnsknqvslklssvtaadtavyycakhyyyggsyamd ywgqgtlvtvss
99789 CAR5 -	65	atggccctcccagtgaccgctctgctgctgcctctcgcacttcttct ccatgccgctcggcctgagatcgtcatgacccaaagccccgctaccc

scFv - nt Soluble		tgtccctgtcacccggcgagagggcaacccttcatgcagggccagc caggacatttctaagtacctcaactggtatcagcagaagccagggca ggctcctcgcctgctgatctaccacaccagccgcctccacagcggta tccccgccagattttccgggagcgggtctggaaccgactacaccctc accatctcttctctgcagcccgaggatttcgccgtctatttctgcca gcaggggaatactctgccgtacaccttcggtcaaggtaccaagctgg aaatcaagggaggcggaggatcaggcggtggcggaagcggaggaggt ggctccggaggaggaggttcccaagtgcagcttcaagaatcaggacc cggacttgtgaagccatcagaaaccctctccctgacttgtaccgtgt ccggtgtgagcctccccgactacggagtctcttggattcgccagcct ccggggaagggtcttgaatggattggggtgatttggggatcagagac tacttactactcttcatcacttaagtcacgggtcaccatcagcaaag ataatagcaagaaccaagtgtcacttaagctgtcatctgtgaccgcc gctgacaccgccgtgtactattgtgccaaacattactattacggagg gtcttatgctatggactactggggacaggggaccctggtgactgtct ctagccatcaccatcaccaccatcatcac
99789 CAR5 - scFv -aa Soluble	77	**MALPVTALLLPLALLLHAARP**eivmtqspatlslspgeratlscras qdiskylnwyqqkpgqaprlliyhtsrlhsgiparfsgsgsgtdytl tisslqpedfavyfcqqgntlpytfgqgtkleikggggsggggsggg gsggggsqvqlqesgpglvkpsetlsltctvsgvslpdygvswirqp pgkglewigviwgsettyyssslksrvtiskdnsknqvslklssvta adtavyycakhyyyggsyamdywgqgtlvtvss**hhhhhhhh**
104879 CAR 5 – completo - nt	89	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggcccgaaattgtgatgacccagtcacccgccactc ttagcctttcacccggtgagcgcgcaaccctgtcttgcagagcctcc caagacatctcaaaataccttaattggtatcaacagaagcccggaca ggctcctcgccttctgatctaccacaccagccggctccattctggaa tccctgccaggttcagcggtagcggatctgggaccgactacaccctc actatcagctcactgcagccagaggacttcgctgtctatttctgtca gcaagggaacaccctgccctacacctttggacagggcaccaagctcg agattaaaggtggaggtggcagcggaggaggtgggtccggcggtgga ggaagcggcggaggcgggagccaggtccaactccaagaaagcggacc

		gggtcttgtgaagccatcagaaactctttcactgacttgtactgtga gcggagtgtctctccccgattacggggtgtcttggatcagacagcca ccggggaagggtctggaatggattggagtgatttggggctctgagac tacttactactcttcatccctcaagtcacgcgtcaccatctcaaagg acaactctaagaatcaggtgtcactgaaactgtcatctgtgaccgca gccgacaccgccgtgtactattgcgctaagcattactattatggcgg gagctacgcaatggattactggggacagggtactctggtcaccgtgt ccagcaccactaccccagcaccgaggccacccaccccggctcctacc atcgcctcccagcctctgtccctgcgtccggaggcatgtagacccgc agctggtggggccgtgcatacccggggtcttgacttcgcctgcgata tctacatttgggcccctctggctggtacttgcggggtcctgctgctt tcactcgtgatcactctttactgtaagcgcggtcggaagaagctgct gtacatctttaagcaacccttcatgaggcctgtgcagactactcaag aggaggacggctgttcatgccggttcccagaggaggaggaaggcggc tgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagccta caagcaggggcagaaccagctctacaacgaactcaatcttggtcgga gagaggagtacgacgtgctggacaagcggagaggacgggacccagaa atgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaa cgagctccaaaaggataagatggcagaagcctatagcgagattggta tgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccag ggactcagcaccgccaccaaggacacctatgacgctcttcacatgca ggccctgccgcctcgg
104879 CAR 5 – completo - aa	35	MALPVTALLLPLALLLHAARPeivmtqspatlslspgeratlsc**rasqdiskyln**wyqqkpgqaprlliy**htsrlhs**giparfsgsgsgtdytl tisslqpedfavyfc**qqgntlpyt**fgqgtkleikggggsggggsggg gsggggsqvqlqesgpglvkpsetlsltctvsgvslp**dygvs**wirqp pgkglewig**viwgsettyyssslks**rvtiskdnsknqvslklssvta adtavyycak**hyyyggsyamdy**wgqgtlvtvsstttpaprpptpapt iasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlll slvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeegg celrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpe mggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyq

		glstatkdtydalhmqalppr
CAR 6		
Dominio CAR6 scFv	6	eivmtqspatlslspgeratlscrasqdiskylnwyqqkpgqaprll iyhtsrlhsgiparfsgsgsgtdytltisslqpedfavyfcqqgntl pytfgqgtkleikggggsggggsggggsggggsqvqlqesgpglvkp setlsltctvsgvslpdygvswirqppgkglewigviwgsettyyqs slksrvtiskdnsknqvslklssvtaadtavyycakhyyyggsyamd ywgqgtlvtvss
99790 CAR6 - scFv - nt Soluble	66	atggccctcccagtgaccgctctgctgctgcctctcgcacttcttct ccatgccgctcggcctgagatcgtcatgacccaaagccccgctaccc tgtccctgtcacccggcgagagggcaacccctttcatgcagggccagc caggacatttctaagtacctcaactggtatcagcagaagccagggca ggctcctcgcctgctgatctaccacaccagccgcctccacagcggta tccccgccagattttccgggagcgggtctggaaccgactacaccctc accatctcttctctgcagcccgaggatttcgccgtctatttctgcca gcaggggaatactctgccgtacaccttcggtcaaggtaccaagctgg aaatcaagggaggcggaggatcaggcggtggcggaagcggaggaggt ggctccggaggaggaggttcccaagtgcagcttcaagaatcaggacc cggacttgtgaagccatcagaaaccctctccctgacttgtaccgtgt ccggtgtgagcctccccgactacggagtctcttggattcgccagcct ccggggaagggtcttgaatggattggggtgatttggggatcagagac tacttactaccagtcatcacttaagtcacgggtcaccatcagcaaag ataatagcaagaaccaagtgtcacttaagctgtcatctgtgaccgcc gctgacaccgccgtgtactattgtgccaaacattactattacggagg gtcttatgctatggactactggggacaggggaccctggtgactgtct ctagccatcaccatcaccaccatcatcac
99790 CAR6 - scFv - aa Soluble	78	**MALPVTALLLPLALLLHAARP**eivmtqspatlslspgeratlscras qdiskylnwyqqkpgqaprlliyhtsrlhsgiparfsgsgsgtdytl tisslqpedfavyfcqqgntlpytfgqgtkleikggggsggggsgggg gsggggsqvqlqesgpglvkpsetlsltctvsgvslpdygvswirqp pgkglewigviwgsettyyqsslksrvtiskdnsknqvslklssvta adtavyycakhyyyggsyamdywgqgtlvtvss**hhhhhhhh**

104880 CAR6 – completo - nt	90	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggcccgaaattgtgatgacccagtcacccgccactc ttagcctttcacccggtgagcgcgcaaccctgtcttgcagagcctcc caagacatctcaaaataccttaattggtatcaacagaagcccggaca ggctcctcgccttctgatctaccacaccagccggctccattctggaa tccctgccaggttcagcggtagcggatctgggaccgactacaccctc actatcagctcactgcagccagaggacttcgctgtctatttctgtca gcaagggaacaccctgccctacacctttggacagggcaccaagctcg agattaaaggtggaggtggcagcggaggaggtgggtccggcggtgga ggaagcggaggcggagggagccaggtccaactccaagaaagcggacc gggtcttgtgaagccatcagaaactctttcactgacttgtactgtga gcggagtgtctctccccgattacggggtgtcttggatcagacagcca ccggggaagggtctggaatggattggagtgatttggggctctgagac tacttactaccaatcatccctcaagtcacgcgtcaccatctcaaagg acaactctaagaatcaggtgtcactgaaactgtcatctgtgaccgca gccgacaccgccgtgtactattgcgctaagcattactattatggcgg gagctacgcaatggattactggggacagggtactctggtcaccgtgt ccagcaccactaccccagcaccgaggccacccaccccggctcctacc atcgcctcccagcctctgtccctgcgtccggaggcatgtagacccgc agctggtggggccgtgcatacccggggtcttgacttcgcctgcgata tctacatttgggcccctctggctggtacttgcggggtcctgctgctt tcactcgtgatcactctttactgtaagcgcggtcggaagaagctgct gtacatctttaagcaacccttcatgaggcctgtgcagactactcaag aggaggacggctgttcatgccggttcccagaggaggaggaaggcggc tgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagccta caagcaggggcagaaccagctctacaacgaactcaatcttggtcgga gagaggagtacgacgtgctggacaagcggagaggacgggacccagaa atgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaa cgagctccaaaaggataagatggcagaagcctatagcgagattggta tgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccag ggactcagcaccgccaccaaggacacctatgacgctcttcacatgca ggccctgccgcctcgg

104880 CAR6 – completo – aa	36	MALPVTALLLPLALLLHAARPeivmtqspatlslspgeratlsc**rasqdiskyln**wyqqkpgqaprlliy**htsrlhs**giparfsgsgsgtdytltisslqpedfavyfc**qqgntlpyt**fgqgtkleikggggsggggsgggggsggggsqvqlqesgpglvkpsetlsltctvsgvslp**dygvs**wirqppgkglewig**viwgsettyyqsslks**rvtiskdnsknqvslklssvtaadtavyycak**hyyyggsyamdy**wgqgtlvtvsstttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr
CAR 7		
Dominio CAR7 scFv	**7**	qvqlqesgpglvkpsetlsltctvsgvslpdygvswirqppgkglewigviwgsettyyssslksrvtiskdnsknqvslklssvtaadtavyycakhyyyggsyamdywgqgtlvtvssggggsggggsggggsggggseivmtqspatlslspgeratlscrasqdiskylnwyqqkpgqaprlliyhtsrlhsgiparfsgsgsgtdytltisslqpedfavyfcqqgntlpytfgqgtkleik
100796 CAR7 - scFv - nt Soluble	67	atggcactgcctgtcactgccctcctgctgcctctggccctccttctgcatgccgccaggccccaagtccagctgcaagagtcaggacccggactggtgaagccgtctgagactctctcactgacttgtaccgtcagcggcgtgtccctccccgactacggagtgtcatggatccgccaacctcccgggaaagggcttgaatggattggtgtcatctggggttctgaaaccacctactactcatcttccctgaagtccagggtgaccatcagcaaggataattccaagaaccaggtcagccttaagctgtcatctgtgaccgctgctgacaccgccgtgtattactgcgccaagcactactattacggaggaagctacgctatggactattggggacagggcactctcgtgactgtgagcagcggcggtggagggtctggaggtggaggatccggtggtggtgggtcaggcggaggagggagcgagattgtgatgactcagtcaccagccacccttctctttcacccggcgagagagcaaccctgagctgtagagccagccagacatttctaagtacctcaactggtatcagcaaaaaccggggcaggccctcgcctcctgatctaccatacctcacgccttcactctggtatcc

		ccgctcggtttagcggatcaggatctggtaccgactacactctgacc atttccagcctgcagccagaagatttcgcagtgtatttctgccagca gggcaataccttccttacaccttcggtcagggaaccaagctcgaaa tcaagcaccatcaccatcatcaccaccat
100796 CAR7 - scFv - aa Soluble	79	**MALPVTALLLPLALLLHAARP**qvqlqesgpglvkpsetlsltctvsg vslpdygvswirqppgkglewigviwgsettyyssslksrvtiskdn sknqvslklssvtaadtavyycakhyyyggsyamdywgqgtlvtvss ggggsggggsggggsggggseivmtqspatlslspgeratlscrasq diskylnwyqqkpgqaprlliyhtsrlhsgiparfsgsgsgtdytlt isslqpedfavyfcqqgntlpytfgqgtkleik**hhhhhhhh**
104881 CAR 7 completo - nt	91	atggctctgcccgtgaccgcactcctcctgccactggctctgctgct tcacgccgctcgcccacaagtccagcttcaagaatcagggcctggtc tggtgaagccatctgagactctgtccctcacttgcaccgtgagcgga gtgtccctcccagactacggagtgagctggattagacagcctcccgg aaagggactggagtggatcggagtgatttggggtagcgaaaccactt actattcatcttccctgaagtcacgggtcaccatttcaaaggataac tcaaagaatcaagtgagcctcaagctctcatcagtcaccgccgctga caccgccgtgtattactgtgccaagcattactactatggagggtcct acgccatggactactggggccagggaactctggtcactgtgtcatct ggtggaggaggtagcggaggaggcgggagcggtggaggtggctccgg aggtggcggaagcgaaatcgtgatgacccagagccctgcaaccctgt ccctttctcccggggaacgggctacccttcttgtcgggcatcacaa gatatctcaaaatacctcaattggtatcaacagaagccgggacaggc ccctaggcttcttatctaccacacctctcgcctgcatagcgggattc ccgcacgctttagcgggtctggaagcgggaccgactacactctgacc atctcatctctccagcccgaggacttcgccgtctacttctgccagca gggtaacaccctgccgtacaccttcggccagggcaccaagcttgaga tcaaaaccactactcccgctccaaggccacccacccctgccccgacc atcgcctctcagccgctttccctgcgtccggaggcatgtagacccgc agctggtggggccgtgcatacccggggtcttgacttcgcctgcgata tctacatttgggcccctctggctggtacttgcggggtcctgctgctt tcactcgtgatcactctttactgtaagcgcggtcggaagaagctgct

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104881 CAR 7 completo - aa	37	MALPVTALLLPLALLLHAARPqvqlqesgpglvkpsetlsltctvsg vslp**dygvs**wirqppgkglewig**viwgsettyyssslks**rvtiskdn sknqvslklssvtaadtavyycak**hyyyggsyamdy**wgqgtlvtvss ggggsggggsggggsggggseivmtqspatlslspgeratlsc**rasq diskyln**wyqqkpgqaprlliy**htsrlhs**giparfsgsgsgtdytlt isslqpedfavyfc**qqgntlpyt**fgqgtkleikttpaprpptpapt iasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlll slvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeegg celrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpe mggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyq glstatkdtydalhmqalppr
CAR 8		
Dominio CAR8 scFv	8	qvqlqesgpglvkpsetlsltctvsgvslpdygvswirqppgkglew igviwgsettyyqsslksrvtiskdnsknqvslklssvtaadtavyy cakhyyyggsyamdywgqgtlvtvssggggsggggsggggsggggse ivmtqspatlslspgeratlscrasqdiskylnwyqqkpgqaprlli yhtsrlhsgiparfsgsgsgtdytltisslqpedfavyfcqqgntlp ytfgqgtkleik
100798 CAR8 - scFv - nt Soluble	68	atggcactgcctgtcactgccctcctgctgcctctggccctccttct gcatgccgccaggccccaagtccagctgcaagagtcaggacccggac tggtgaagccgtctgagactctctcactgacttgtaccgtcagcggc gtgtccctccccgactacggagtgtcatggatccgccaacctcccgg

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100798 CAR8 - scFv - aa Soluble	80	**MALPVTALLLPLALLLHAARP**qvqlqesgpglvkpsetlsltctvsg vslpdygvswirqppgkglewigviwgsettyyqsslksrvtiskdn sknqvslklssvtaadtavyycakhyyyggsyamdywgqgtlvtvss ggggsggggsggggsggggseivmtqspatlslspgeratlscrasq diskylnwyqqkpgqaprlliyhtsrlhsgiparfsgsgsgtdytlt isslqpedfavyfcqqgntlpytfgqgtkleik**hhhhhhhh**
104882 CAR 8 – completo - nt	92	atggctctgcccgtgaccgcactcctcctgccactggctctgctgct tcacgccgctcgcccacaagtccagcttcaagaatcagggcctggtc tggtgaagccatctgagactctgtccctcacttgcaccgtgagcgga gtgtccctcccagactacggagtgagctggattagacagcctcccgg aaagggactggagtggatcggagtgatttggggtagcgaaaccactt actatcaatcttccctgaagtcacgggtcaccatttcaaaggataac tcaaagaatcaagtgagcctcaagctctcatcagtcaccgccgctga caccgccgtgtattactgtgccaagcattactactatggagggtcct acgccatggactactggggccagggaactctggtcactgtgtcatct ggtggaggaggtagcggaggaggcgggagcggtggaggtggctccgg aggcggtgggtcagaaatcgtgatgacccagagccctgcaaccctgt ccctttctcccggggaacgggctacccttttcttgtcgggcatcacaa

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104882 CAR 8 – completo - aa	38	MALPVTALLLPLALLLHAARPqvqlqesgpglvkpsetlsltctvsg vslp**dygvs**wirqppgkglewig**viwgsettyyqsslks**rvtiskdn sknqvslklssvtaadtavyycak**hyyyggsyamdy**wgqgtlvtvss ggggsggggsggggsggggseivmtqspatlslspgeratlsc**rasq diskyln**wyqqkpgqaprlliy**htsrlhs**giparfsgsgsgtdytlt isslqpedfavyfc**qqgntlpyt**fgqgtkleikttpaprpptpapt iasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlll slvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeegg celrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpe mggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyq glstatkdtydalhmqalppr
CAR 9		

Dominio CAR9 scFv	9	eivmtqspatlslspgeratlscrasqdiskylnwyqqkpgqaprll iyhtsrlhsgiparfsgsgsgtdytltisslqpedfavyfcqqgntl pytfgqgtkleikggggsggggsggggsggggsqvqlqesgpglvkp setlsltctvsgvslpdygvswirqppgkglewigviwgsettyyns slksrvtiskdnsknqvslklssvtaadtavyycakhyyyggsyamd ywgqgtlvtvss
99789 CAR9 - scFv - nt Soluble	69	atggccctcccagtgaccgctctgctgctgcctctcgcacttcttct ccatgccgctcggcctgagatcgtcatgacccaaagccccgctaccc tgtccctgtcacccggcgagagggcaacccttcatgcagggccagc caggacatttctaagtacctcaactggtatcagcagaagccagggca ggctcctcgcctgctgatctaccacaccagccgcctccacagcggta tccccgccagattttccgggagcgggtctggaaccgactacaccctc accatctcttctctgcagcccgaggatttcgccgtctatttctgcca gcaggggaatactctgccgtacaccttcggtcaaggtaccaagctgg aaatcaagggaggcggaggatcaggcggtggcggaagcggaggaggt ggctccggaggaggaggttcccaagtgcagcttcaagaatcaggacc cggacttgtgaagccatcagaaaccctctccctgacttgtaccgtgt ccggtgtgagcctccccgactacggagtctcttggattcgccagcct ccggggaagggtcttgaatggattggggtgatttggggatcagagac tacttactacaattcatcacttaagtcacgggtcaccatcagcaaag ataatagcaagaaccaagtgtcacttaagctgtcatctgtgaccgcc gctgacaccgccgtgtactattgtgccaaacattactattacggagg gtcttatgctatggactactggggacaggggaccctggtgactgtct ctagccatcaccatcaccaccatcatcac
99789 CAR9 - scFv - aa Soluble	81	**MALPVTALLLPLALLLHAARP**eivmtqspatlslspgeratlscras qdiskylnwyqqkpgqaprlliyhtsrlhsgiparfsgsgsgtdytl tisslqpedfavyfcqqgntlpytfgqgtkleikggggsggggsgggg gsggggsqvqlqesgpglvkpsetlsltctvsgvslpdygvswirqp pgkglewigviwgsettyynsslksrvtiskdnsknqvslklssvta adtavyycakhyyyggsyamdywgqgtlvtvss**hhhhhhhh**
105974 CAR 9 –	93	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggcccgaaattgtgatgacccagtcacccgccactc

completo - nt		ttagcctttcacccggtgagcgcgcaaccctgtcttgcagagcctcc caagacatctcaaaataccttaattggtatcaacagaagcccggaca ggctcctcgccttctgatctaccacaccagccggctccattctggaa tccctgccaggttcagcggtagcggatctgggaccgactacaccctc actatcagctcactgcagccagaggacttcgctgtctatttctgtca gcaagggaacaccctgccctacacctttggacagggcaccaagctcg agattaaaggtggaggtggcagcggaggaggtgggtccggcggtgga ggaagcggaggcggtgggagccaggtccaactccaagaaagcggacc gggtcttgtgaagccatcagaaactctttcactgacttgtactgtga gcggagtgtctctccccgattacggggtgtcttggatcagacagcca ccggggaagggtctggaatggattggagtgatttggggctctgagac tacttactacaactcatccctcaagtcacgcgtcaccatctcaaagg acaactctaagaatcaggtgtcactgaaactgtcatctgtgaccgca gccgacaccgccgtgtactattgcgctaagcattactattatggcgg gagctacgcaatggattactggggacagggtactctggtcaccgtgt ccagcaccactaccccagcaccgaggccacccaccccggctcctacc atcgcctcccagcctctgtccctgcgtccggaggcatgtagacccgc agctggtggggccgtgcatacccggggtcttgacttcgcctgcgata tctacatttgggcccctctggctggtacttgcggggtcctgctgctt tcactcgtgatcactctttactgtaagcgcggtcggaagaagctgct gtacatctttaagcaacccttcatgaggcctgtgcagactactcaag aggaggacggctgttcatgccggttcccagaggaggaggaaggcggc tgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagccta caagcaggggcagaaccagctctacaacgaactcaatcttggtcgga gagaggagtacgacgtgctggacaagcggagaggacgggacccagaa atgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaa cgagctccaaaaggataagatggcagaagcctatagcgagattggta tgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccag ggactcagcaccgccaccaaggacacctatgacgctcttcacatgca ggccctgccgcctcgg
105974 CAR 9 –	39	MALPVTALLLPLALLLHAARPeivmtqspatlslspgeratlsc**ras qdiskyln**wyqqkpgqaprlliy**htsrlhs**giparfsgsgsgtdytl

completo - aa		tisslqpedfavyfc**qqgntlpyt**fgqgtkleikggggsggggsggg gsggggsqvqlqesgpglvkpsetlsltctvsgvslp**dygvs**wirqp pgkglewig**viwgsettyynsslks**rvtiskdnsknqvslklssvta adtavyycak**hyyyggsyamdy**wgqgtlvtvsstttpaprpptpapt iasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlll slvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeegg celrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpe mggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyq glstatkdtydalhmqalppr
CAR10		
Dominio CAR10 scFv	10	qvqlqesgpglvkpsetlsltctvsgvslpdygvswirqppgkglew igviwgsettyynsslksrvtiskdnsknqvslklssvtaadtavyy cakhyyyggsyamdywgqgtlvtvssggggsggggsggggsggggse ivmtqspatlslspgeratlscrasqdiskylnwyqqkpgqaprlli yhtsrlhsgiparfsgsgsgtdytltisslqpedfavyfcqqgntlp ytfgqgtkleik
100796 CAR10 - scFv - nt Soluble	70	atggcactgcctgtcactgccctcctgctgcctctggccctccttct gcatgccgccaggccccaagtccagctgcaagagtcaggacccggac tggtgaagccgtctgagactctctcactgacttgtaccgtcagcggc gtgtccctccccgactacggagtgtcatggatccgccaacctcccgg gaaagggcttgaatggattggtgtcatctggggttctgaaaccacct actacaactcttccctgaagtccagggtgaccatcagcaaggataat tccaagaaccaggtcagccttaagctgtcatctgtgaccgctgctga caccgccgtgtattactgcgccaagcactactattacggaggaagct acgctatggactattggggacagggcactctcgtgactgtgagcagc ggcggtggagggtctggaggtggaggatccggtggtggtgggtcagg cggaggagggagcgagattgtgatgactcagtcaccagccacccttt ctctttcacccggcgagagagcaaccctgagctgtagagccagccag gacatttctaagtacctcaactggtatcagcaaaaaccggggcaggc ccctcgcctcctgatctaccatacctcacgccttcactctggtatcc ccgctcggtttagcggatcaggatctggtaccgactacactctgacc atttccagcctgcagccagaagatttcgcagtgtatttctgccagca

		gggcaataccttccttacaccttcggtcagggaaccaagctcgaaa tcaagcaccatcaccatcatcaccaccat
100796 CAR10 - scFv - aa Soluble	82	**MALPVTALLLPLALLLHAARP**qvqlqesgpglvkpsetlsltctvsg vslpdygvswirqppgkglewigviwgsettyynsslksrvtiskdn sknqvslklssvtaadtavyycakhyyyggsyamdywgqgtlvtvss ggggsggggsggggsggggseivmtqspatlslspgeratlscrasq diskylnwyqqkpgqaprlliyhtsrlhsgiparfsgsgsgtdytlt isslqpedfavyfcqqgntlpytfgqgtkleik**hhhhhhhh**
105975 CAR 10 completo - nt	94	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggcccgaaattgtgatgacccagtcacccgccactc ttagcctttcacccggtgagcgcgcaaccctgtcttgcagagcctcc caagacatctcaaaataccttaattggtatcaacagaagcccggaca ggctcctcgccttctgatctaccacaccagccggctccattctggaa tccctgccaggttcagcggtagcggatctgggaccgactacaccctc actatcagctcactgcagccagaggacttcgctgtctatttctgtca gcaagggaacaccctgccctacacctttggacagggcaccaagctcg agattaaaggtggaggtggcagcggaggaggtgggtccggcggtgga ggaagcggaggcggtgggagccaggtccaactccaagaaagcggacc gggtcttgtgaagccatcagaaactctttcactgacttgtactgtga gcggagtgtctctccccgattacggggtgtcttggatcagacagcca ccggggaagggtctggaatggattggagtgatttggggctctgagac tacttactacaactcatccctcaagtcacgcgtcaccatctcaaagg acaactctaagaatcaggtgtcactgaaactgtcatctgtgaccgca gccgacaccgccgtgtactattgcgctaagcattactattatggcgg gagctacgcaatggattactggggacagggtactctggtcaccgtgt ccagcaccactaccccagcaccgaggccacccaccccggctcctacc atcgcctcccagcctctgtccctgcgtccggaggcatgtagacccgc agctggtggggccgtgcatacccggggtcttgacttcgcctgcgata tctacatttgggcccctctggctggtacttgcggggtcctgctgctt tcactcgtgatcactctttactgtaagcgcggtcggaagaagctgct gtacatctttaagcaacccttcatgaggcctgtgcagactactcaag aggaggacggctgttcatgccggttcccagaggaggaggaaggcggc

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105975 CAR 10 completo - aa	40	MALPVTALLLPLALLLHAARPEIVMTQSPATLSLSPGERATLSC**RAS** **QDISKYLN**WYQQKPGQAPRLLIY**HTSRLHS**GIPARFSGSGSGTDYTL TISSLQPEDFAVYFC**QQGNTLPYT**FGQGTKLEIKGGGGSGGGGSGGG GSGGGGSQVQLQESGPGLVKPSETLSLTCTVSGVSLP**DYGVS**WIRQP PGKGLEWIG**VIWGSETTYYNSSLKS**RVTISKDNSKNQVSLKLSSVTA ADTAVYYCAK**HYYYGGSYAMDY**WGQGTLVTVSSTTTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGG CELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPE MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQ GLSTATKDTYDALHMQALPPR
CAR11		
Dominio CAR11 scFv	11	eivmtqspatlslspgeratlscrasqdiskylnwyqqkpgqaprll iyhtsrlhsgiparfsgsgsgtdytltisslqpedfavyfcqqgntl pytfgqgtkleikggggsggggsggggsqvqlqesgpglvkpsetls ltctvsgvslpdygvswirqppgkglewigviwgsettyynsslksr vtiskdnsknqvslklssvtaadtavyycakhyyyggsyamdywgqg tlvtvss
103101 CAR11 - scFv - nt	71	Atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggcccgaaattgtgatgacccagtcacccgccactc ttagcctttcacccggtgagcgcgcaaccctgtcttgcagagcctcc

Soluble		caagacatctcaaaataccttaattggtatcaacagaagcccggaca ggctcctcgccttctgatctaccacaccagccggctccattctggaa tccctgccaggttcagcggtagcggatctgggaccgactacaccctc actatcagctcactgcagccagaggacttcgctgtctatttctgtca gcaagggaacaccctgccctacacctttggacagggcaccaagctcg agattaaaggtggaggtggcagcggaggaggtgggtccggcggtgga ggaagccaggtccaactccaagaaagcggaccgggtcttgtgaagcc atcagaaactctttcactgacttgtactgtgagcggagtgtctctcc ccgattacggggtgtcttggatcagacagccaccggggaagggtctg gaatggattggagtgatttggggctctgagactacttactacaattc atccctcaagtcacgcgtcaccatctcaaaggacaactctaagaatc aggtgtcactgaaactgtcatctgtgaccgcagccgacaccgccgtg tactattgcgctaagcattactattatggcgggagctacgcaatgga ttactggggacagggtactctggtcaccgtgtccagccaccaccatc atcaccatcaccat
103101 CAR11 - scFv - aa Soluble	83	**MALPVTALLLPLALLLHAARP**eivmtqspatlslspgeratlscras qdiskylnwyqqkpgqaprlliyhtsrlhsgiparfsgsgsgtdytl tisslqpedfavyfcqqgntlpytfgqgtkleikggggsggggsggg gsqvqlqesgpglvkpsetlsltctvsgvslpdygvswirqppgkgl ewigviwgsettyynsslksrvtiskdnsknqvslklssvtaadtav yycakhyyyggsyamdywgqgtlvtvss**hhhhhhhh**
105976 CAR 11 completo - nt	95	atggctctgcccgtgaccgcactcctcctgccactggctctgctgct tcacgccgctcgcccacaagtccagcttcaagaatcagggcctggtc tggtgaagccatctgagactctgtccctcacttgcaccgtgagcgga gtgtccctcccagactacggagtgagctggattagacagcctcccgg aaagggactggagtggatcggagtgatttggggtagcgaaaccactt actataactcttccctgaagtcacgggtcaccatttcaaaggataac tcaaagaatcaagtgagcctcaagctctcatcagtcaccgccgctga caccgccgtgtattactgtgccaagcattactactatggagggtcct acgccatggactactggggccagggaactctggtcactgtgtcatct ggtggaggaggtagcggaggaggcgggagcggtggaggtggctccgg aggtggcggaagcgaaatcgtgatgacccagagccctgcaaccctgt

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105976 CAR 11 completo - aa	41	MALPVTALLLPLALLLHAARPQVQLQESGPGLVKPSETLSLTCTVSG VSLP**DYGVS**WIRQPPGKGLEWIG**VIWGSETTYYNSSLKS**RVTISKDN SKNQVSLKLSSVTAADTAVYYCAK**HYYYGGSYAMDY**WGQGTLVTVSS GGGGSGGGGSGGGGSGGGGSEIVMTQSPATLSLSPGERATLSC**RASQ** **DISKYLN**WYQQKPGQAPRLLIY**HTSRLHS**GIPARFSGSGSGTDYTLT ISSLQPEDFAVYFC**QQGNTLPYT**FGQGTKLEIKTTTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGG CELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPE MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQ

		GLSTATKDTYDALHMQALPPR
CAR12		
Dominio CAR12 scFv	12	qvqlqesgpglvkpsetlsltctvsgvslpdygvswirqppgkglew igviwgsettyynsslksrvtiskdnsknqvslklssvtaadtavyy cakhyyyggsyamdywgqgtlvtvssggggsggggsggggseivmtq spatlslspgeratlscrasqdiskylnwyqqkpgqaprlliyhtsr lhsgiparfsgsgsgtdytltisslqpedfavyfcqqgntlpytfgq gtkleik
103104 CAR12 - scFv - nt Soluble	72	atggctctgcccgtgaccgcactcctcctgccactggctctgctgct tcacgccgctcgcccacaagtccagcttcaagaatcagggcctggtc tggtgaagccatctgagactctgtccctcacttgcaccgtgagcgga gtgtccctcccagactacggagtgagctggattagacagcctcccgg aaagggactggagtggatcggagtgatttggggtagcgaaaccactt actataactcttccctgaagtcacgggtcaccatttcaaaggataac tcaaagaatcaagtgagcctcaagctctcatcagtcaccgccgctga caccgccgtgtattactgtgccaagcattactactatggagggtcct acgccatggactactggggccagggaactctggtcactgtgtcatct ggtggaggaggtagcggaggaggcgggagcggtggaggtggctccga aatcgtgatgacccagagccctgcaaccctgtccctttctcccgggg aacgggctacccttttcttgtcgggcatcacaagatatctcaaaatac ctcaattggtatcaacagaagccgggacaggcccctaggcttcttat ctaccacacctctcgcctgcatagcgggattcccgcacgctttagcg ggtctggaagcgggaccgactacactctgaccatctcatctctccag cccgaggacttcgccgtctacttctgccagcagggtaacaccctgcc gtacaccttcggccagggcaccaagcttgagatcaaacatcaccacc atcatcaccatcac
103104 CAR12 - scFv -aa Soluble	84	**MALPVTALLLPLALLLHAARP**qvqlqesgpglvkpsetlsltctvsg vslpdygvswirqppgkglewigviwgsettyynsslksrvtiskdn sknqvslklssvtaadtavyycakhyyyggsyamdywgqgtlvtvss ggggsggggsggggseivmtqspatlslspgeratlscrasqdisky lnwyqqkpgqaprlliyhtsrlhsgiparfsgsgsgtdytltisslq

		pedfavyfcqqgntlpytfgqgtkleik**<u>hhhhhhhh</u>**
105977 CAR 12 – completo - nt	96	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggcccgaaattgtgatgacccagtcacccgccactc ttagcctttcacccggtgagcgcgcaaccctgtcttgcagagcctcc caagacatctcaaaataccttaattggtatcaacagaagcccggaca ggctcctcgccttctgatctaccacaccagccggctccattctggaa tccctgccaggttcagcggtagcggatctgggaccgactacaccctc actatcagctcactgcagccagaggacttcgctgtctatttctgtca gcaagggaacaccctgccctacacctttggacagggcaccaagctcg agattaaaggtggaggtggcagcggaggaggtgggtccggcggtgga ggaagccaggtccaactccaagaaagcggaccgggtcttgtgaagcc atcagaaactctttcactgacttgtactgtgagcggagtgtctctcc ccgattacggggtgtcttggatcagacagccaccggggaagggtctg gaatggattggagtgatttggggctctgagactacttactacaactc atccctcaagtcacgcgtcaccatctcaaaggacaactctaagaatc aggtgtcactgaaactgtcatctgtgaccgcagccgacaccgccgtg tactattgcgctaagcattactattatggcgggagctacgcaatgga ttactggggacagggtactctggtcaccgtgtccagcaccactaccc cagcaccgaggccacccaccccggctcctaccatcgcctcccagcct ctgtccctgcgtccggaggcatgtagacccgcagctggtggggccgt gcatacccggggtcttgacttcgcctgcgatatctacatttgggccc ctctggctggtacttgcggggtcctgctgctttcactcgtgatcact ctttactgtaagcgcggtcggaagaagctgctgtacatctttaagca acccttcatgaggcctgtgcagactactcaagaggaggacggctgtt catgccggttcccagaggaggaggaaggcggctgcgaactgcgcgtg aaattcagccgcagcgcagatgctccagcctacaagcaggggcagaa ccagctctacaacgaactcaatcttggtcggagagaggagtacgacg tgctggacaagcggagaggacgggacccagaaatgggcgggaagccg cgcagaaagaatccccaagagggcctgtacaacgagctccaaaagga taagatggcagaagcctatagcgagattggtatgaaaggggaacgca gaagaggcaaaggccacgacggactgtaccagggactcagcaccgcc accaaggacacctatgacgctcttcacatgcaggccctgccgcctcg

		g
105977 CAR 12 – completo - aa	42	MALPVTALLLPLALLLHAARPEIVMTQSPATLSLSPGERATLSC**RAS QDISKYLN**WYQQKPGQAPRLLIY**HTSRLHS**GIPARFSGSGSGTDYTL TISSLQPEDFAVYFC**QQGNTLPYT**FGQGTKLEIKGGGGSGGGGSGGG GSQVQLQESGPGLVKPSETLSLTCTVSGVSLP**DYGVS**WIRQPPGKGL EWIG**VIWGSETTYYNSSLKS**RVTISKDNSKNQVSLKLSSVTAADTAV YYCAK**HYYYGGSYAMDY**WGQGTLVTVSSTTTPAPRPPTPAPTIASQP LSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVIT LYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRV KFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKP RRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTA TKDTYDALHMQALPPR

Tabla 3: Constructos CD19 CAR Murinos

CTL019		
CTL019 – scFv-Histag - nt Soluble	97	Atggccctgcccgtcaccgctctgctgctgcccttgctctgcttct tcatgcagcaaggccggacatccagatgacccaaaccacctcatccc tctctgcctctcttggagacagggtgaccatttcttgtcgcgccagc caggacatcagcaagtatctgaactggtatcagcagaagccggacgg aaccgtgaagctcctgatctaccatacctctcgcctgcatagcggcg tgccctcacgcttctctggaagcggatcaggaaccgattattctctc actatttcaaatcttgagcaggaagatattgccacctatttctgcca gcagggtaataccctgccctacaccttcggaggagggaccaagctcg aaatcaccggtggaggaggcagcggcggtggagggtctggtggaggt ggttctgaggtgaagctgcaagaatcaggccctggacttgtggcccc ttcacagtccctgagcgtgacttgcaccgtgtccggagtctccctgc ccgactacggagtgtcatggatcagacaacctccacggaaaggactg gaatggctcggtgtcatctggggtagcgaaactacttactacaattc agccctcaaaagcaggctgactattatcaaggacaacagcaagtccc

		aagtctttcttaagatgaactcactccagactgacgacaccgcaatc tactattgtgctaagcactactactacggaggatcctacgctatgga ttactggggacaaggtacttccgtcactgtctcttcacaccatcatc accatcaccatcac
CTL019 – scFv-Histag - aa Soluble	98	**MALPVTALLLPLALLLHAARP**diqmtqttsslsaslgdrvtiscras qdiskylnwyqqkpdgtvklliyhtsrlhsgvpsrfsgsgsgtdysl tisnleqediatyfcqqgntlpytfgggtkleitggggsggggsggg gsevklqesgpglvapsqslsvtctvsgvslpdygvswirqpprkgl ewlgviwgsettyynsalksrltiikdnsksqvflkmnslqtddtai yycakhyyyggsyamdywgqgtsvtvss**hhhhhhhh**
CTL019 completo - nt	99	atggccttaccagtgaccgccttgctcctgccgctggccttgctgct ccacgccgccaggccggacatccagatgacacagactacatcctccc tgtctgcctctctgggagacagagtcaccatcagttgcagggcaagt caggacattagtaaatatttaaattggtatcagcagaaaccagatgg aactgttaaactcctgatctaccatacatcaagattacactcaggag tcccatcaaggttcagtggcagtgggtctggaacagattattctctc accattagcaacctggagcaagaagatattgccacttactttgcca acagggtaatacgcttccgtacacgttcggaggggggaccaagctgg agatcacaggtggcggtggctcgggcggtggtgggtcgggtggcggc ggatctgaggtgaaactgcaggagtcaggacctggcctggtggcgcc ctcacagagcctgtccgtcacatgcactgtctcaggggtctcattac ccgactatggtgtaagctggattcgccagcctccacgaaagggtctg gagtggctgggagtaatatggggtagtgaaaccacatactataattc agctctcaaatccagactgaccatcatcaaggacaactccaagagcc aagttttcttaaaaatgaacagtctgcaaactgatgacacagccatt tactactgtgccaaacattattactacggtggtagctatgctatgga ctactggggccaaggaacctcagtcaccgtctcctcaaccacgacgc cagcgccgcgaccaccaacaccggcgcccaccatcgcgtcgcagccc ctgtccctgcgcccagaggcgtgccggccagcggcgggggcgcagt gcacacgaggggctggacttcgcctgtgatatctacatctgggcgc ccttggccgggacttgtggggtccttctcctgtcactggttatcacc ctttactgcaaacggggcagaaagaaactcctgtatatattcaaaca

		accatttatgagaccagtacaaactactcaagaggaagatggctgta gctgccgatttccagaagaagaagaaggaggatgtgaactgagagtg aagttcagcaggagcgcagacgcccccgcgtacaagcagggccagaa ccagctctataacgagctcaatctaggacgaagagaggagtacgatg ttttggacaagagacgtggccgggaccctgagatgggggggaaagccg agaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaaga taagatggcggaggcctacagtgagattgggatgaaaggcgagcgcc ggaggggcaaggggcacgatggcctttaccagggtctcagtacagcc accaaggacacctacgacgcccttcacatgcaggccctgcccccctcg c
CTL019 completo - aa	58	MALPVTALLLPLALLLHAARPdiqmtqttsslsaslgdrvtiscras qdiskylnwyqqkpdgtvklliyhtsrlhsgvpsrfsgsgsgtdysl tisnleqediatyfcqqgntlpytfgggtkleitggggsggggsggg gsevklqesgpglvapsqslsvtctvsgvslpdygvswirqpprkgl ewlgviwgsettyynsalksrltiikdnsksqvflkmnslqtddtai yycakhyyyggsyamdywgqgtsvtvsstttpaprpptpaptiasqp lslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvlllslvit lyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggcelrv kfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkp rrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglsta tkdtydalhmqalppr
Dominio CTL019 scFv	59	Diqmtqttsslsaslgdrvtiscrasqdiskylnwyqqkpdgtvkll iyhtsrlhsgvpsrfsgsgsgtdysltisnleqediatyfcqqgntl pytfgggtkleitggggsggggsggggsevklqesgpglvapsqsls vtctvsgvslpdygvswirqpprkglewlgviwgsettyynsalksr ltiikdnsksqvflkmnslqtddtaiyycakhyyyggsyamdywgqg tsvtvss
mCAR1 scFv	109	QVQLLESGAELVRPGSSVKISCKASGYAFSSYWMNWVKQRPGQGLEW IGQIYPGDGDTNYNGKFKGQATLTADKSSSTAYMQLSGLTSEDSAVY SCARKTISSVVDFYFDYWGQGTTVTGGGSGGGSGGGSGGGSELVLTQ SPKFMSTSVGDRVSVTCKASQNVGTNVAWYQQKPGQSPKPLIYSATY RNSGVPDRFTGSGSGTDFTLTITNVQSKDLADYFCQYNRYPYTSFFF

		TKLEIKRRS
mCAR1 completo - aa	110	QVQLLESGAELVRPGSSVKISCKASGYAFSSYWMNWVKQRPGQGLEW IGQIYPGDGDTNYNGKFKGQATLTADKSSSTAYMQLSGLTSEDSAVY SCARKTISSVVDFYFDYWGQGTTVTGGGSGGGSGGGSGGGSELVLTQ SPKFMSTSVGDRVSVTCKASQNVGTNVAWYQQKPGQSPKPLIYSATY RNSGVPDRFTGSGSGTDFTLTITNVQSKDLADYFCQYNRYPYTSFFF TKLEIKRRSKIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPS KPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPR RPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNEL NLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAY SEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
mCAR2 scFv	111	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLL IYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTL PYTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQ SLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSAL KSRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYW GQGTSVTVSSE
mCAR2 CAR - aa	112	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLL IYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTL PYTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQ SLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSAL KSRLTIIKDNSKSQVFLKMNSLQTDDTAIY YCAKHYYYGGSYAMDYWGQGTSVTVSSESKYGPPCPPCPMFWVLVVV GGVLACYSLLVTVAFIIFWVKRGRKKLLYIFKQPFMRPVQTTQEEDG CSCRFEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYD VLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGER RRGKGHDGLYQGLSTATKDTYDALHMQALPPRL
mCAR2 completo - aa	113	DIQMTQTT SSLSASLGDR VTISCRASQD ISKYLNWYQQ KPDGTVKLLI YHTSRLHSGV PSRFSGSGSG TDYSLTISNL EQEDIATYFC QQGNTLPYTF GGGTKLEITG STSGSGKPGS GEGSTKGEVK LQESGPGLVA PSQSLSVTCT VSGVSLPDYG VSWIRQPPRK GLEWLGVIWG SETTYYNSAL KSRLTIIKDN

		SKSQVFLKMN SLQTDDTAIY YCAKHYYYGG SYAMDYWGQG TSVTVSSESK YGPPCPPCPM FWVLVVVGGV LACYSLLVTV AFIIFWVKRG RKKLLYIFKQ PFMRPVQTTQ EEDGCSCRFE EEEGGCELRV KFSRSADAPA YQQGQNQLYN ELNLGRREEY DVLDKRRGRD PEMGGKPRRK NPQEGLYNEL QKDKMAEAYS EIGMKGERRR GKGHDGLYQG LSTATKDTYD ALHMQALPPR LEGGGEGRGS LLTCGDVEEN PGPRMLLLVT SLLLCELPHP AFLLIPRKVC NGIGIGEFKD SLSINATNIK HFKNCTSISG DLHILPVAFR GDSFTHTPPL DPQELDILKT VKEITGFLLI QAWPENRTDL HAFENLEIIR GRTKQHGQFS LAVVSLNITS LGLRSLKEIS DGDVIISGNK NLCYANTINW KKLFGTSGQK TKIISNRGEN SCKATGQVCH ALCSPEGCWG PEPRDCVSCR NVSRGRECVD KCNLLEGEPR EFVENSECIQ CHPECLPQAM NITCTGRGPD NCIQCAHYID GPHCVKTCPA GVMGENNTLV WKYADAGHVC HLCHPNCTYG CTGPGLEGCP TNGPKIPSIA TGMVGALLLL LVVALGIGLF M
mCAR3 scFv	114	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLL IYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTL PYTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQ SLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSAL KSRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYW GQGTSVTVSS
mCAR3 completo – aa	115	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLL IYHTSRLHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTL PYTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVKLQESGPGLVAPSQ SLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSAL KSRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYW GQGTSVTVSSAAAIEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFP GPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNM TPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLY NELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMA EAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

En ciertas modalidades, el dominio de union a antígeno comprende una HC CDR1, una HC CDR2, y una HC CDR3 de cualquier secuencia de dominio de unión de la cadena pesada listada en la **Tabla 2**. En ciertas modalidades, el dominio de unión a antígeno comprende adicionalmente una LC CDR1, una LC CDR2, y una LC CDR3. En ciertas modalidades, el dominio de unión a antígeno comprende una LC CDR1, una LC CDR2, y una LC CDR3 de cualquiera de las secuenciaas de aminoácidos de domino de unión de la cadena ligera listadas en la **Tabla 2**.

En algunas modalidades, el dominio d eunión a antígeno comprende una, dos o todas las LC CDR1, LC CDR2, y LC CDR3 de las secuencias de dominio de unión de la cadena ligera listadas en la **Tabla 2**, y una, dos o tadas de las HC CDR1, HC CDR2, y HC CDR3 de cualquier secuencia del dominio de unión de la cadena pesada listada en la **Tabla 2**.

En algunas modalidades, las CDRs están definidas de acuerdo con el esquema de numeración de Kabat, el esquema de numeración de Chothia, o una combinación de los mismos.

Las secuencias de las secuencias de las CDR humanizadas de los dominios scFv se muestran en la **Tabla 4** para los dominios variables de la cadena pesada y en la **Tabla 5** para los dominios variables de la cadena ligera. La "ID" aparece para su respective SEQ ID NO para cada CDR.

Table 4. CDRs de domino variable para la cadena pesada (Kabat)

Candidato	FW	HCDR1	ID	HCDR2	ID	HCDR3	ID
CART19 murino		GVSLPDYGVS	19	VIWGSETTYYNSALKS	20	HYYYGGSYAMDY	24
CART19a humanizado	VH4	GVSLPDYGVS	19	VIWGSETTYY***S***S***S***LKS	21	HYYYGGSYAMDY	24
CART19b humanizado	VH4	GVSLPDYGVS	19	VIWGSETTYY***Q***S***S***LKS	22	HYYYGGSYAMDY	24
CART19c humanizado	VH4	GVSLPDYGVS	19	VIWGSETTYYNS***S***LKS	23	HYYYGGSYAMDY	24

Table 5. CDRs de domino variable para la cadena ligera

Candidato	FW	LCDR1	ID	LCDR2	ID	LCDR3	ID
CART19 murino		RASQDISKYLN	25	HTSRLHS	26	QQGNTLPYT	27
CART19a humanizado	VK3	RASQDISKYLN	25	HTSRLHS	26	QQGNTLPYT	27
CART19b humanizado	VK3	RASQDISKYLN	25	HTSRLHS	26	QQGNTLPYT	27
CART19c humanizado	VK3	RASQDISKYLN	25	HTSRLHS	26	QQGNTLPYT	27

Los fragmentos de CAR scFv fueron clonados posteriormente en vectores lentivirales para crear un constructo CAR de longitud completa en un único marco de codificación, y usando el promotor EF1 alfa para la expresión (SEQ ID NO: 100).

Promotor EF1 alfa

CGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGGG
GGGAGGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGAT
GTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCG
CCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGAACACAGGTAAGTGCCGTGTGTGGTTC
CCGCGGGCCTGGCCTCTTTACGGGTTATGGCCCTTGCGTGCCTTGAATTACTTCCACCTGGCTG
CAGTACGTGATTCTTGATCCCGAGCTTCGGGTTGGAAGTGGGTGGGAGAGTTCGAGGCCTTGCG
CTTAAGGAGCCCCTTCGCCTCGTGCTTGAGTTGAGGCCTGGCCTGGGCGCTGGGGCCGCCGCGT
GCGAATCTGGTGGCACCTTCGCGCCTGTCTCGCTGCTTTCGATAAGTCTCTAGCCATTTAAAAT
TTTTGATGACCTGCTGCGACGCTTTTTTTCTGGCAAGATAGTCTTGTAAATGCGGGCCAAGATC
TGCACACTGGTATTTCGGTTTTTGGGGCCGCGGGCGGCGACGGGGCCCGTGCGTCCCAGCGCAC
ATGTTCGGCGAGGCGGGGCCTGCGAGCGCGGCCACCGAGAATCGGACGGGGGTAGTCTCAAGCT
GGCCGGCCTGCTCTGGTGCCTGGCCTCGCGCCGCCGTGTATCGCCCCGCCCTGGGCGGCAAGGC
TGGCCCGGTCGGCACCAGTTGCGTGAGCGGAAAGATGGCCGCTTCCCGGCCCTGCTGCAGGGAG
CTCAAAATGGAGGACGCGGCGCTCGGGAGAGCGGGCGGGTGAGTCACCCACACAAAGGAAAAGG
GCCTTTCCGTCCTCAGCCGTCGCTTCATGTGACTCCACGGAGTACCGGGCGCCGTCCAGGCACC
TCGATTAGTTCTCGAGCTTTTGGAGTACGTCGTCTTTAGGTTGGGGGGAGGGGTTTTATGCGAT
GGAGTTTCCCCACACTGAGTGGGTGGAGACTGAAGTTAGGCCAGCTTGGCACTTGATGTAATTC
TCCTTGGAATTTGCCCTTTTTGAGTTTGGATCTTGGTTCATTCTCAAGCCTCAGACAGTGGTTC
AAAGTTTTTTTCTTCCATTTCAGGTGTCGTGA (SEQ ID NO: 100).

Constructos de CAR22: diseño y función

Se aislaron los fragmentos variables de cadena única anti-CD22 completamente humanos. Los clones anti-CD22 ScFvs fueron clonados en vectores lentivirales de expresión de

CAR con la cadena CD3zeta y la molécula coestimuladora 4-1BB. Los plásmidos que contienen CAR fueron amplificados mediante transformación bacteriana en células STBL3, seguido de Maxiprep usando el kit Qiagen Plasmid Maki libre de endotoxina. El sobrenadante lentiviral fue producido en células 293T usando técnicas estándar.

Las secuencias de los CARs humanos se proporcionan a continuación en la **Tabla 6A y 6B**.

Todos estos clones contenían un cambio de residuo Q/K en el dominio señal del dominio coestimulador derivado de la cadena CD3zeta.

Tabla 6A: Constructos de CD22 CAR Humano

Nombre	SEQ ID	Secuencia
m971 NT	200	gtgcacgagtgggttacatcgaactggatctcaacagcggtaagatc cttgagagttttcgccccgaagaacgttttccaatgatgagcacttt taaagttctgctatgtggcgcggtattatcccgtattgacgccgggc aagagcaactcggtcgccgcatacactattctcagaatgacttggtt gagtactcaccagtcacagaaaagcatcttacggatggcatgacagt aagagaattatgcagtgctgccataaccatgagtgataacactgcgg ccaacttacttctgacaacgatcggaggaccgaaggagctaaccgct tttttgcacaacatgggggatcatgtaactcgccttgatcgttggga accggagctgaatgaagccataccaaacgacgagcgtgacaccacga tgcctgtagcaatggcaacaacgttgcgcaaactattaactggcgaa ctacttactctagcttcccggcaacaattaatagactggatggaggc ggataaagttgcaggaccacttctgcgctcggcccttccggctggct ggtttattgctgataaatctggagccggtgagcgtgggtctcgcggt atcattgcagcactggggccagatggtaagccctcccgtatcgtagt tatctacacgacggggagtcaggcaactatggatgaacgaaatagac agatcgctgagataggtgcctcactgattaagcattggtaactgtca gaccaagtttactcatatatactttagattgatttaaaacttcattt ttaatttaaaaggatctaggtgaagatccttttgataatctcatga ccaaaatcccttaacgtgagttttcgttccactgagcgtcagacccc

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CAR22-9 NT lentivirus completo	255	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggcccgaagtgcagctcgtggaatcgggcggtggac tggtcaagccaggaggttccctgcggctgtcctgcgtggcctccggt ttcacattctccaacgcgtggatgaattgggtgcgccaagcccctgg aaagggacttgaatgggtcggacggatcaagagcaaaaccgacggag gaactgccgattacgccgcacccgtgaagggcagattcaccatttcg cgggatgactcgaagaacaccatgtacctccagatgaactcgctcaa gaccgaggataccggcgtctactactgcatcaccggcgctactgacg tctggggacagggaactaccgtgactgtgtcctccggcggaggcgga agcggaggaggggcagcgggggcgggggatcatcctacgtgctcac tcagccgccttcagcctccggtaccccgggccagcgcgtgaccattt catgctcgggctcctcctcaaacatcgggagcaactacgtgtactgg taccagcagctgcccggtactgcccccaagctgctgatctaccggaa caaccaacgcccgagcggagtgccggacagattctccgggtccaagt ctgggacctccgctagcctggcgatctccggtctgaggagcgaggac gaggcagactactattgtgcggcctgggacgattccctgtcggggcc tgtgtttggaggcggcacgaagttgaccgtgctgaccactaccccag caccgaggccacccaccccggctcctaccatcgcctcccagcctctg tccctgcgtccggaggcatgtagacccgcagctggtggggccgtgca tacccggggtcttgacttcgcctgcgatatctacatttgggcccctc tggctggtacttgcggggtcctgctgctttcactcgtgatcactctt tactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacc cttcatgaggcctgtgcagactactcaagaggaggacggctgttcat gccggttcccagaggaggaggaaggcggctgcgaactgcgcgtgaaa ttcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgc tggacaagcggagaggacgggacccagaaatgggcgggaagccgcgc agaaagaatccccaagagggcctgtacaacgagctccaaaaggataa gatggcagaagcctatagcgagattggtatgaaaggggaacgcagaa gaggcaaaggccacgacggactgtaccagggactcagcaccgccacc aaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
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CAR22-16 NT Completo	297	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggcccgaagtgcaactcgtcgaatctggagcggaag tcaagaagcctggagcaagcgtgaaagtgtcctgtaaagcgtccggt tacaccttcacttcgtattacatgcactgggtccgccaagctccggg acagggactggaatggatgggcatcatcaaccctagcggaggatcga cctcctacgcccaaaagttccagggcagagtgaccatgacccgggac accagcacatcaactgcctacatggagctgtcatcactgaggtccga ggataccgccgtgtactattgcgcccgcgaggccggcgtggtggccg tcgactactggggacagggcactctcgtgaccgtgtcatcgggaggc ggcggttccgggggggggagggtcgggggggcggaggctcccagtccgc actgacgcagccggcttccgtgtctggttcgcccggacagtccatca ccatttcctgcactggaaccagcagcgacgtgggcggttacaactac gtgtcatggtaccagcagcatcccggaaaggccccaaagcttatgat ctacgacgtgtccaatcggccgtcgggcgtcagcaaccggttctccg gctccaagtccgggaacactgccagcctgaccattagcgggctgcag gccgaggacgaagcggattactactgctcctcctacacttcctcctc gacctgggtgtttggtggaggcaccaagttgactgtgctgaccacta ccccagcaccgaggccacccaccccggctcctaccatcgcctcccag cctctgtccctgcgtccggaggcatgtagacccgcagctggtggggc cgtgcatacccggggtcttgacttcgcctgcgatatctacatttggg cccctctggctggtacttgcggggtcctgctgctttcactcgtgatc actctttactgtaagcgcggtcggaagaagctgctgtacatctttaa gcaacccttcatgaggcctgtgcagactactcaagaggaggacggct gttcatgccggttcccagaggaggaggaaggcggctgcgaactgcgc gtgaaattcagccgcagcgcagatgctccagcctacaagcaggggca gaaccagctctacaacgaactcaatcttggtcggagagaggagtacg acgtgctggacaagcggagaggacgggacccagaaatgggcgggaag ccgcgcagaaagaatccccaagagggcctgtacaacgagctccaaaa ggataagatggcagaagcctatagcgagattggtatgaaaggggaac gcagaagaggcaaaggccacgacggactgtaccagggactcagcacc gccaccaaggacacctatgacgctcttcacatgcaggccctgccgcc tcgg
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CAR22-17 scFV NT soluble	300	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggccccaagtgcagttggtccagagcggaggaggag tggtgcaacccggaagatcattgaggctctcatgtgctgcaagcgga ttcaccttctcgagctacgcaatgtcctgggtgcgccaggcccctgg aaagggactggaatgggtgtccgccatctcgggctccggcggatcaa cgtactacgccgactccgtgaagggccgctttactatttcaagagac aactccaagaacactctgtacctccaaatgaactctctgcgggccga ggacaccgccgtgtactactgcgcgaaggagccgctgttcggcgtgg tggaggaagatgtggactactggggccagggcactctcgtcaccgtg tcctccggcggtggaggatcgggaggcggaggcagcgggggtggtgg ctccgacgtcgtgatgacccagtcgcccctgtccctgcccgtgaccc ctggggaaccggcctccatttcctgccggtccagccagtcgctgctg gctggaaacggacacaattaccttgattggtatctgcaaaagcctgg gcagtcaccgcagctgctgatctacctcggaagcaaccgggcgtccg gggtgccggaccggttctccggttccgggagcggcaccgacttcacc ctgaaaatctcgagggtggaggccgaagatgtcggagtgtactattg catgcaggcgcttcagaacccactcactttcgggggcggtactaagc tggaaatcaagcgcggatcgcaccaccatcaccatcatcatcac
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CAR22-19 scFV NT soluble	312	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggccccaagtgcaactcgtccagtccggtgcagaag tcaagaaacccggagcctccgtgaaagtgtcctgcaaggcctccggc tacacgttcacttcatactacatgcactgggtccgccaggcgcccgg acagggactggagtggatgggcatcatcaacccttccggcggctcga cctcctacgcccaaaagttccagggaagagtgacaatgaccagggat acttcaaccagcactgtctacatggaactgtctagcttgcggtccga ggacactgccgtgtactattgcgctcgggacggtttcggggagctgt ccggggcctttgacatctggggccaggggactatggtgaccgtgtcc tcgggcggaggcggcagcggaggaggaggttcgggaggcggaggaag ccagtcagcactgacccagccagcctcggtgtccgggagcccgggcc agagcatcactatttcctgtaccgggacctcctccgacgtgggaggg tacaattacgtgtcatggtatcaacagcatccgggaaaggcgccgaa gctgatgatctacgacgtgtcgaaccgccctagcggagtgtccaacc ggttctccggttcgaagtccgggaacaccgcgagcctgaccattagc ggactccaggccgaggatgaagccgactactactgctcctcctacgc ttcatcgtccaccctggtgttcggtggtggcaccaaggtcaccgtgc ttggatcgcaccaccatcaccatcatcatcac
CAR22-19 scFV AA soluble	313	malpvtalllplalllhaarpqvqlvqsgaevkkpgasvkvsckasg ytftsyymhwvrqapgqglewmgiinpsggstsyaqkfqgrvtmtrd tststvymelsslrsedtavyycardgfgelsgafdiwgqgtmvtvs sggggsggggsggggsqsaltqpasvsgspgqsitisctgtssdvgg ynyvswyqqhpgkapklmiydvsnrpsgvsnrfsgsksgntasltis glqaedeadyycssyassstlvfgggtkvtvlgshhhhhhhh
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CAR22-23 scFV AA soluble	337	malpvtalllplalllhaarpqvqlvqsgaevkkpgasvkvsckasg ytftsyymhwvrqapgqglewmgiinpsggstsyaqkfqgrvtmtrd tststvymelsslrsedtavyycargdyymdvwgkgttvtvssgggg sggggsggggsqsaltqpasasgspgqsvtisctgtssdvggynyvs

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		tggtggggccgtgcatacccggggtcttgacttcgcctgcgatatct acatttgggcccctctggctggtacttgcggggtcctgctgctttca ctcgtgatcactctttactgtaagcgcggtcggaagaagctgctgta catctttaagcaacccttcatgaggcctgtgcagactactcaagagg aggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaa gcaggggcagaaccagctctacaacgaactcaatcttggtcggagag aggagtacgacgtgctggacaagcggagaggacgggacccagaaatg ggcgggaagccgcgcagaaagaatccccaagagggcctgtacaacga gctccaaaaggataagatggcagaagcctatagcgagattggtatga aaggggaacgcagaagaggcaaaggccacgacggactgtaccaggga ctcagcaccgccaccaaggacacctatgacgctcttcacatgcaggc cctgccgcctcgg
CAR22-37 scFv AA	418	qvqlvqsgaevkkpgasvkvsckasgytftsyymhwvrqapgqglew mgiinpsggstsyaqkfqgrvtmtrdtststvymelsslrsedtavy ycarpegvsyydssvldywgqgtlvtvssggggsggggsggggsqsa ltqpasvsgspgqsitisctgtssdvggykhvswyqhhpgkapklmi ydvsnrpsgvsnrfsgsksgntasltvsglqaedeahyycvsyrnfn slvfgtgtkvtvl
CAR22-37 scFv NT	117	caagtccaactcgtccagtccggtgcagaagtcaagaaacccggagc ttccgtgaaagtgtcctgcaaggcctcggggtataccttcacttcct actacatgcactgggtccggcaggcgccgggacagggactggaatgg atgggtatcatcaacccctcgggcggttccactagctacgcccagaa gttccagggaagagtgaccatgacccgggacacttccacttcgaccg tgtacatggaactgagcagcctgaggagcgaggacaccgccgtgtac tactgtgcccggcccgagggagtgtcctactacgattcctccgtgct ggattactggggacagggaacacttgtgaccgtgtcctcgggaggag gcggaagcgggggcggagggtctgggggaggcggctcccagtccgct ctgacgcagcctgcgtccgtgtccgggagccctggccagagcattac tatttcatgcaccggtaccagctccgacgtgggcggatataagcacg tgtcatggtaccagcatcacccgggaaaggccccaaagctgatgatc tacgacgtgtcgaacagaccgagcggggtgtcaaatcgcttttccgg ttcaaagtcgggcaacactgcctcactcaccgtgtcgggcctccaag cggaggacgaagcccactactactgcgtgtcctaccgcaacttcaac tccttggtgttcggcaccggcaccaaggtcaccgtcctg
CAR22-37 scFv NT soluble	419	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggccccaagtccaactcgtccagtccggtgcagaag tcaagaaacccggagcttccgtgaaagtgtcctgcaaggcctcgggg tataccttcacttcctactacatgcactgggtccggcaggcgccggg acagggactggaatggatgggtatcatcaacccctcgggcggttcca ctagctacgcccagaagttccagggaagagtgaccatgacccgggac acttccacttcgaccgtgtacatggaactgagcagcctgaggagcga ggacaccgccgtgtactactgtgcccggcccgagggagtgtcctact acgattcctccgtgctggattactggggacagggaacacttgtgacc gtgtcctcgggaggaggcggaagcgggggcggagggtctgggggagg cggctcccagtccgctctgacgcagcctgcgtccgtgtccgggagcc ctggccagagcattactatttcatgcaccggtaccagctccgacgtg ggcggatataagcacgtgtcatggtaccagcatcacccgggaaaggc

		cccaaagctgatgatctacgacgtgtcgaacagaccgagcggggtgt caaatcgcttttccggttcaaagtcgggcaacactgcctcactcacc gtgtcgggcctccaagcggaggacgaagcccactactactgcgtgtc ctaccgcaacttcaactccttggtgttcggcaccggcaccaaggtca ccgtcctgggatcgcaccaccatcaccatcatcatcac
CAR22-37 scFv AA soluble	420	Malpvtalllplalllhaarpqvqlvqsgaevkkpgasvkvsckasg ytftsyymhwvrqapgqglewmgiinpsggstsyaqkfqgrvtmtrd tststvymelsslrsedtavyycarpegvsyydssvldywgqgtlvt vssggggsggggsggggsqsaltqpasvsgspgqsitisctgtssdv ggykhvswyqhhpgkapklmiydvsnrpsgvsnrfsgsksgntaslt vsglqaedeahyycvsyrnfnslvfgtgtkvtvlgshhhhhhhh
CAR22-37 completo AA	421	malpvtalllplalllhaarpqvqlvqsgaevkkpgasvkvsckasg ytftsyymhwvrqapgqglewmgiinpsggstsyaqkfqgrvtmtrd tststvymelsslrsedtavyycarpegvsyydssvldywgqgtlvt vssggggsggggsggggsqsaltqpasvsgspgqsitisctgtssdv ggykhvswyqhhpgkapklmiydvsnrpsgvsnrfsgsksgntaslt vsglqaedeahyycvsyrnfnslvfgtgtkvtvltttpaprpptpap tiasqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvll lslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeg gcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdp emggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdgly qglstatkdtydalhmqalppr
CAR22-37 completo NT	422	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggccccaagtccaactcgtccagtccggtgcagaag tcaagaaacccggagcttccgtgaaagtgtcctgcaaggcctcgggg tataccttcacttcctactacatgcactgggtccggcaggcgccggg acagggactggaatggatgggtatcatcaacccctcgggcggttcca ctagctacgcccagaagttccagggaagagtgaccatgacccgggac acttccacttcgaccgtgtacatggaactgagcagcctgaggagcga ggacaccgccgtgtactactgtgcccggcccgagggagtgtcctact acgattcctccgtgctggattactggggacagggaacacttgtgacc gtgtcctcgggaggaggcggaagcgggggcggagggtctgggggagg cggctcccagtccgctctgacgcagcctgcgtccgtgtccgggagcc ctggccagagcattactatttcatgcaccggtaccagctccgacgtg ggcggatataagcacgtgtcatggtaccagcatcacccgggaaaggc cccaaagctgatgatctacgacgtgtcgaacagaccgagcggggtgt caaatcgcttttccggttcaaagtcgggcaacactgcctcactcacc gtgtcgggcctccaagcggaggacgaagcccactactactgcgtgtc ctaccgcaacttcaactccttggtgttcggcaccggcaccaaggtca ccgtcctgaccactaccccagcaccgaggccacccaccccggctcct accatcgcctcccagcctctgtccctgcgtccggaggcatgtagacc cgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcg atatctacatttgggcccctctggctggtacttgcggggtcctgctg ctttcactcgtgatcactctttactgtaagcgcggtcggaagaagct gctgtacatctttaagcaacccttcatgaggcctgtgcagactactc aagaggaggacggctgttcatgccggttcccagaggaggaggaaggc ggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagc ctacaagcaggggcagaaccagctctacaacgaactcaatcttggtc

		ggagagaggagtacgacgtgctggacaagcggagaggacgggaccca gaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgta caacgagctccaaaaggataagatggcagaagcctatagcgagattg gtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtac cagggactcagcaccgccaccaaggacacctatgacgctcttcacat gcaggccctgccgcctcgg
CAR22-38 scFv AA	423	qvqlvqsgaevkkpgasvkvsckasgytftsyymhwvrqapgqglew mgiinpsggstsyaqkfqgrvtmtrdtststvymelsslraedtavy ycarggygdyldafdiwgqgttvtvssggggsggggsgsggsqsalt qpasvsgspgqsitisctgtssdvggynyvswyqqhpgkapklmiye vsnrpsgvsnrfsgsksgntasltisglqaedeadyycssytssstl vfgtgtqltvl
CAR22-38 scFv NT	424	caagtccaactcgtccaatccggtgcagaagtcaagaaacctggagc atccgtgaaagtgtcctgcaaggcgtccgggtatacgttcacctcct actacatgcactgggtgcgccaggccccgggacagggactggaatgg atgggaatcatcaatcctagcggcggcagcaccagctacgcccagaa gtttcagggccgcgtgaccatgaccagggacactagcacctccaccg tgtacatggaattgtccagcctgagagccgaggatactgctgtgtac tactgcgcccggggcggatacggagattatctggacgccttcgacat ttggggacagggcactactgtgaccgtgtcctcgggggggaggcggct cgggggggcggcggatcaggatcaggcggttcccagtccgcgctgaca cagcccgcttccgtgagcggttcgcccgggcagtccatcaccatttc gtgtaccggaacttcctccgacgtcggtggctacaactacgtgtcgt ggtaccagcaacatccgggaaaggccccaaagctcatgatctacgag gtgtccaaccggccgtccggggtgtcaaaccggttcagcggctcaaa gagcggaaacaccgcctccctcaccatctcgggactgcaggccgagg atgaagcggactactactgctcgagctacacttcctcatctaccctg gtgttcgggactggtacccagcttaccgtgctg
CAR22-38 scFv NT soluble	425	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggccccaagtccaactcgtccaatccggtgcagaag tcaagaaacctggagcatccgtgaaagtgtcctgcaaggcgtccggg tatacgttcacctcctactacatgcactgggtgcgccaggccccggg acagggactggaatggatgggaatcatcaatcctagcggcggcagca ccagctacgcccagaagtttcagggccgcgtgaccatgaccagggac actagcacctccaccgtgtacatggaattgtccagcctgagagccga ggatactgctgtgtactactgcgcccggggcggatacggagattatc tggacgccttcgacatttggggacagggcactactgtgaccgtgtcc tcgggggggaggcggctcgggggggcggcggatcaggatcaggcggttc ccagtccgcgctgacacagcccgcttccgtgagcggttcgcccgggc agtccatcaccatttcgtgtaccggaacttcctccgacgtcggtggc tacaactacgtgtcgtggtaccagcaacatccgggaaaggccccaaa gctcatgatctacgaggtgtccaaccggccgtccggggtgtcaaacc ggttcagcggctcaaagagcggaaacaccgcctccctcaccatctcg ggactgcaggccgaggatgaagcggactactactgctcgagctacac ttcctcatctaccctggtgttcgggactggtacccagcttaccgtgc tgggatcgcaccaccatcaccatcatcatcac
CAR22-38 scFv AA	426	malpvtalllplalllhaarpqvqlvqsgaevkkpgasvkvsckasg ytftsyymhwvrqapgqglewmgiinpsggstsyaqkfqgrvtmtrd

soluble		tststvymelsslraedtavyycarggygdyldafdiwgqgttvtvs sggggsggggsgsggsqsaltqpasvsgspgqsitisctgtssdvgg ynyvswyqqhpgkapklmiyevsnrpsgvsnrfsgsksgntasltis glqaedeadyycssytssstlvfgtgtqltvlgshhhhhhhh
CAR22-38 completo AA	427	malpvtalllplalllhaarpqvqlvqsgaevkkpgasvkvsckasg ytftsyymhwvrqapgqglewmgiinpsggstsyaqkfqgrvtmtrd tststvymelsslraedtavyycarggygdyldafdiwgqgttvtvs sggggsggggsgsggsqsaltqpasvsgspgqsitisctgtssdvgg ynyvswyqqhpgkapklmiyevsnrpsgvsnrfsgsksgntasltis glqaedeadyycssytssstlvfgtgtqltvlttttpaprpptpapti asqplslrpeacrpaaggavhtrgldfacdiyiwaplagtcgvllls lvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeggc elrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpem ggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqg lstatkdtydalhmqalppr
CAR22-38 completo NT	428	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggccccaagtccaactcgtccaatccggtgcagaag tcaagaaacctggagcatccgtgaaagtgtcctgcaaggcgtccggg tatacgttcacctcctactacatgcactgggtgcgccaggccccggg acagggactggaatggatgggaatcatcaatcctagcggcggcagca ccagctacgcccagaagtttcagggccgcgtgaccatgaccagggac actagcacctccaccgtgtacatggaattgtccagcctgagagccga ggatactgctgtgtactactgcgcccggggcggatacggagattatc tggacgccttcgacatttggggacagggcactactgtgaccgtgtcc tcgggggaggcggctcgggggcggcggatcaggatcaggcggttc ccagtccgcgctgacacagcccgcttccgtgagcggttcgcccgggc agtccatcaccatttcgtgtaccggaacttcctccgacgtcggtggc tacaactacgtgtcgtggtaccagcaacatccgggaaaggccccaaa gctcatgatctacgaggtgtccaaccggccgtccggggtgtcaaacc ggttcagcggctcaaagagcggaaacaccgcctccctcaccatctcg ggactgcaggccgaggatgaagcggactactactgctcgagctacac ttcctcatctaccctggtgttcgggactggtacccagcttaccgtgc tgaccactaccccagcaccgaggccacccaccccggctcctaccatc gcctcccagcctctgtccctgcgtccggaggcatgtagacccgcagc tggtggggccgtgcatacccggggtcttgacttcgcctgcgatatct acatttgggcccctctggctggtacttgcggggtcctgctgctttca ctcgtgatcactctttactgtaagcgcggtcggaagaagctgctgta catctttaagcaacccttcatgaggcctgtgcagactactcaagagg aggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaa gcaggggcagaaccagctctacaacgaactcaatcttggtcggagag aggagtacgacgtgctggacaagcggagaggacgggacccagaaatg ggcgggaagccgcgcagaaagaatccccaagagggcctgtacaacga gctccaaaaggataagatggcagaagcctatagcgagattggtatga aaggggaacgcagaagaggcaaaggccacgacggactgtaccaggga ctcagcaccgccaccaaggacacctatgacgctcttcacatgcaggc cctgccgcctcgg

Se generaron algunas secuencias adicionales de scFv de CD22 y se describen en la **Tabla 6B**, a continuación. Los clones CD22-46 y CD22-65 se lograron a partir de la maduración de la afinidad del clon CD22-12 anterior. En alguna smodalidades, la afinidad de un dominio d eunión a CD22 con afinidad madurada es mayor que aquella que de CD22-12 por CD22. En algunas modalidades, la tasa de aumento de un dominio de unión con afinidad madurada por CD22 es más rápida que aquella de CD22-12 para CD22.

Tabla 6B: Secuencias de scFv de CD22 humano

Nombre	SEQ ID	Secuencia
CAR22-53 scFv dominio AA	131	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWYSDYAVS VKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARDPYDFWSGYPDAFDIWGQGTMVTVSSGGGGS GGGGSGGGGSQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKVIISEVNNR PSGVSHRFSGSKSGNTASLTISGLQAEDEADYFCSSYTSGRTLYVFGTGSKVTVLG
CAR22-53 scFv NT	1108	GAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCCTCTCACTCACCTGT GCCATCTCCGGGGACAGTGTCTCTAGCAACAGTGCTGCTTGGAACTGGATCAGGCAGTCCCCATCG AGAGGCCTTGAGTGGCTGGGAAGGACATACTACAGGTCCAAGTGGTATAGTGATTATGCAGTATCT GTGAAAAGTCGAATAACCATCAACCCAGACACATCCAAGAACCAGTTCTCCCTGCAGCTGAACTCT GTGACTCCCGAGGACACGGCTGTGTATTACTGTGCAAGAGATCCTTACGATTTTTGGAGTGGTTAT CCTGATGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGGTGGTGGTGGCAGC GGCGGCGGCGGCTCTGGTGGTGGTGGATCCCAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGG TCTCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTACAACTAT GTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAGGTCATAATTTCTGAGGTCAATAATCGG CCCTCAGGGGTTTCTCATCGCTTCTCTGGGTCCAAGTCTGGCAACACGGCCTCCCTGACCATCTCT GGGCTCCAGGCTGAGGACGAGGCTGATTATTTCTGCAGCTCATATACAAGTGGCAGGACTCTTTAT GTCTTCGGAACTGGGAGCAAGGTCACCGTCCTAGGT
CAR22-53 completo AA	1109	MALPVTALLLPLALLLHAARPEVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSR GLEWLGRTYYRSKWYSDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARDPYDFWSGYP DAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYV SWYQQHPGKAPKVIISEVNNRPSGVSHRFSGSKSGNTASLTISGLQAEDEADYFCSSYTSGRTLYV FGTGSKVTVLGTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGT CGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADA PAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
CAR22-53 completo NT (CD22-53 scFv + humanoCD8 alfa + 41-BB + CD3zeta)	1110	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCCCGAG GTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCCTCTCACTCACCTGTGCC ATCTCCGGGGACAGTGTCTCTAGCAACAGTGCTGCTTGGAACTGGATCAGGCAGTCCCCATCGAGA GGCCTTGAGTGGCTGGGAAGGACATACTACAGGTCCAAGTGGTATAGTGATTATGCAGTATCTGTG AAAAGTCGAATAACCATCAACCCAGACACATCCAAGAACCAGTTCTCCCTGCAGCTGAACTCTGTG ACTCCCGAGGACACGGCTGTGTATTACTGTGCAAGAGATCCTTACGATTTTTGGAGTGGTTATCCT GATGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGGTGGTGGTGGCAGCGGC GGCGGCGGCTCTGGTGGTGGTGGATCCCAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCT CCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTACAACTATGTC TCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAGGTCATAATTTCTGAGGTCAATAATCGGCCC TCAGGGGTTTCTCATCGCTTCTCTGGGTCCAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGG CTCCAGGCTGAGGACGAGGCTGATTATTTCTGCAGCTCATATACAAGTGGCAGGACTCTTTATGTC TTCGGAACTGGGAGCAAGGTCACCGTCCTAGGTACCACTACCCCAGCACCGAGGCCACCCACCCCG GCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAGGCATGTAGACCCGCAGCTGGTGGG GCCGTGCATACCCGGGGTCTTGACTTCGCCTGCGATATCTACATTTGGGCCCCTCTGGCTGGTACT TGCGGGGTCCTGCTGCTTTCACTCGTGATCACTCTTTACTGTAAGCGCGGTCGGAAGAAGCTGCTG TACATCTTTAAGCAACCCTTCATGAGGCCTGTGCAGACTACTCAAGAGGAGGACGGCTGTTCATGC CGGTTCCCAGAGGAGGAGGAAGGCGGCTGCGAACTGCGCGTGAAATTCAGCCGCAGCGCAGATGCT CCAGCCTACAAGCAGGGGCAGAACCAGCTCTACAACGAACTCAATCTTGGTCGGAGAGAGGAGTAC

		GACGTGCTGGACAAGCGGAGAGGACGGGACCCAGAAATGGGCGGGAAGCCGCGCAGAAAGAATCCC CAAGAGGGCCTGTACAACGAGCTCCAAAAGGATAAGATGGCAGAAGCCTATAGCGAGATTGGTATG AAAGGGGAACGCAGAAGAGGCAAAGGCCACGACGGACTGTACCAGGGACTCAGCACCGCCACCAAG GACACCTATGACGCTCTTCACATGCAGGCCCTGCCGCCTCGG
CAR 22-57	132	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSNNNAAWNWIRQSPSRGLEWLGRTYHRSTWYNDYVGS VKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARETDYGDYGAFDIWGQGTTVTVSSGGGGSGGG GSGGGGSQSALTQPASVSGSPGQSITISCTGSRNDIGAYESVSWYQQHPGNAPKLIIHGVNNRPSG VFDRFSVSQSGNTASLTISGLQAEDEADYYCSSHTTTSTLYVFGTGTKVTVLG
CAR22-58	133	EVQLQQSGPGLVNPSQTLSITCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRTFYRSKWYNDYAVS VKGRITISPDTSKNQFSLQLNSVTPEDTAVYYCAGGDYYYGLDVWGQGTTVTVSSGGGGSGGGGSG GGGSQSALTQPASVSGSPGQSITISCTGSSSDVGGYNSVSWYQQHPGKAPKLMIYEVINRPSGVSH RFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTYVFGTGTKVTVLG
CAR22-59	134	EVQLQQSGPGLVKPSQTLSLTCAISGDSVLSNSDTWNWIRQSPSRGLEWLGRTYHRSTWYDDYASS VRGRVSINVDTSKNQYSLQLNAVTPEDTGVYYCARDRLQDGNSWSDAFDVWGQGTMVTVSSGGGGS GGGGSGGGGSQSALTQPASVSGSPGQSITISCTGSSSDIGGFNYVSWYQQHAGEAPKLMIYEVTNR PSGVSDRFSGSKSDNTASLTISGLQAEDEADYYCSSYASGSPLYVFGTGTKVTVLG
CAR22-60	135	EVQLQQSGPGLVKPSQTLSLTCAISGDSVLSNSDTWNWIRQSPSRGLEWLGRTYHRSTWYDDYASS VRGRVSINVDTSKNQYSLQLNAVTPEDTGVYYCARDRLQDGNSWSDAFDVWGQGTMVTVSSGGGGS GGGGSGSGGGSQSALTQPASVSGSPGQSITFSCTGTSSDIGGYNYVSWYQQHPGKAPKLMIYEVSNR PSGVSNRFSGTKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTKLTVLG
CAR22-61	136	QVQLQESGPGLVKPSQTLSLTCAISGDSVLSNSDTWNWIRQSPSRGLEWLGRTYHRSTWYDDYASS VRGRVSINVDTSKNQYSLQLNAVTPEDTGVYYCARDRLQDGNSWSDAFDVWGQGTMVTVSSGGGGS GGGGSGSGGGSQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSNR PSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTKVTVLG
CAR22-62	137	EVQLQQSGPGLVKPSQTLSLTCAISGDSVLSNSDTWNWIRQSPSRGLEWLGRTYHRSTWYDDYASS VRGRVSINVDTSKNQYSLQLNAVTPEDTGVYYCARDRLQDGNSWSDAFDVWGQGTMVTVSSGGGGS GGGGSGGGGSQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNR PSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTKVTVLG
CAR22-63	138	EVQLQQSGPGLVKPSQTLSLTCAISGDSVLSNSDTWNWIRQSPSRGLEWLGRTYHRSTWYDDYASS VRGRVSINVDTSKNQYSLQLNAVTPEDTGVYYCARDRLQDGNSWSDAFDVWGQGTMVTVSSGGGGS GGGGSGGGGSQSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSNR PSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYIFGTGTKVTVLG
CAR22-64	139	EVQLQQSGPGLVKPSQTLPLTCAISGDSVLSNSDTWNWIRQSPSRGLEWLGRTYHRSTWYDDYASS VRGRVSINVDTSKNQYSLQLNAVTPEDTGVYYCARVRLQDGNSWSDAFDVWGQGTMVTVSSGGGGS GGGGSGGGGPQSALTQPASASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNR PSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTQLTVL
CAR22-65	140	EVQLQQSGPGLVKPSQTLSLTCAISGDSMLSNSDTWNWIRQSPSRGLEWLGRTYHRSTWYDDYASS VRGRVSINVDTSKNQYSLQLNAVTPEDTGVYYCARVRLQDGNSWSDAFDVWGQGTMVTVSSGGGGS GGGGSGGGGSQSALTQPASASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNR PSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTQLTVL

En algunas modalidades, el dominio de unión a antígeno comprende una HC CDR1, una HC CDR2, y una HC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada listadas en la **Tabla 6A o 6B**. En modalidades, el dominio de unión al antígeno comprende adicionalmente una LC CDR1, una LC CDR2, y una LC CDR3. En modalidades, el dominio de union a antígeno comprende una LC CDR1, una LC CDR2, y una LC

CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera listadas en la **Tabla 6A o 6B**.

En algunas modalidades, el dominio de unión a antígeno cmoprende una, dos o todas de las LC CDR1, LC CDR2, y LC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera listadas en la **Tabla 6A o 6B** y una, dos o todas de las HC CDR1, HC CDR2, y HC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada listadas en la **Tabla 6A o 6B**.

En algunas modalidades, las CDRs están definidas de acuerdo con el esquema de numeración de Kabat, el esquema de numeración de Chothia, o una combinación de los mismos.

CD22-64 y CD22-65 se basaron en la maduración de afinidad del clon CD22-12. Las tres construcciones fueron probados y se encontró que la actividad (véase el ejemplo 25 en este documento). Basándose en estas observaciones, un género estructural fue diseñado para abarcar los ejemplos de trabajo. Por lo tanto, en algunas realizaciones, un dominio de unión a CD22 descrito en este documento comprende un HCDR3 tiene una secuencia: XRLQDGNSWSDAFDV (SEQ ID NO: 141). En algunas realizaciones, X es cualquier aminoácido, cualquier aminoácido canónica, un aminoácido no polar (por ejemplo, G, A, V, L, I, P, M, F, o W), un aminoácido no polar y sin un anillo aromático (por ejemplo, G, A, V, L, I, P, o M), o un aminoácido ácido (por ejemplo, D o E).

Las secuencias de las secuencias de las CDR humanas de los dominios de scFv se muestran en la **Tabla 7A, 7B o 7C** para los dominios variables de la cadena pesada y en la **Tabla 8A o 8B** para los dominios variables de la cadena ligera. Las "ID" aparecen para su respectivo SEQ ID NO para cada CDR.

Tabla 7A. CDRs de domino variable de la cadena pesada para CARs CD22. Las CDRs están definidas de acuerdo a la definición de "combinada".

Candidato	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:
m971	GDSVSSNSAAWN	142	RTYYRSKWYNDYAVSVKS	181	EVTGDLEDAFDI	449
CAR22-1	GFTVSSNYMS	143	VIYSGGSTYYADSVKG	182	QSTPYDSSGYYSGDAFDI	450

CAR22-2	GDSVSSNSAAWN	144	RTYYRSKWYNDYAVSVKS	183	DLGWIAVAGTFDY	451
CAR22-3	GDSVLSNSDTWN	145	RTYHRSTWYDDYASSVRG	184	DRLQDGNSWSDAFDV	452
CAR22-4	GFTFDDYAMH	146	GISWNSGSIGYADSVKG	185	GLSSWHFHDALDI	453
CAR22-5	GFTFDDYAMH	147	GISWNSGSIGYADSVKG	186	DKGGGYYDFWSGSDY	454
CAR22-6	GDSVSSNSATWT	148	RTYYRSTWYNDYAVSVKS	187	EGSGSYYAY	455
CAR22-7	GYTFTGYYMH	149	WINPNSGGTNYAQKFQG	188	DYWGYYGSGTLDY	456
CAR22-8	GYTFTSYGIS	150	WISAYNGNTNYAQKLQG	189	AGLALYSNYVPYYYYGMDV	457
CAR22-9	GFTFSNAWMN	151	RIKSKTDGGTADYAAPVKG	190	GATDV	458
CAR22-10	GDSVLSNSDTWN	152	RTYHRSTWYDDYASSVRG	191	DRLQDGNSWSDAFDV	459
CAR22-11	GDSVSSNSAAWN	153	RTYYRSKWYNDYAVSVKS	192	EESSSGWYEGNWFDP	460
CAR22-12	GDSVLSNSDTWN	154	RTYHRSTWYDDYASSVRG	193	DRLQDGNSWSDAFDV	461
CAR22-13	GGSISSSSYYWG	155	SIYYSGSTYYNPSLKS	194	GRMDTAMAQI	462
CAR22-14	GYTFTSYYMH	156	IINPSGGSTSYAQKFQG	195	DLDVSLDI	463
CAR22-15	GFTFSSYAMH	157	AISSNGGSTYYANSVKD	196	VHSSGYYHPGPNDY	464
CAR22-16	GYTFTSYYMH	158	IINPSGGSTSYAQKFQG	197	EAGVVAVDY	465
CAR22-17	GFTFSSYAMS	159	AISGSGGSTYYADSVKG	198	EPLFGVVEEDVDY	466
CAR22-18	GYTFTSYYMH	160	IINPSGGSTSYAQKFQG	199	GSGSLGDAFDI	467
CAR22-19	GYTFTSYYMH	161	IINPSGGSTSYAQKFQG	429	DGFGELSGAFDI	468
CAR22-20	GYTFTSYYMH	162	IINPSGGSTSYAQKFQG	430	GPIGCSGGSCLDY	469
CAR22-21	GYTFTSYYMH	163	IINPSGGSTSYAQKFQG	431	GSYGDYGDAFDI	470
CAR22-22	GGTFSSYAIS	164	GIIPIFGTANYAQKFQG	432	DHKVVRFGY	471
CAR22-23	GYTFTSYYMH	165	IINPSGGSTSYAQKFQG	433	GDYYMDV	472
CAR22-24	GFTFSSYAMS	166	YISSSSSTIYYADSVKG	434	DGPIRYFDHSKAFDI	473
CAR22-25	GYTFTSYYMH	167	IINPSGGSTSYAQKFQG	435	EMDDSSGPDY	474
CAR22-26	GYSFTGSWIG	168	IIYPGDSDTRYSPSFQG	436	GFLRGGDCCGALDI	475
CAR22-27	GGSINSYYWS	169	FTSHSGNVKYNPSLTG	437	GLDPLFAYDAFEI	476

CAR22-28	GFTFSDYYMS	170	YISSSGSTIYYADSVKG	438	DDFWSGSVDY	477
CAR22-29	GYTFTSYYMH	171	IINPSGGSTSYAQKFQG	439	EDDSSGYTSPFDY	478
CAR22-30	GYTFTGYYMH	172	WINPNSGGTNYAQKFQG	440	EPASSSWYGYYYYMDV	479
CAR22-31	GYTFTSYDIN	173	WMNPNSGNTGYAQKFQG	441	GDSNYWSYYGMDV	480
CAR22-32	GYTFTSYGIS	174	WISAYNGNTNYAQKLQG	442	FSSSDSYDY	481
CAR22-33	GFSLNTFGMSVS	175	LIDWDDDKYYSTSLRT	443	IYGGDRTNTQAPYFFDL	482
CAR22-34	GASITSRHWWN	176	QIYHSGTTTYNPSLGS	444	DYLELATYYGMDV	483
CAR22-35	GYTFTSYYMH	177	IINPSGGSTSYAQKFQG	445	DLAAAGNYYYYGMDV	484
CAR22-36	GYTFTSYYMH	178	IINPSGGSTSYAQKFQG	446	DDDFWSGSGAFDI	485
CAR22-37	GYTFTSYYMH	179	IINPSGGSTSYAQKFQG	447	PEGVSYYDSSVLDY	486
CAR22-38	GYTFTSYYMH	180	IINPSGGSTSYAQKFQG	448	GGYGDYLDAFDI	487

Tabla 7B: CDRs de domino variable de la cadena pesada para CARs CD22

Candidato	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:
CAR22-53 Kabat	SNSAAWN	488	RTYYRSKWYSDYAVSVKS	499	DPYDFWSGYPDAFDI	510
CAR22-53 Chothia	GDSVSSNSA	489	YYRSKWY	500	DPYDFWSGYPDAFDI	511
CAR22-53 Combinado Kabat/Chothia	GDSVSSNSAAWN	1111	RTYYRSKWYSDYAVSVKS	1113	DPYDFWSGYPDAFDI	1115
CAR22-53 IMGT	GDSVSSNSAA	1112	TYYRSKWYS	1114	ARDPYDFWSGYPDAFDI	1116
CAR22-57 Combinado	GDSVSNNNAAWN	490	RTYHRSTWYNDYVGSVKS	501	ETDYGDYGAFDI	512
CAR22-57 Kabat	NNNAAWN		RTYHRSTWYNDYVGSVKS		ETDYGDYGAFDI	
CAR22-58	GDSVSSNSAAWN	491	RTFYRSKWYNDYAVSVKG	502	GDYYYGLDV	513

Combinado						
CAR22-58 Kabat	SNSAAWN		RTFYRSKWYNDYAVSVKG		GDYYYGLDV	
CAR22-59 Combinado	GDSVLSNSDTWN	492	RTYHRSTWYDDYASSVRG	503	DRLQDGNSWSDAFDV	514
CAR22-59 Kabat	SNSDTWN		RTYHRSTWYDDYASSVRG		DRLQDGNSWSDAFDV	
CAR22-60 Combinado	GDSVLSNSDTWN	493	RTYHRSTWYDDYASSVRG	504	DRLQDGNSWSDAFDV	515
CAR22-60 Kabat	SNSDTWN		RTYHRSTWYDDYASSVRG		DRLQDGNSWSDAFDV	
CAR22-61 Combinado	GDSVLSNSDTWN	494	RTYHRSTWYDDYASSVRG	505	DRLQDGNSWSDAFDV	516
CAR22-61 Kabat	SNSDTWN		RTYHRSTWYDDYASSVRG		DRLQDGNSWSDAFDV	
CAR22-62 Combinado	GDSVLSNSDTWN	495	RTYHRSTWYDDYASSVRG	506	DRLQDGNSWSDAFDV	517
CAR22-62 Kabat	SNSDTWN		RTYHRSTWYDDYASSVRG		DRLQDGNSWSDAFDV	
CAR22-63 Combinado	GDSVLSNSDTWN	496	RTYHRSTWYDDYASSVRG	507	DRLQDGNSWSDAFDV	518
CAR22-63 Kabat	SNSDTWN		RTYHRSTWYDDYASSVRG		DRLQDGNSWSDAFDV	
CAR22-64 Combinado	GDSVLSNSDTWN	497	RTYHRSTWYDDYASSVRG	508	VRLQDGNSWSDAFDV	519
CAR22-64 Kabat	SNSDTWN		RTYHRSTWYDDYASSVRG		VRLQDGNSWSDAFDV	
CAR22-65 Combinado	GDSMLSNSDTWN	498	RTYHRSTWYDDYASSVRG	509	VRLQDGNSWSDAFDV	520
CAR22-65 Kabat	SNSDTWN		RTYHRSTWYDDYASSVRG		VRLQDGNSWSDAFDV	

Tabla 7C. CDRs de dominio variable d ela cadena pesada de CARs de CD22. Las CDRs

se identifican de acuerdo con Kabat.

Candidato	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:
m971	SNSAAWN		RTYYRSKWYNDYAVSVKS		EVTGDLEDAFDI	
CAR22-1	SNYMS		VIYSGGSTYYADSVKG		QSTPYDSSGYYSGDAFDI	
CAR22-2	SNSAAWN		RTYYRSKWYNDYAVSVKS		DLGWIAVAGTFDY	
CAR22-3	SNSDTWN		RTYHRSTWYDDYASSVRG		DRLQDGNSWSDAFDV	
CAR22-4	DYAMH		GISWNSGSIGYADSVKG		GLSSWHFHDALDI	
CAR22-5	DYAMH		GISWNSGSIGYADSVKG		DKGGGYYDFWSGSDY	
CAR22-6	SNSATWT		RTYYRSTWYNDYAVSVKS		EGSGSYYAY	
CAR22-7	GYYMH		WINPNSGGTNYAQKFQG		DYWGYYGSGTLDY	
CAR22-8	SYGIS		WISAYNGNTNYAQKLQG		AGLALYSNYVPYYYYGMDV	
CAR22-9	NAWMN		RIKSKTDGGTADYAAPVKG		GATDV	
CAR22-10	SNSDTWN		RTYHRSTWYDDYASSVRG		DRLQDGNSWSDAFDV	
CAR22-11	SNSAAWN		RTYYRSKWYNDYAVSVKS		EESSSGWYEGNWFDP	
CAR22-12	SNSDTWN		RTYHRSTWYDDYASSVRG		DRLQDGNSWSDAFDV	
CAR22-13	SSSYYWG		SIYYSGSTYYNPSLKS		GRMDTAMAQI	
CAR22-14	SYYMH		IINPSGGSTSYAQKFQG		DLDVSLDI	
CAR22-15	SYAMH		AISSNGGSTYYANSVKD		VHSSGYYHPGPNDY	
CAR22-16	SYYMH		IINPSGGSTSYAQKFQG		EAGVVAVDY	
CAR22-17	SYAMS		AISGSGGSTYYADSVKG		EPLFGVVEEDVDY	
CAR22-18	SYYMH		IINPSGGSTSYAQKFQG		GSGSLGDAFDI	
CAR22-19	SYYMH		IINPSGGSTSYAQKFQG		DGFGELSGAFDI	
CAR22-20	SYYMH		IINPSGGSTSYAQKFQG		GPIGCSGGSCLDY	
CAR22-21	SYYMH		IINPSGGSTSYAQKFQG		GSYGDYGDAFDI	

CAR22-22	SYAIS		GIIPIFGTANYAQKFQG		DHKVVRFGY	
CAR22-23	SYYMH		IINPSGGSTSYAQKFQG		GDYYMDV	
CAR22-24	SYAMS		YISSSSSTIYYADSVKG		DGPIRYFDHSKAFDI	
CAR22-25	SYYMH		IINPSGGSTSYAQKFQG		EMDDSSGPDY	
CAR22-26	GSWIG		IIYPGDSDTRYSPSFQG		GFLRGGDCCGALDI	
CAR22-27	SYYWS		FTSHSGNVKYNPSLTG		GLDPLFAYDAFEI	
CAR22-28	DYYMS		YISSSGSTIYYADSVKG		DDFWSGSVDY	
CAR22-29	SYYMH		IINPSGGSTSYAQKFQG		EDDSSGYTSPFDY	
CAR22-30	GYYMH		WINPNSGGTNYAQKFQG		EPASSSWYGYYYYMDV	
CAR22-31	SYDIN		WMNPNSGNTGYAQKFQG		GDSNYWSYYGMDV	
CAR22-32	SYGIS		WISAYNGNTNYAQKLQG		FSSSDSYDY	
CAR22-33	TFGMSVS		LIDWDDDKYYSTSLRT		IYGGDRTNTQAPYFFDL	
CAR22-34	TSRHWWN		QIYHSGTTTYNPSLGS		DYLELATYYGMDV	
CAR22-35	SYYMH		IINPSGGSTSYAQKFQG		DLAAAGNYYYYGMDV	
CAR22-36	SYYMH		IINPSGGSTSYAQKFQG		DDDFWSGSGAFDI	
CAR22-37	SYYMH		IINPSGGSTSYAQKFQG		PEGVSYYDSSVLDY	
CAR22-38	SYYMH		IINPSGGSTSYAQKFQG		GGYGDYLDAFDI	

Tabla 8A. CDRs de domino variable de la cadena ligera para CARs CD22: Las secuencias de LC CDR en esta tabla tienen la misma secuencia de acuerdo con las combinaciones de Kabat o combinada.

Candidato	LCDR1	SEQ ID NO:	LCDR2	SEQ ID NO:	LCDR3	SEQ ID NO:
m971	RASQTIWSYLN	521	AASSLQS	560	QQSYSIPQT	599
CAR22-1	SGSSSNIGSNYVY	522	RNNQRPS	561	AAWDDSLSGYV	600
CAR22-2	TGTSSDVGGYNYVS	523	DVSKRPS	562	SSYTSSSLNHV	601

CAR22-3	TGTSSDVGGYNYVS	524	DVSNRPS	563	SSYTSSSTPYV	602
CAR22-4	QGDSLRSYYAS	525	GKNNRPS	564	NSRDSSGNHLWV	603
CAR22-5	QGDSLRSYYAS	526	GKNNRPS	565	NSRDSSGWV	604
CAR22-6	TGTSSDVGGYNYVS	527	DVSNRPS	566	SSYTSSSTLYV	605
CAR22-7	TGTSSDVGGYNYVS	528	DVSSRPS	567	SSYAGSNTLV	606
CAR22-8	TRSSGSIASNYVQ	529	EDNQRPS	568	QSYDSSNPWV	607
CAR22-9	SGSSSNIGSNYVY	530	RNNQRPS	569	AAWDDSLSGPV	608
CAR22-10	TGTSSDVGGYNYVS	531	DVSNRPS	570	SSYTSSSTLVYV	609
CAR22-11	QGDSLRSYYAS	532	GKNHRPS	571	HSRDSSGNHL	610
CAR22-12	TGTSSDVGGYNYVS	533	DVSNRPS	572	SSYTSSSTLYV	611
CAR22-13	TGSSGSFASSYVQ	534	EDNQRPS	573	QSYDGATWV	612
CAR22-14	SGTSSDVGGYNSVS	535	DVNNRPS	574	SSYTSSSTLF	613
CAR22-15	QGDSLRTYYAT	536	DENNRPS	575	SSRDSSGNPSCV	614
CAR22-16	TGTSSDVGGYNYVS	537	DVSNRPS	576	SSYTSSSTWV	615
CAR22-17	RSSQSLLAGNGHNYLD	538	LGSNRAS	577	MQALQNPLT	616
CAR22-18	TGSSSDVGGYNYVS	539	EVSNRPS	578	SSYTSSSTLV	617
CAR22-19	TGTSSDVGGYNYVS	540	DVSNRPS	579	SSYASSSTLV	618
CAR22-20	TGTNSDVGRYNYVS	541	EVSYRPS	580	SSYTTSSTLD	619
CAR22-21	TGTSSDVGGYKYVS	542	DVSNRPS	581	SSYTSSSTLV	620
CAR22-22	TLSSGHSSYAIA	543	VNSDGSLSKGD	582	QTWGSGMAI	621
CAR22-23	TGTSSDVGGYNYVS	544	EVSKRPS	583	SSYTSSGTLV	622
CAR22-24	QGDSLRSYYAS	545	GKNNRPS	584	NSRDSSGNPYV	623
CAR22-25	TGTSSDVGGYNYVS	546	EVSNRPS	585	SSYTSSSTLV	624
CAR22-26	RSSQSLLHSNGYNYLD	547	LGSNRAS	586	MQALQTPPWT	625
CAR22-27	RSSQSLLHSNGYNYLD	548	LGSNRAS	587	MQVLQTPPLT	626
CAR22-28	GGTNIGSKNVH	549	YDSDRPS	588	QVWDSSSDHWV	627
CAR22-29	GGHNIRSKNVH	550	YDGDRPS	589	QVWDSDSDHYV	628
CAR22-30	RASQSINTYLN	551	AASNLQS	590	QQSYSSLLT	629
CAR22-31	TGTSSDVGGYNYVS	552	DADKRPS	591	CSYAGGSTWV	630
CAR22-32	RASQSVTSNLA	553	AASTRAT	592	QQYHTWPPLT	631

CAR22-33	RSSQSLLHSNGYNYLD	554	LGSNRAS	593	MQALQTPWT	632
CAR22-34	RSSQSLLYSDGYNYLD	555	LGSNRAS	594	MQALQTQS	633
CAR22-35	QGDSLRSYFTS	556	GNNNRPS	595	DSRDSSGDHLV	634
CAR22-36	QGDSLRSYYAS	557	GKNNRPS	596	NSRDSSGNHPVV	635
CAR22-37	TGTSSDVGGYKHVS	558	DVSNRPS	597	VSYRNFNSLV	636
CAR22-38	TGTSSDVGGYNYVS	559	EVSNRPS	598	SSYTSSSTLV	637

Tabla 8B. CDRs del dominio variable de la cadena ligera de CARs CD22. Las secuencias de LC CDR en esta tabla tienen la misma secuencia de acuerdo con las combinaciones de Kabat o combinada.

Candidate	LCDR1	SEQ ID NO:	LCDR2	SEQ ID NO:	LCDR3	SEQ ID NO:
CAR22-53 Kabat	TGTSSDVGGYNYVS	638	EVNNRPS	649	SSYTSGRTLYV	660
CAR22-53 Chothia	TSSDVGGYNY	639	EVN	650	YTSGRTLY	661
CAR22-53 Combinado	TGTSSDVGGYNYVS	1117	EVNNRPS	1119	SSYTSGRTLYV	1121
CAR22-53 IMGT	SSDVGGYNY	1118	EVN	1120	SSYTSGRTLYV	1122
CAR22-57 Combinado	TGSRNDIGAYESVS	640	GVNNRPS	651	SSHTTTSTLYV	662
CAR22-58 Combinado	TGSSSDVGGYNSVS	641	EVINRPS	652	SSYTSSSTYV	663
CAR22-59 Combinado	TGSSSDIGGFNYVS	642	EVTNRPS	653	SSYASGSPLYV	664
CAR22-60 Combinado	TGTSSDIGGYNYVS	643	EVSNRPS	654	SSYTSSSTLYV	665
CAR22-61 Combinado	TGTSSDVGGYNYVS	644	EVSNRPS	655	SSYTSSSTLYV	666

CAR22-62 Combinado	TGTSSDVGGYNYVS	645	DVSNRPS	656	SSYTSSSTLYV	667
CAR22-63 Combinado	TGTSSDVGGYNYVS	646	EVSNRPS	657	SSYTSSSTLYI	668
CAR22-64 Combinado	TGTSSDVGGYNYVS	647	DVSNRPS	658	SSYTSSSTLYV	669
CAR22-65 Combinado	TGTSSDVGGYNYVS	648	DVSNRPS	659	SSYTSSSTLYV	670

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Tabla 9A. Regiones variables de la cadena pesada de las moléculas de anticuerpo de CD22

Candidato	**ID**	**Region variable de la cadena pesada**
m971	700	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSR GLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQLNSVT PEDTAVYYCAREVTGDLEDAFDIWGQGTMVTV
CAR22-1	701	QVQLVQSGGGLIQPGGSLRLSCAASGFTVSSNYMSWVRQAPGKG LEWVSVIYSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAED TAVYYCASQSTPYDSSGYYSGDAFDIWGQGTMVTV
CAR22-2	702	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSR GLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQLNSVT PEDTAVYYCARDLGWIAVAGTFDYWGQGTLVTV
CAR22-3	703	EVQLQQSGPGLVKPSQTLSLTCAISGDSVLSNSDTWNWIRQSPSR GLEWLGRTYHRSTWYDDYASSVRGRVSINVDTSKNQYSLQLNA VTPEDTGAYYCARDRLQDGNSWSDAFDVWGQGTMVTV
CAR22-4	704	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGK GLEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTALYYCAKGLSSWHFHDALDIWGQGTMVTV

CAR22-5	705	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGK GLEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTALYYCAKDKGGGYYDFWSGSDYWGQGTLVTV
CAR22-6	706	EVQLQQSGPGLVKPSLTLSLTCAISGDSVSSNSATWTWIRQSPSRG LEWLGRTYYRSTWYNDYAVSVKSRITINPDTSKNQFSLQLNSVTP EDTAVYYCAREGSGSYYAYWGQGTLVTV
CAR22-7	707	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPG QGLEWMGWINP- NSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCA RDYWGYYGSGTLDYWGQGTLVTV
CAR22-8	708	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQG LEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLR SDDTAVYYCARAGLALYSNYVPYYYYGMDVWGQGTTVTV
CAR22-9	709	EVQLVESGGGLVKPGGSLRLSCVASGFTFSNAWMNWVRQAPGK GLEWVGRIKSKTDGGTADYAAPVKGRFTISRDDSKNTMYLQMNS LKTEDTGVYYCITGATDVWGQGTTVTV
CAR22-10	710	EVQLQQSGPGLVKPSQTLSLTCAISGDSVLSNSDTWNWIRQSPSR GLEWLGRTYHRSTWYDDYASSVRGRVSINVDTSKNQYSLQLNA VTPEDTGVYYCARDRLQDGNSWSDAFDVWGQGTMVTV
CAR22-11	711	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSR GLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQLNSVT PEDTAVYYCAREESSSGWYEGNWFDPWGQGTLVTV
CAR22-12	712	EVQLQQSGPGLVKPSQTLSLTCAISGDSVLSNSDTWNWIRQSPSR GLEWLGRTYHRSTWYDDYASSVRGRVSINVDTSKNQYSLQLNA VTPEDTGVYYCARDRLQDGNSWSDAFDVWGQGTMVTV
CAR22-13	713	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKG LEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADT AVYYCARGRMDTAMAQIWGQGTMVTV

CAR22-14	714	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARDLDVSLDIWGQGTMVTV
CAR22-15	715	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMHWVRQAPGKG LEYVSAISSNGGSTYYANSVKDRFTISRDNSKNTLYLQMGSLRAE DMAVYYCARVHSSGYYHPGPNDYWGQGTLVTV
CAR22-16	716	EVQLVESGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTAYMELSSLRS EDTAVYYCAREAGVVAVDYWGQGTLVTV
CAR22-17	717	QVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMSWVRQAPGKG LEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAE DTAVYYCAKEPLFGVVEEDVDYWGQGTLVTV
CAR22-18	718	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARGSGSLGDAFDIWGQGTMVTV
CAR22-19	719	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARDGFGELSGAFDIWGQGTMVTV
CAR22-20	720	EVQLVESGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARGPIGCSGGSCLDYWGQGTLVTV
CAR22-21	721	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARGSYGDYGDAFDIWGQGTTVTV
CAR22-22	722	EVQLVESGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQG LEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARDHKVVRFGYWGQGTLVTV

CAR22-23	723	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARGDYYMDVWGKGTTVTV
CAR22-24	724	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKG LEWVSYISSSSSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAED TAVYYCARDGPIRYFDHSKAFDIWGQGTMVTV
CAR22-25	725	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSISTAYMELSRLRS DDTAVYYCAREMDDSSGPDYWGQGTLVTV
CAR22-26	726	EVQLVESGAEVKKPGESLKISCKGSGYSFTGSWIGWGRQMPGKG LEWMGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASD TAMYYCARGFLRGGDCCGALDIWGQGTMVTV
CAR22-27	727	QVQLQESGPGLVKPSETLSLTCSVSGGSINSYYWSWIRQAPGKGL EWIAFTSHSGNVKYNPSLTGRVTIAVDTSKNQFYLEVTSVTAADT AVYFCARGLDPLFAYDAFEIWGLGTMVTV
CAR22-28	728	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKG LEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAE DTAVYYCARDDFWSGSVDYWGQGTLVTV
CAR22-29	729	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCAREDDSSGYTSPFDYWGQGTLVTV
CAR22-30	730	EVQLVESGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQ GLEWMGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLR SDDTAVYYCAREPASSSWYGYYYYMDVWGKGTLVTV
CAR22-31	731	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQ GLEWMGWMNPNSGNTGYAQKFQGRVTMTRNTSISTAYMELSSL RSEDTAVYYCARG-DSNYWSYYGMDVWGQGTLVTV

CAR22-32	732	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQG LEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLR SDDTAVYYCASFSSSDSYDYWGQGTLVTV
CAR22-33	733	QVNLRESGPALVKPTQTLTLTCTFSGFSLNTFGMSVSWIRQPPGK ALEWLALIDWDDDKYYSTSLRTRLTISKDTAKNQVVLRMTNMDP MDTATYYCARIYGGDRTNTQAPYFFDLWGQGTLVTV
CAR22-34	734	QVQLQESGPGLVKPSGTLSLTCAVSGASITSRHWWNWVRHSPGK GLEWIGQIYHSGTTTYNPSLGSRVTISVDKSKNQISLELRSVTAAD TATYYCVRDYLELATYYGMDVWGQGTTVTV
CAR22-35	735	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARDLAAAGNYYYYGMDVWGQGTTVTV
CAR22-36	736	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARDDDFWSGSGAFDIWGQGTTVTV
CAR22-37	737	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARPEGVSYYDSSVLDYWGQGTLVTV
CAR22-38	738	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRA EDTAVYYCARGGYGDYLDAFDIWGQGTTVTV

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Tabla 9B. Regiones variables de la cadena pesada de las moléculas de anticuerpo de CD22

Candidato	**SEQ ID NO:**	**Región Variable de la Cadena Pesada**
CAR22-53	671	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEW LGRTYYRSKWYSDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYY

		CARDPYDFWSGYPDAFDIWGQGTMVTVSS
CAR22-57	672	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSNNNAAWNWIRQSPSRGLEW LGRTYHRSTWYNDYVGSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYY CARETDYGDYGAFDIWGQGTTVTVSS
CAR22-58	673	EVQLQQSGPGLVNPSQTLSITCAISGDSVSSNSAAWNWIRQSPSRGLEWL GRTFYRSKWYNDYAVSVKGRITISPDTSKNQFSLQLNSVTPEDTAVYYC AGGDYYYGLDVWGQGTTVTVSS
CAR22-59	674	EVQLQQSGPGLVKPSQTLSLTCAISGDSVLSNSDTWNWIRQSPSRGLEW LGRTYHRSTWYDDYASSVRGRVSINVDTSKNQYSLQLNAVTPEDTGVY YCARDRLQDGNSWSDAFDVWGQGTMVTVSS
CAR22-60	675	EVQLQQSGPGLVKPSQTLSLTCAISGDSVLSNSDTWNWIRQSPSRGLEW LGRTYHRSTWYDDYASSVRGRVSINVDTSKNQYSLQLNAVTPEDTGVY YCARDRLQDGNSWSDAFDVWGQGTMVTVSS
CAR22-61	676	QVQLQESGPGLVKPSQTLSLTCAISGDSVLSNSDTWNWIRQSPSRGLEW LGRTYHRSTWYDDYASSVRGRVSINVDTSKNQYSLQLNAVTPEDTGVY YCARDRLQDGNSWSDAFDVWGQGTMVTVSS
CAR22-62	677	EVQLQQSGPGLVKPSQTLSLTCAISGDSVLSNSDTWNWIRQSPSRGLEW LGRTYHRSTWYDDYASSVRGRVSINVDTSKNQYSLQLNAVTPEDTGVY YCARDRLQDGNSWSDAFDVWGQGTMVTVSS
CAR22-63	678	EVQLQQSGPGLVKPSQTLSLTCAISGDSVLSNSDTWNWIRQSPSRGLEW LGRTYHRSTWYDDYASSVRGRVSINVDTSKNQYSLQLNAVTPEDTGVY YCARDRLQDGNSWSDAFDVWGQGTMVTVSS
CAR22-64	679	EVQLQQSGPGLVKPSQTLPLTCAISGDSVLSNSDTWNWIRQSPSRGLEW LGRTYHRSTWYDDYASSVRGRVSINVDTSKNQYSLQLNAVTPEDTGVY YCARVRLQDGNSWSDAFDVWGQGTMVTVSS
CAR22-65	680	EVQLQQSGPGLVKPSQTLSLTCAISGDSMLSNSDTWNWIRQSPSRGLEW LGRTYHRSTWYDDYASSVRGRVSINVDTSKNQYSLQLNAVTPEDTGVY YCARVRLQDGNSWSDAFDVWGQGTMVTVSS

Tabla 10A. Regiones variables de la cadena ligera para las moléculas de anticuerpo CD22

Candidato	**ID**	**Región variable de la cadena ligera**
m971	739	DIQMTQSPSSLSASVGDRVTITCRASQTIWSYLNWYQQRPGKAPNLLIYAASSLQSGVPSRFSGRGSGTDFTLTISSLQAEDFATYYCQQSYSIPQTFGQGTKLEIK
CAR22-1	740	SYVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLSGYVFGTGTKLTVL
CAR22-2	741	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSLNHVFGTGTKVTVL
CAR22-3	742	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTPYVFGTGTQLTVL
CAR22-4	743	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHLWVFGGGTKLTVL
CAR22-5	744	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGWVFGGGTKLTVL
CAR22-6	745	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTKVTVL
CAR22-7	746	QSALTQPGSVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLIIYDVSSRPSGVSNRFSGSQSGNTASLTISGLQAEDEADYSCSSYAGSNTLVFGTGTKVTVL

CAR22-8	747	NFMLTQPHSVSESPGKTVTISCTRSSGSIASNYVQWYQQRPGSSPT TVIYEDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYCQS YDSSNPWVFGGGTKLTVL
CAR22-9	748	SYVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAPK LLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAA WDDSLSGPVFGGGTKLTVL
CAR22-10	749	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKA PKLMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCS SYTSSSTLVYVFGTGTKVTVL
CAR22-11	750	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPV LVIYGKNHRPSGIPDRFSGSSSGDTDSLTITGAQAEDEADYYCHSR DSSGNHLFGGGTKLTVL
CAR22-12	751	QSALTQPASASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGK APKLMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYY CSSYTSSSTLYVFGTGTQLTVL
CAR22-13	752	NFMLTQPHSVSESPGKTVTIPCTGSSGSFASSYVQWYQQRPGSAP ATVIYEDNQRPSGVPDRFSGSVDSSSNSASLTISGLKTEDEAVYYC QSYDGATWVFGGGTKLTVL
CAR22-14	753	QSALTQPASVSGSPGQSITISCSGTSSDVGGYNSVSWYQQYPGKAP KLMIYDVNNRPSGVSSRFSGSKSGNTASLTISGLQAEDEADYYCSS YTSSSTLFFGAGTKVTVL
CAR22-15	754	SSELTQDPAVSVALGQTVRITCQGDSLRTYYATWYQQKPGQAPV LVFYDENNRPSGIPDRFSGSSSGNTASLTITGTQAEDEADYYCSSR DSSGNPSCVFGGGTKLTVL
CAR22-16	755	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKA PKLMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCS SYTSSSTWVFGGGTKLTVL

CAR22-17	756	DVVMTQSPLSLPVTPGEPASISCRSSQSLLAGNGHNYLDWYLQKP GQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVY YCMQALQNPLTFGGGTKLEIKR
CAR22-18	757	QSALTQPASVSGSPGQSITISCTGSSSDVGGYNYVSWYQQHPGKA PKLMIYEVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCS SYTSSSTLVFGTGTKVTVL
CAR22-19	758	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKA PKLMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCS SYASSSTLVFGGGTKVTVL
CAR22-20	759	QSALTQPAYVSGSPGQSITISCTGTNSDVGRYNYVSWYQQHPGKA PKLMIYEVSYRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCS SYTTSSTLDFGTGTKVTVL
CAR22-21	760	QSALTQPASVSGSPGQSITISCTGTSSDVGGYKYVSWYQQHPGKA PKLMIYDVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCS SYTSSSTLVFGGGTKLTVL
CAR22-22	761	HVILTQPPSASASLGASVKLTCTLSSGHSSYAIAWHQQQPEKGPRY LMKVNSDGSLSKGDGIPDRFSGSTSGAERYLTISSLQSEDEADYYC QTWGSGMAIFGGGTKLTVL
CAR22-23	762	QSALTQPASASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGK APKLMIYEVSKRPSGVPDRFSGSKSGNTASLTISGLQAEDEADYY CSSYTSSGTLVFGGGTKLTVL
CAR22-24	763	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPV LVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYRNSR DSSGNPYVFGTGTKVTVL
CAR22-25	764	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKA PKLMIYEVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCS SYTSSSTLVFGTGTKLTVL

CAR22-26	765	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPG QSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYY CMQALQTPPWTFGQGTKLEIKR
CAR22-27	766	EIVLTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPG QSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYY CMQVLQTPPLTFGGGTKVDIKR
CAR22-28	767	SYVLTQPPSVSVAPGKTATITCGGTNIGSKNVHWYQQKPGQAPVL AIYYDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYFCQVWD SSSDH-WVFGGGTKLTVL
CAR22-29	768	SYELTQPPSVSVAPGETASIACGGHNIRSKNVHWYQQKPGQAPVL VISYDGDRPSGIPERFSGSNLGSTATLTISRVEAGDEADYYCQVWD SDSDH-YVFGTGTKVTVL
CAR22-30	769	DIQMTQSPSSLSASVGDRVTITCRASQSINTYLNWYQQKPGKPPKL LIYAASNLQSGVPSRFSGSGSGTHFTLTISSLQPDDFATYYCQQSYS SLLTFGGGTKLEIK
CAR22-31	770	QSVLTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGEA PKLIIYDADKRPSGISNRFSSGKSGNTASLTISGLQVEDEADYYCCS YAGGSTWVFGGGTKVTVL
CAR22-32	771	EIVLTQSPATLSVSPGERATLSCRASQSVTSNLAWYQQKPGQAPR LLIYAASTRATGIPARFSGSGSGTEFTLTISSMQSEDFAVYFCQQYH TWPPLTFGGGTKVEIKT
CAR22-33	772	DVVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKP GQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVY YCMQALQTPWTFGQGTKLEIK
CAR22-34	773	EIVLTQSPLSLPVTPGEPASISCRSSQSLLYSDGYNYLDWYLQKPG QSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLQISGVETEDVGVYY CMQALQTQSFGQGTKLEIK

CAR22-35	774	SSELTQDPAVSVALGQTARITCQGDSLRSYFTSWYHQKPGQAPVL VIYGNNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEGDYYCDSRD SSGDHLVFGGGTKLTVL
CAR22-36	775	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPV LVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSR DSSGNHPVVFGGGTKLTVL
CAR22-37	776	QSALTQPASVSGSPGQSITISCTGTSSDVGGYKHVSWYQHHPGKA PKLMIYDVSNRPSGVSNRFSGSKSGNTASLTVSGLQAEDEAHYYC VSYRNFNSLVFGTGTKVTVL
CAR22-38	777	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKA PKLMIYEVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCS SYTSSSTLVFGTGTQLTVL

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Tabla 10B. Regiones variables de la cadena ligera de las moléculas de anticuerpo de CD22

Candidato	**ID**	**Región Variable de Cadena Ligera**
CAR22-53	681	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKVIISEVNNRPSGVS HRFSGSKSGNTASLTISGLQAEDEADYFCSSYTSGRTLYVFGTGSKVTVLG
CAR22-57	682	QSALTQPASVSGSPGQSITISCTGSRNDIGAYESVSWYQQHPGNAPKLIIHGVNNRPSGVFD RFSVSQSGNTASLTISGLQAEDEADYYCSSHTTTSTLYVFGTGTKVTVLG
CAR22-58	683	QSALTQPASVSGSPGQSITISCTGSSSDVGGYNSVSWYQQHPGKAPKLMIYEVINRPSGVS HRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTYVFGTGTKVTVLG
CAR22-59	684	QSALTQPASVSGSPGQSITISCTGSSSDIGGFNYVSWYQQHAGEAPKLMIYEVTNRPSGVS DRFSGSKSDNTASLTISGLQAEDEADYYCSSYASGSPLYVFGTGTKVTVLG
CAR22-60	685	QSALTQPASVSGSPGQSITFSCTGTSSDIGGYNYVSWYQQHPGKAPKLMIYEVSNRPSGVS NRFSGTKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTKLTVLG
CAR22-61	686	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSNRPSGVS NRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTKVTVLG
CAR22-62	687	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTKVTVLG
CAR22-63	688	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSNRPSGVS NRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYIFGTGTKVTVLG

CAR22-64	689	QSALTQPASASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTQLTVL
CAR22-65	690	QSALTQPASASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGV SNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLYVFGTGTQLTVL

En algunas modalidades, el dominio de unión a antígeno comprende una HC CDR1, una HC CDR2, y una HC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada listadas en la **Tabla 9A o 9B**. En modalidades, el dominio de unión al antígeno comprende adicionalmente una LC CDR1, una LC CDR2, y una LC CDR3. En modalidades, el dominio de union a antígeno comprende una LC CDR1, una LC CDR2, y una LC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera listadas en la **Tabla 10A o 10B**.

En algunas modalidades, el dominio de unión a antígeno cmoprende una, dos o todas de las LC CDR1, LC CDR2, y LC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera listadas en la **Tabla 10A o 10B**, y una, dos o todas de las HC CDR1, HC CDR2, y HC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada listadas en la **Tabla 9A o 9B**.

En algunas modalidades, las CDRs están definidas de acuerdo con el esquema de numeración de Kabat, el esquema de numeración de Chothia, o una combinación de los mismos.

El orden en el cual aparecen los dominios VL y VH en el scFv puedeser variado (es decir, orientación VL-VH, o VH-VL), y en donde, ya sea tres o cuatro copias de la subunidad "G4S" (SEQ ID NO:18), en la cual cada subunidad comprende la secuencia GGGGS (SEQ ID NO:18) (por ejemplo, $(G4S)_3$ (SEQ ID NO:107) o $(G4S)_4$(SEQ ID NO:106)), pueden conectar los dominios variables para crear la totalidad del dominio scFv. Alternativamente, el constructo CAR puede incluir, por ejemplo, un enlazador que incluya la secuencia GSTSGSGKPGSGEGSTKG (SEQ ID NO: 1322).

Todos estos clones contenían un cambio de residuo Q/K en el dominio señal del dominio coestimulatorio derivado de la cadena CD3zeta.

constructos CAR20

Se aislaron los fragmentos de cadena única anti-CD20. Véase la **Tabla 11A o 11B**. Los

scFvs anti-CD20 fueron clonados en vectores de expression lentivirales de CAR con la cadena CD3zeta y la molécula coestimuladora 4-1BB. Los plásmidos que contienen el CAR fueron amplificados mediante transformación bacteriana en células STBL3, seguido de Maxiprep usando el kit Qiagen Plasmid Maki libre de endotoxina. El sobrenadante lentiviral fue producido en células 293T usando técnicas estándar.

Las secuencias de los CARs se proporcionan a continuación en la **Tabla 11A o 11B**. Los components adicionales de los CARs (por ejemplo, los dominios líder, bisagra, transmembrana, y de señalización) se describen en el presente documento.

Table 11A: Constructos CAR CD20 de Rata

Nombre	**SEQ ID NO:**	**Secuencia**
dominio CAR20-1 scFv	800	qiqlvqsgpelkkpgesvkiscktseytftdyafhwvkqapgkglkwmgwintysgkpt yaddfkgrfvfsledsartanlqisnlknedtatyfcargayygyrdwftywgqgtlvtvssg gggsggggsggggsggggsdivmtqtpssqavsagekvtmscksqsllysenkknyla wyqqkpgqspklliywastresgvpdrfigsgsgtdftltissvqaedlavyycqqyynfp pwtfgggtklelk
dominio CAR20-1 scFv nt	801	caaattcaactggtccagtccggccctgagctgaagaagccgggagaatccgtgaagatctc ctgcaagacctcggagtacaccttcactgactacgccttccactgggtcaagcaggcacctgg gaaaggcctgaagtggatgggctggatcaacacttactcggggaagccaacctacgccgat gatttcaagggaagattcgtgtttagcctggaggactccgcccggacagctaacctccaaatct ccaaccttaagaacgaggacactgcgacctacttctgcgcgcggggagcctattacggttatc gcgactggttcacctactggggacagggcaccctcgtgaccgtgtcctccggcggtggagg ctcaggggggggcggctcgggaggggggtggaagcggaggaggaggctccgatattgtgat gacccagaccccgtcgagccaggcagtgtccgctggagaaaaggtcaccatgtcctgcaag agctcacagtccctgttgtactccgaaaacaagaagaattacctggcctggtaccagcagaag cccggacagtcccctaaactgctgatctactgggcctcgactagggaatctggcgtgcccgac cgctttatcggaagcggttcagggactgacttcaccctgaccattagcagcgtgcaggccgag gacctggcggtgtactactgtcaacagtactacaacttcccgccctggactttcggcggtggaa cgaagctcgaactcaag
CAR20-1 scFv - nt Soluble	802	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccc aaattcaactggtccagtccggccctgagctgaagaagccgggagaatccgtgaagatctcct gcaagacctcggagtacaccttcactgactacgccttccactgggtcaagcaggcacctggg aaaggcctgaagtggatgggctggatcaacacttactcggggaagccaacctacgccgatga tttcaagggaagattcgtgtttagcctggaggactccgcccggacagctaacctccaaatctcc aaccttaagaacgaggacactgcgacctacttctgcgcgcggggagcctattacggttatcgc gactggttcacctactggggacagggcaccctcgtgaccgtgtcctccggcggtggaggctc agggggggcggctcgggaggggggtggaagcggaggaggaggctccgatattgtgatga cccagaccccgtcgagccaggcagtgtccgctggagaaaaggtcaccatgtcctgcaagag ctcacagtccctgttgtactccgaaaacaagaagaattacctggcctggtaccagcagaagcc cggacagtcccctaaactgctgatctactgggcctcgactagggaatctggcgtgcccgacc gctttatcggaagcggttcagggactgacttcaccctgaccattagcagcgtgcaggccgagg acctggcggtgtactactgtcaacagtactacaacttcccgccctggactttcggcggtggaac

		gaagctcgaactcaagggatcgcaccaccatcaccatcatcatcac
CAR20-1 scFv - aa Soluble	803	malpvtalllplalllhaarpqiqlvqsgpelkkpgesvkiscktseytftdyafhwvkqapg kglkwmgwintysgkptyaddfkgrfvfsledsartanlqisnlknedtatyfcargayyg yrdwftywgqgtlvtvssggggsggggsggggsggggsdivmtqtpssqavsagekvt mscksqsllysenkknylawyqqkpgqspklliywastresgvpdrfigsgsgtdftltis svqaedlavyycqqyynfppwtfgggtklelkgshhhhhhhh
CAR20-1 Completo – nt lentivirus	804	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccc aaattcaactggtccagtccggccctgagctgaagaagccgggagaatccgtgaagatctcct gcaagacctcggagtacaccttcactgactacgccttccactgggtcaagcaggcacctggg aaaggcctgaagtggatgggctggatcaacacttactcggggaagccaacctacgccgatga tttcaagggaagattcgtgtttagcctggaggactccgcccggacagctaacctccaaatctcc aaccttaagaacgaggacactgcgacctacttctgcgcgcggggagcctattacggttatcgc gactggttcacctactggggacagggcaccctcgtgaccgtgtcctccggcggtggaggctc agggggggcggctcgggaggggtggaagcggaggaggaggctccgatattgtgatga cccagaccccgtcgagccaggcagtgtccgctggagaaaaggtcaccatgtcctgcaagag ctcacagtccctgttgtactccgaaaacaagaagaattacctggcctggtaccagcagaagcc cggacagtcccctaaactgctgatctactgggcctcgactagggaatctggcgtgcccgacc gctttatcggaagcggttcagggactgacttcaccctgaccattagcagcgtgcaggccgagg acctggcggtgtactactgtcaacagtactacaacttcccgccctggactttcggcggtggaac gaagctcgaactcaagaccactaccccagcaccgaggccacccaccccggctcctaccatc gcctcccagcctctgtccctgcgtccggaggcatgtagacccgcagctggtggggccgtgca tacccggggtcttgacttcgcctgcgatatctacatttgggcccctctggctggtacttgcgggg tcctgctgctttcactcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctt taagcaacccttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggtt cccagaggaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgc tccagcctacaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagag gagtacgacgtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgc gcagaaagaatccccaagagggcctgtacaacgagctccaaaaggataagatggcagaag cctatagcgagattggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgta ccagggactcagcaccgccaccaaggacacctatgacgctcttcacatgcaggccctgccg cctcgg
CAR20-1 – Completo - aa	805	malpvtalllplalllhaarpqiqlvqsgpelkkpgesvkiscktseytftdyafhwvkqapg kglkwmgwintysgkptyaddfkgrfvfsledsartanlqisnlknedtatyfcargayyg yrdwftywgqgtlvtvssggggsggggsggggsggggsdivmtqtpssqavsagekvt mscksqsllysenkknylawyqqkpgqspklliywastresgvpdrfigsgsgtdftltis svqaedlavyycqqyynfppwtfgggtklelktttpaprpptpaptiasqplslrpeacrpaa ggavhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeed gcscrfpeeeeggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpem ggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydal hmqalppr
dominio CAR20-2 scFv	806	evqlvesggglvqpgrslklsclasgftfskygmnwirqapgkglewvasisstsiyiyyad tvkgrftisrenakntlylqmtslrsedtalyycarhdyssysywgqgvmvtvssggggsg gggsggggsggggsqvvltqpksvstslestvklsckinsgnigsyfihwyqqhegrsptt miyrddkrphgvpdrfsgsidsssnsafltinnvqtedeaiyfchsydsginivfgggtkltv l
dominio CAR20-2	807	gaggtgcagctcgtcgaatccggtggaggactggtgcagccaggaagatccctgaagctgt cctgtctcgcctcgggcttcactttctccaaatacggcatgaattggattcgccaggcacccgg

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CAR20-2 - scFv - nt Soluble	808	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg aggtgcagctcgtcgaatccggtggaggactggtgcagccaggaagatccctgaagctgtcc tgtctcgcctcgggcttcactttctccaaatacggcatgaattggattcgccaggcacccggaa aggggctggaatgggtggccagcatcagctcgactagcatctacatctactatgccgataccg tcaagggccgcttcactatctcccgcgagaacgctaagaacacccttacttgcaaatgacctc cctgaggtccgaagataccgccctgtactattgcgcccggcacgactactcatcctactcctac tggggacagggagtcatggtgaccgtgtcctccggcggtggaggctcaggggggggcggc tcgggaggggtggaagcggaggaggaggctcccaagtcgtgctgacgcaacccaagtcc gtgagcaccagcctggagagcaccgtgaagctcagctgcaagattaactcgggcaacattgg gtcctacttcatccattggtaccagcagcacgaaggacggtcccctaccactatgatctaccgg gacgacaagcggccgcacggagtgccggacagattctcgggttcaatcgattcctcatctaac tcggcgtttctcaccatcaacaacgtgcagaccgaggacgaagcgatctacttctgccactcct acgactcgggtattaacattgtgttcggcggcgggactaagctgacagtgctgggatcgcacc accatcaccatcatcatcac
CAR20-2 - scFv - aa Soluble	809	malpvtalllplalllhaarpevqlvesggglvqpgrslklsclasgftfskygmnwirqapg kglewvasisstsiyiyyadtvkgrftisrenakntlylqmtslrsedtalyycarhdyssysy wgqgvmvtvssggggsggggsggggsggggsqvvltqpksvstslestvklsckinsgn igsyfihwyqqhegrspttmiyrddkrphgvpdrfsgsidsssnsafltinnvqtedeaiyf chsydsginivfgggtkltvlgshhhhhhhh
CAR20- 2 - Completo - nt	810	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg aggtgcagctcgtcgaatccggtggaggactggtgcagccaggaagatccctgaagctgtcc tgtctcgcctcgggcttcactttctccaaatacggcatgaattggattcgccaggcacccggaa aggggctggaatgggtggccagcatcagctcgactagcatctacatctactatgccgataccg tcaagggccgcttcactatctcccgcgagaacgctaagaacacccttacttgcaaatgacctc cctgaggtccgaagataccgccctgtactattgcgcccggcacgactactcatcctactcctac tggggacagggagtcatggtgaccgtgtcctccggcggtggaggctcaggggggggcggc tcgggaggggtggaagcggaggaggaggctcccaagtcgtgctgacgcaacccaagtcc gtgagcaccagcctggagagcaccgtgaagctcagctgcaagattaactcgggcaacattgg gtcctacttcatccattggtaccagcagcacgaaggacggtcccctaccactatgatctaccgg gacgacaagcggccgcacggagtgccggacagattctcgggttcaatcgattcctcatctaac tcggcgtttctcaccatcaacaacgtgcagaccgaggacgaagcgatctacttctgccactcct acgactcgggtattaacattgtgttcggcggcgggactaagctgacagtgctgaccactaccc cagcaccgaggccacccaccccggctcctaccatcgcctcccagcctctgtccctgcgtccg gaggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcga tatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactctt actgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgca gactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc

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CAR20- 2 - Completo - aa	811	malpvtalllplalllhaarpevqlvesggglvqpgrslklsclasgftfskygmnwirqapg kglewvasisstsiyiyyadtvkgrftisrenakntlylqmtslrsedtalyycarhdyssysy wgqgvmvtvssggggsggggsggggsggggsqvvltqpksvstslestvklsckinsgn igsyfihwyqqhegrspttmiyrddkrphgvpdrfsgsidsssnsafltinnvqtedeaiyf chsydsginivfgggtkltvltttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfac diyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeegg celrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeg lynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr
dominio CAR20-3 scFv	812	evqlvesggglvqpgrslklscaasgftfrdyymawvrqapkkglewvasisyegnpyy gdsvkgrftisrnnakstlylqmnslrsedtatyycarhdhnnvdwfaywgqgtlvtvssg gggsggggsggggsggggsdivmtqtpssqavsagekvtmscksqsllysenkknyla wyqqkpgqspkllifwastresgvpdrfigsgsgtdftltissvqaedlavyycqqyynfpt fgsgtkleik
dominio CAR20-3 scFv nt	813	gaagtgcagcttgtggagtctggcggcggtctggtgcagccgggaagatccctgaagctgtc atgcgccgcgtccgggtttaccttccgcgattactacatggcctgggtcagacaggcacctaa gaaggggctggaatgggtggcatccatctcatatgaaggaaacccgtactacggagactcgg tgaaaggccgcttcactatctcacggaacaacgctaagagcacgctgtacttgcaaatgaact ccctccggtcggaggacacagccacttactactgtgcccggcacgaccataacaacgtcgatt ggttcgcctactggggtcaaggaaccctcgtgaccgtgtcctccggcggtggaggctcaggg gggggcggctcgggaggggggtggaagcggaggaggaggctccgacatcgtgatgactca gactccaagcagccaggccgtgtccgccggagagaaagtcaccatgtcgtgcaagagctcc cagtccctgctgtactccgaaaacaagaagaattatctcgcctggtaccagcagaagcctgga cagtccccgaagctcctgatcttttgggcgtcgaccagggaatccggcgtgcccgatcgcttc attggctccggttccggcaccgacttcaccctgaccattagcagcgtccaggcggaggacct ggctgtgtactactgccaacagtactacaacttccccactttcggatcggggaccaagctgga gatcaag
CAR20- 3 - scFv - nt Soluble	814	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg aagtgcagcttgtggagtctggcggcggtctggtgcagccgggaagatccctgaagctgtca tgcgccgcgtccgggtttaccttccgcgattactacatggcctgggtcagacaggcacctaag aaggggctggaatgggtggcatccatctcatatgaaggaaacccgtactacggagactcggt gaaaggccgcttcactatctcacggaacaacgctaagagcacgctgtacttgcaaatgaactc cctccggtcggaggacacagccacttactactgtgcccggcacgaccataacaacgtcgatt ggttcgcctactggggtcaaggaaccctcgtgaccgtgtcctccggcggtggaggctcaggg gggggcggctcgggaggggggtggaagcggaggaggaggctccgacatcgtgatgactca gactccaagcagccaggccgtgtccgccggagagaaagtcaccatgtcgtgcaagagctcc cagtccctgctgtactccgaaaacaagaagaattatctcgcctggtaccagcagaagcctgga cagtccccgaagctcctgatcttttgggcgtcgaccagggaatccggcgtgcccgatcgcttc attggctccggttccggcaccgacttcaccctgaccattagcagcgtccaggcggaggacct ggctgtgtactactgccaacagtactacaacttccccactttcggatcggggaccaagctgga gatcaagggatcgcaccaccatcaccatcatcatcac
CAR20- 3	815	malpvtalllplalllhaarpevqlvesggglvqpgrslklscaasgftfrdyymawvrqap

- scFv - aa Soluble		kkglewvasisyegnpyygdsvkgrftisrnnakstlylqmnslrsedtatyycarhdhnn vdwfaywgqgtlvtvssggggsggggsggggsggggsdivmtqtpssqavsagekvt mscksqsllysenkknylawyqqkpgqspkllifwastresgvpdrfigsgsgtdftltiss vqaedlavyycqqyynfptfgsgtkleikgshhhhhhhh
CAR20- 3 – Completo - nt	816	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg aagtgcagcttgtggagtctggcggcggtctggtgcagccgggaagatccctgaagctgtca tgcgccgcgtccgggtttaccttccgcgattactacatggcctgggtcagacaggcacctaag aaggggctggaatgggtggcatccatctcatatgaaggaaacccgtactacggagactcggt gaaaggccgcttcactatctcacggaacaacgctaagagcacgctgtacttgcaaatgaactc cctccggtcggaggacacagccacttactactgtgcccggcacgaccataacaacgtcgatt ggttcgcctactggggtcaaggaaccctcgtgaccgtgtcctccggcggtggaggctcaggg gggggcggctcgggaggggtggaagcggaggaggaggctccgacatcgtgatgactca gactccaagcagccaggccgtgtccgccggagagaaagtcaccatgtcgtgcaagagctcc cagtccctgctgtactccgaaaacaagaagaattatctcgcctggtaccagcagaagcctgga cagtccccgaagctcctgatcttttgggcgtcgaccagggaatccggcgtgcccgatcgcttc attggctccggttccggcaccgacttcaccctgaccattagcagcgtccaggcggaggacct ggctgtgtactactgccaacagtactacaacttccccactttcggatcggggaccaagctgga gatcaagaccactaccccagcaccgaggccacccaccccggctcctaccatcgcctcccag cctctgtccctgcgtccggaggcatgtagacccgcagctggtggggccgtgcatacccggg gtcttgacttcgcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgc tttcactcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaac ccttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagagg aggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagccta caagcaggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacgac gtgctggacaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaaga atccccaagagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcga gattggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggact cagcaccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR20- 3 – Completo - aa	817	malpvtalllplalllhaarpevqlvesggglvqpgrslklscaasgftfrdyymawvrqap kkglewvasisyegnpyygdsvkgrftisrnnakstlylqmnslrsedtatyycarhdhnn vdwfaywgqgtlvtvssggggsggggsggggsggggsdivmtqtpssqavsagekvt mscksqsllysenkknylawyqqkpgqspkllifwastresgvpdrfigsgsgtdftltiss vqaedlavyycqqyynfptfgsgtkleiktttpaprpptpaptiasqplslrpeacrpaagga vhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcs crfpeeeeggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemgg kprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhm qalppr
dominio CAR20-4 scFv	818	qvtlkesgpgilqpsqtlsltctftrfslstygmsvgwirqpsgkglewladiwwdddkhyn pslknrltiskdtsknqaflkitnvdtadtatyycarssttdgivtyvmdvwgqgasvtvssg gggsggggsggggsggggsdvqmtqspsllsasvgdavtinckasqninrylnwyqqkl gegprlliysanslqtgipsrfsgsgsgadftltitspqpedvatyfclqhnswpltfgsgtklei k
dominio CAR20-4 scFv nt	819	caagtcacgctgaaggaatcgggccctggaattctgcagccaagccagaccctctcgcttact tgcaccttcacccgcttctcactgtccacttacggaatgtccgtgggatggattcggcagccca gcggaaagggtttggagtggctggccgacatttggtgggatgacgacaagcattacaaccct agcctgaagaatcggctcaccatcagcaaagacacctccaagaaccaggcgttcctgaagat caccaacgtggataccgccgacactgcaacatactattgtgcccgctcctcaaccaccgatgg

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CAR20-4 – scFv - nt Soluble	820	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccc aagtcacgctgaaggaatcgggccctggaattctgcagccaagccagaccctctcgcttactt gcaccttcacccgcttctcactgtccacttacggaatgtccgtgggatggattcggcagcccag cggaaagggtttggagtggctggccgacatttggtgggatgacgacaagcattacaacccta gcctgaagaatcggctcaccatcagcaaagacacctccaagaaccaggcgttcctgaagatc accaacgtggataccgccgacactgcaacatactattgtgcccgctcctcaaccaccgatggg atcgtgacctacgtgatggacgtctggggccagggagcttccgtgaccgtgtcctccggcggt ggaggctcaggggggggcggctcgggaggggtggaagcggaggaggaggctccgac gtgcagatgactcagtccccgtcgctcctgtccgcctccgtcggcgacgccgtgactattaact gcaaggcgtcccagaacatcaatcggtacctgaactggtaccagcaaaaactgggagaagg gccgagacttctcatctactccgccaactccctgcaaactggcatcccgtcgaggttcagcgg atcaggctctggtgccgacttcactttgaccatcacgagccctcagcccgaagatgtggccac ctacttctgcctccaacacaactcctggcccctgacctttggttcgggcaccaagctggagatc aagggatcgcaccaccatcaccatcatcatcac
CAR20-4 – scFv -aa Soluble	821	malpvtalllplalllhaarpqvtlkesgpgilqpsqtlsltctftrfslstygmsvgwirqpsgk glewladiwwdddkhynpslknrltiskdtsknqaflkitnvdtadtatyycarssttdgivt yvmdvwgqgasvtvssggggsggggsggggsggggsdvqmtqspsllsasvgdavti nckasqninrylnwyqqklgegprlliysanslqtgipsrfsgsgsgadftltitspqpedvat yfclqhnswpltfgsgtkleikgshhhhhhhh
CAR20- 4 – Completo - nt	822	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccc aagtcacgctgaaggaatcgggccctggaattctgcagccaagccagaccctctcgcttactt gcaccttcacccgcttctcactgtccacttacggaatgtccgtgggatggattcggcagcccag cggaaagggtttggagtggctggccgacatttggtgggatgacgacaagcattacaacccta gcctgaagaatcggctcaccatcagcaaagacacctccaagaaccaggcgttcctgaagatc accaacgtggataccgccgacactgcaacatactattgtgcccgctcctcaaccaccgatggg atcgtgacctacgtgatggacgtctggggccagggagcttccgtgaccgtgtcctccggcggt ggaggctcaggggggggcggctcgggaggggtggaagcggaggaggaggctccgac gtgcagatgactcagtccccgtcgctcctgtccgcctccgtcggcgacgccgtgactattaact gcaaggcgtcccagaacatcaatcggtacctgaactggtaccagcaaaaactgggagaagg gccgagacttctcatctactccgccaactccctgcaaactggcatcccgtcgaggttcagcgg atcaggctctggtgccgacttcactttgaccatcacgagccctcagcccgaagatgtggccac ctacttctgcctccaacacaactcctggcccctgacctttggttcgggcaccaagctggagatc aagaccactaccccagcaccgaggccacccaccccggctcctaccatcgcctcccagcctct gtccctgcgtccggaggcatgtagacccgcagctggtggggccgtgcatacccggggtcttg acttcgcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcac tcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttca tgaggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagaggagga ggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaag caggggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacgacgtgct

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CAR20- 4 – Completo - aa	823	malpvtalllplalllhaarpqvtlkesgpgilqpsqtlsltctftrfslstygmsvgwirqpsgk glewladiwwdddkhynpslknrltiskdtsknqaflkitnvdtadtatyycarssttdgivt yvmdvwgqgasvtvssggggsggggsggggsggggsdvqmtqspsllsasvgdavti nckasqninrylnwyqqklgegprlliysanslqtgipsrfsgsgsgadftltitspqpedvat yfclqhnswpltfgsgtkleiktttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfa cdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeg gcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqe glynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr
dominio CAR20-5 scFv	824	evqlvesggglvqpgtslklscvasgftfsssgmqwirqapkkglewisgiyydsykksy adsvkgrftisrdnskntlylemnslrsedtatyycaksayygykdyfdywgqgvmvtvs sggggsggggsggggsggggsdiqmtqsppslsaslgdkvtitcqasqninkyiawyqq kpgkaprllirytstlesgtpsrfsgsgsgrdysfsisnvesgdvasyyclqyddlpytfgpgt klelk
dominio CAR20-5 scFv nt	825	gaggtccagcttgtggaatcaggaggcggactcgtccagccgggtactagcctgaagctcag ctgtgtggccagcggttttaccttctcgtcctccgggatgcagtggattcggcaggctcccaag aagggactggaatggatctcgggcatctactacgactcgtacaagaagtcctacgccgattcc gtgaaaggtcgcttcaccatctcccgggacaacagcaagaacactctgtacctcgagatgaac tccttgcgctccgaggataccgcaacctattactgcgccaagtcggcctactacggctacaag gactacttcgactattggggccagggagtgatggtgaccgtgtcctccggcggtggaggctc agggggggcggctcgggaggggtggaagcggaggaggaggctccgacatccaaatg acacagtcacccccttctctttccgcgagcctgggagataaggtcaccattacgtgccaagcgt cccagaacatcaacaagtacatcgcctggtaccagcagaaaccgggaaaggccccgcggct gctgattagatacacctcgactctggaatccggcactccatcaagattcagcggctccggcag cgggagggactactcgttctccatctccaatgtggagtccggggacgtggccagctactattg cctgcaatacgacgatctgccctacaccttcggacctggaaccaagctggaactcaag
CAR20-5 - scFv - nt Soluble	826	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg aggtccagcttgtggaatcaggaggcggactcgtccagccgggtactagcctgaagctcagc tgtgtggccagcggttttaccttctcgtcctccgggatgcagtggattcggcaggctcccaaga agggactggaatggatctcgggcatctactacgactcgtacaagaagtcctacgccgattccg tgaaaggtcgcttcaccatctcccgggacaacagcaagaacactctgtacctcgagatgaact ccttgcgctccgaggataccgcaacctattactgcgccaagtcggcctactacggctacaagg actacttcgactattggggccagggagtgatggtgaccgtgtcctccggcggtggaggctca ggggggggcggctcgggaggggtggaagcggaggaggaggctccgacatccaaatga cacagtcacccccttctctttccgcgagcctgggagataaggtcaccattacgtgccaagcgtc ccagaacatcaacaagtacatcgcctggtaccagcagaaaccgggaaaggccccgcggct gctgattagatacacctcgactctggaatccggcactccatcaagattcagcggctccggcag cgggagggactactcgttctccatctccaatgtggagtccggggacgtggccagctactattg cctgcaatacgacgatctgccctacaccttcggacctggaaccaagctggaactcaagggatc gcaccaccatcaccatcatcatcac
CAR20-5 - scFv -aa Soluble	827	malpvtalllplalllhaarpevqlvesggglvqpgtslklscvasgftfsssgmqwirqapk kglewisgiyydsykksyadsvkgrftisrdnskntlylemnslrsedtatyycaksayygy kdyfdywgqgvmvtvssggggsggggsggggsggggsdiqmtqsppslsaslgdkvti tcqasqninkyiawyqqkpgkaprllirytstlesgtpsrfsgsgsgrdysfsisnvesgdva

		syyclqyddlpytfgpgtklelkgshhhhhhhh
CAR20- 5 – Completo - nt	828	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg aggtccagcttgtggaatcaggaggcggactcgtccagccgggtactagcctgaagctcagc tgtgtggccagcggttttaccttctcgtcctccgggatgcagtggattcggcaggctcccaaga agggactggaatggatctcgggcatctactacgactcgtacaagaagtcctacgccgattccg tgaaaggtcgcttcaccatctcccgggacaacagcaagaacactctgtacctcgagatgaact ccttgcgctccgaggataccgcaacctattactgcgccaagtcggcctactacggctacaagg actacttcgactattggggccagggagtgatggtgaccgtgtcctccggcggtggaggctca ggggggggcggctcgggaggggggtggaagcggaggaggaggctccgacatccaaatga cacagtcacccccttctctttccgcgagcctgggagataaggtcaccattacgtgccaagcgtc ccagaacatcaacaagtacatcgcctggtaccagcagaaaccgggaaaggccccgcggct gctgattagatacacctcgactctggaatccggcactccatcaagattcagcggctccggcag cgggagggactactcgttctccatctccaatgtggagtccggggacgtggccagctactattg cctgcaatacgacgatctgccctacaccttcggacctggaaccaagctggaactcaagacca ctaccccagcaccgaggccacccaccccggctcctaccatcgcctcccagcctctgtccctg cgtccggaggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgc ctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgat cactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggc ctgtgcagactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaagg cggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcagggg cagaaccagctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaa gcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagag ggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagattggtatgaa aggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccgcca ccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR20- 5 – Completo - aa	829	malpvtalllplalllhaarpevqlvesggglvqpgtslklscvasgftfsssgmqwirqapk kglewisgiyydsykksyadsvkgrftisrdnskntlylemnslrsedtatyycaksayygy kdyfdywgqgvmvtvssggggsggggsggggsggggsdiqmtqsppslsaslgdkvti tcqasqninkyiawyqqkpgkaprllirytstlesgtpsrfsgsgsgrdysfsisnvesgdva syyclqyddlpytfgpgtklelktttpaprpptpaptiasqplslrpeacrpaaggavhtrgld facdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeee eggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknp qeglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr
dominio CAR20-6 scFv	830	qvtlkesgpgllqpsqtlsltctfagfslnthgmgvgwirqpsgkglewlaniwwdddky ynpslknrltmskdtsnnqaflkitnvdtadtatyycariegspvvttvfdywgqgvmvtv ssggggsggggsggggsggggsdiqmtqspsflsasvgdrvtinckasqninrylnwyq qklgeapklliynanslqtgipsrfsgsgsgtdftltisslqpadvatyfclqhnsrpltfgsgtil eik
dominio CAR20-6 scFv nt	831	caagtcactcttaaggaatccgggccaggactgttgcagccgagccagaccctgtccctcact tgtaccttcgccggcttttcactgaacacccacggaatgggcgtgggatggattaggcagccc tcgggaaagggactggagtggctggccaacatttggtgggacgacgacaagtattacaaccc gagcctcaagaaccgcctgactatgtccaaggatacctccaacaaccaggccttcctgaaaat cactaacgtggataccgctgacaccgcaacgtactactgcgcccggatcgaaggttcccccg tcgtgacaactgtgttcgactactggggacagggcgtgatggtgaccgtgtcctccggcggtg gaggctcaggggggggcggctcgggaggggggtggaagcggaggaggaggctccgacat ccaaatgacccagtcacctagctttctgtcggcctcggtcggcgacagagtgaccattaactgc aaagcgtcccagaacatcaaccgctacctgaattggtaccagcagaagctgggggaagccc

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CAR20-6 - scFv - nt Soluble	832	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccc aagtcactcttaaggaatccgggccaggactgttgcagccgagccagaccctgtccctcactt gtaccttcgccggcttttcactgaacacccacggaatgggcgtgggatggattaggcagccct cgggaaagggactggagtggctggccaacatttggtgggacgacgacaagtattacaaccc gagcctcaagaaccgcctgactatgtccaaggatacctccaacaaccaggccttcctgaaaat cactaacgtggataccgctgacaccgcaacgtactactgcgcccggatcgaaggttcccccg tcgtgacaactgtgttcgactactggggacagggcgtgatggtgaccgtgtcctccggcggtg gaggctcaggggggggcggctcgggaggggtggaagcggaggaggaggctccgacat ccaaatgacccagtcacctagctttctgtcggcctcggtcggcgacagagtgaccattaactgc aaagcgtcccagaacatcaaccgctacctgaattggtaccagcagaagctgggggaagccc cgaagctgctgatctacaacgcgaacagcctccagactggtattccttcccggttctccggga gcggctcgggtaccgatttcaccctcaccatctcctcccttcaacccgctgacgtggccaccta cttctgcttgcaacataattctcggcctctgaccttcggaagcggcactatcctcgagatcaagg gatcgcaccaccatcaccatcatcatcac
CAR20-6 - scFv - aa Soluble	833	malpvtalllplalllhaarpqvtlkesgpgllqpsqtlsltctfagfslnthgmgvgwirqpsg kglewlaniwwdddkyynpslknrltmskdtsnnqaflkitnvdtadtatyycariegspv vttvfdywgqgvmvtvssggggsggggsggggsggggsdiqmtqspsflsasvgdrvti nckasqninrylnwyqqklgeapklliynanslqtgipsrfsgsgsgtdftltisslqpadvat yfclqhnsrpltfgsgtileikgshhhhhhhh
CAR20-6 – Completo - nt	834	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccc aagtcactcttaaggaatccgggccaggactgttgcagccgagccagaccctgtccctcactt gtaccttcgccggcttttcactgaacacccacggaatgggcgtgggatggattaggcagccct cgggaaagggactggagtggctggccaacatttggtgggacgacgacaagtattacaaccc gagcctcaagaaccgcctgactatgtccaaggatacctccaacaaccaggccttcctgaaaat cactaacgtggataccgctgacaccgcaacgtactactgcgcccggatcgaaggttcccccg tcgtgacaactgtgttcgactactggggacagggcgtgatggtgaccgtgtcctccggcggtg gaggctcaggggggggcggctcgggaggggtggaagcggaggaggaggctccgacat ccaaatgacccagtcacctagctttctgtcggcctcggtcggcgacagagtgaccattaactgc aaagcgtcccagaacatcaaccgctacctgaattggtaccagcagaagctgggggaagccc cgaagctgctgatctacaacgcgaacagcctccagactggtattccttcccggttctccggga gcggctcgggtaccgatttcaccctcaccatctcctcccttcaacccgctgacgtggccaccta cttctgcttgcaacataattctcggcctctgaccttcggaagcggcactatcctcgagatcaaga ccactaccccagcaccgaggccacccaccccggctcctaccatcgcctcccagcctctgtcc ctgcgtccggaggcatgtagacccgcagctggtggggccgtgcataccccggggtcttgactt cgcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcactcgt gatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatga ggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagaggaggagga aggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcag gggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctgg acaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaatcccca agagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagattggta tgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcacc gccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR20-6 –	835	malpvtalllplalllhaarpqvtlkesgpgllqpsqtlsltctfagfslnthgmgvgwirqpsg

Completo – aa		kglewlaniwwdddkyynpslknrltmskdtsnnqaflkitnvdtadtatyycariegspv vttvfdywgqgvmvtvssggggsggggsggggsggggsdiqmtqspsflsasvgdrvti nckasqninrylnwyqqklgeapkllliynanslqtgipsrfsgsgsgtdftltisslqpadvat yfclqhnsrpltfgsgtileiktttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfac diyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeegg celrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeg lynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr
dominio CAR20-7 scFv	836	qvtlkesgpgmlqpsktlsltcsfsgfslstsgmvvswirqpsgkslewlaaiawdgdkyy npslksrvtvskdtsntqvflritsvdiadtatyyctrrdydvgyyyfdfwgqgvmvtvssg gggsggggsggggsggggskivltqsptitaaspgekvtitclassrvsniywyqqksgas pkllivstsslasgvpyrfsgsgsgtsysltintmeaedaatyychqwssnpwtfgggtklel k
dominio CAR20-7 scFv nt	837	caagtcaccctgaaagaatcgggtcccggaatgctgcagccatccaagacgctgtcccttaca tgctccttctccgggttcagcctctcaacttccgggatggtggtgtcatggatcagacagccga gcggaaagtccctggagtggctggcggccatcgcatgggatggcgataagtactacaaccc gagcctgaagtcaagggtcactgtgtccaaggacacctccaacacccaagtgttccttcggat cacctccgtggacattgctgacaccgccacctattactgcactcgccgggactacgacgtggg ctactactacttcgatttctggggacagggtgtcatggtgaccgtgtcctccggcggtggaggc tcagggggggggcggctcgggaggggtggaagcggaggaggaggctccaagattgtgct gacccagagccccactattaccgccgcctccccgggggaaaaggtcaccatcacttgtctgg cgtcctcacgcgtgtcgaatatctactggtatcagcagaagtccggcgccagccccaagctgc tgatctactcgacctcctccctcgcgtcgggagtgccttaccggttttctggctcgggaagcgg aaccagctactccttgaccatcaacaccatggaagccgaggacgctgccacttactactgcca ccagtggtcgagcaacccttggactttcggtggaggcaccaaactcgagctcaag
CAR20-7 - scFv - nt Soluble	838	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccc aagtcaccctgaaagaatcgggtcccggaatgctgcagccatccaagacgctgtcccttacat gctccttctccgggttcagcctctcaacttccgggatggtggtgtcatggatcagacagccgag cggaaagtccctggagtggctggcggccatcgcatgggatggcgataagtactacaacccg agcctgaagtcaagggtcactgtgtccaaggacacctccaacacccaagtgttccttcggatc acctccgtggacattgctgacaccgccacctattactgcactcgccgggactacgacgtgggc tactactacttcgatttctggggacagggtgtcatggtgaccgtgtcctccggcggtggaggct cagggggggggcggctcgggaggggtggaagcggaggaggaggctccaagattgtgctg acccagagccccactattaccgccgcctccccgggggaaaaggtcaccatcacttgtctggc gtcctcacgcgtgtcgaatatctactggtatcagcagaagtccggcgccagccccaagctgct gatctactcgacctcctccctcgcgtcgggagtgccttaccggttttctggctcgggaagcgga accagctactccttgaccatcaacaccatggaagccgaggacgctgccacttactactgccac cagtggtcgagcaacccttggactttcggtggaggcaccaaactcgagctcaagggatcgca ccaccatcaccatcatcatcac
CAR20-7 - scFv - aa Soluble	839	malpvtalllplalllhaarpqvtlkesgpgmlqpsktlsltcsfsgfslstsgmvvswirqps gkslewlaaiawdgdkyynpslksrvtvskdtsntqvflritsvdiadtatyyctrrdydvgy yyfdfwgqgvmvtvssggggsggggsggggsggggskivltqsptitaaspgekvtitcl assrvsniywyqqksgaspkllivstsslasgvpyrfsgsgsgtsysltintmeaedaatyyc hqwssnpwtfgggtklelkgshhhhhhhh
CAR20- 7 Completo - nt	840	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccc aagtcaccctgaaagaatcgggtcccggaatgctgcagccatccaagacgctgtcccttacat gctccttctccgggttcagcctctcaacttccgggatggtggtgtcatggatcagacagccgag cggaaagtccctggagtggctggcggccatcgcatgggatggcgataagtactacaacccg

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CAR20- 7 Completo - aa	841	malpvtalllplalllhaarpqvtlkesgpgmlqpsktlsltcsfsgfslstsgmvvswirqps gkslewlaaiawdgdkyynpslksrvtvskdtsntqvflritsvdiadtatyyctrrdydvgy yyfdfwgqgvmvtvssggggsggggsggggsggggskivltqsptitaaspgekvtitcl assrvsniywyqqksgaspkllivstsslasgvpyrfsgsgsgtsysltintmeaedaatyyc hqwssnpwtfgggtklelkttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfac diyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeegg celrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeg lynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr
dominio CAR20-8 scFv	842	qiqlvqsgpelkkpgesvkisckasgntvtgyamhwvrqapgkglkwmgwintysgk ptyaddfkgrcvfsleasastahlqisnlknedtatyfcarstyygykdwfaywgqgtlvtv ssggggsggggsggggsggggsniqltqspsrlsasvgdrvtlsckgsqninnylawyqq klgeapklliyntnnlqtgipsrfsgsgsgtdytftisglqpedvatyfccqynngntfgagtkl elk
dominio CAR20-8 scFv nt	843	caaattcagttggtgcagtccggcccggagctgaagaagcctggagaatccgtgaagatctc gtgcaaagcttccgggaacaccgtgaccggatacgcaatgcactgggtccgccaggcaccg ggaaagggactgaagtggatggggtggatcaacacctacagcggaaagccgacttacgcc gatgactttaagggacgctgtgtgttctccctggaagcgtccgcctcgactgcccatcttcaaat ctccaacctgaagaatgaggacaccgccacttacttctgcgcccggagcacctattacggcta caaggactggttcgcgtattggggccagggcactctcgtgaccgtgtcctccggcggtggag gctcaggggggggcggctcgggaggggtggaagcggaggaggaggctccaacatcca actgactcagagccccagccggctgtccgcctccgtgggggacagggtcacactgagctgc aagggttctcagaacatcaacaactacctcgcgtggtaccagcagaagctgggagaggccc ccaagctgctcatctacaacaccaacaatctgcaaactggcattccatcgagattctcaggatc agggtccggtaccgactacaccttcacgatttcgggacttcagcctgaggatgtggccaccta cttctgctgtcagtacaacaacggcaacaccttcggtgctggcaccaagctggaactcaaa
CAR20-8 - scFv - nt	844	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccc aaattcagttggtgcagtccggcccggagctgaagaagcctggagaatccgtgaagatctcgt

Soluble		gcaaagcttccgggaacaccgtgaccggatacgcaatgcactgggtccgccaggcaccgg gaaagggactgaagtggatggggtggatcaacacctacagcggaaagccgacttacgccga tgactttaagggacgctgtgtgttctccctggaagcgtccgcctcgactgcccatcttcaaatct ccaacctgaagaatgaggacaccgccacttacttctgcgcccggagcacctattacggctaca aggactggttcgcgtattggggccagggcactctcgtgaccgtgtcctccggcggtggaggc tcaggggggggcggctcgggaggggtggaagcggaggaggaggctccaacatccaact gactcagagccccagccggctgtccgcctccgtgggggacagggtcacactgagctgcaag ggttctcagaacatcaacaactacctcgcgtggtaccagcagaagctgggagaggcccccaa gctgctcatctacaacaccaacaatctgcaaactggcattccatcgagattctcaggatcaggg tccggtaccgactacaccttcacgatttcgggacttcagcctgaggatgtggccacctacttctg ctgtcagtacaacaacggcaacaccttcggtgctggcaccaagctggaactcaaaggatcgc accaccatcaccatcatcatcac
CAR20-8 - scFv - aa Soluble	845	malpvtalllplalllhaarpqiqlvqsgpelkkpgesvkisckasgntvtgyamhwvrqa pgkglkwmgwintysgkptyaddfkgrcvfsleasastahlqisnlknedtatyfcarsty ygykdwfaywgqgtlvtvssggggsggggsggggsggggsniqltqspsrlsasvgdrvt lsckgsqninnylawyqqklgeapklliyntnnlqtgipsrfsgsgsgtdytftisglqpedv atyfccqynngntfgagtklelkgshhhhhhhh
CAR20-8 – Completo - nt	846	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccc aaattcagttggtgcagtccggcccggagctgaagaagcctggagaatccgtgaagatctcgt gcaaagcttccgggaacaccgtgaccggatacgcaatgcactgggtccgccaggcaccgg gaaagggactgaagtggatggggtggatcaacacctacagcggaaagccgacttacgccga tgactttaagggacgctgtgtgttctccctggaagcgtccgcctcgactgcccatcttcaaatct ccaacctgaagaatgaggacaccgccacttacttctgcgcccggagcacctattacggctaca aggactggttcgcgtattggggccagggcactctcgtgaccgtgtcctccggcggtggaggc tcaggggggggcggctcgggaggggtggaagcggaggaggaggctccaacatccaact gactcagagccccagccggctgtccgcctccgtgggggacagggtcacactgagctgcaag ggttctcagaacatcaacaactacctcgcgtggtaccagcagaagctgggagaggcccccaa gctgctcatctacaacaccaacaatctgcaaactggcattccatcgagattctcaggatcaggg tccggtaccgactacaccttcacgatttcgggacttcagcctgaggatgtggccacctacttctg ctgtcagtacaacaacggcaacaccttcggtgctggcaccaagctggaactcaaaaccacta ccccagcaccgaggccacccaccccggctcctaccatcgcctcccagcctctgtccctgcgt ccggaggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctg cgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcac tctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctg tgcagactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcgg ctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcag aaccagctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcg gagaggacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggc ctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaagg ggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccgccacca aggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR20-8 – Completo - aa	847	malpvtalllplalllhaarpqiqlvqsgpelkkpgesvkisckasgntvtgyamhwvrqa pgkglkwmgwintysgkptyaddfkgrcvfsleasastahlqisnlknedtatyfcarsty ygykdwfaywgqgtlvtvssggggsggggsggggsggggsniqltqspsrlsasvgdrvt lsckgsqninnylawyqqklgeapklliyntnnlqtgipsrfsgsgsgtdytftisglqpedv atyfccqynngntfgagtklelktttpaprpptpaptiasqplslrpeacrpaaggavhtrgld facdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeee

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dominio CAR20-9 scFv	848	divmtqtpssqavsagekvtmsckssqsllysenkknylawyqqkpgqspkllifwastr esgvpdrfigsgsgtdftltissvqaedlavyycqqyynfptfgsgtkleikggggsggggs ggggsggggsevqlvesggglvqpgrslklscaasgftfrdyymawvrqapkkglewva sisyegnpyygdsvkgrftisrnnakstlylqmnslrsedtatyycarhdhnnvdwfayw gqgtlvtvss
dominio CAR20-9 scFv nt	849	gacatcgtgatgactcagactccaagcagccaggccgtgtccgccggagagaaagtcacca tgtcgtgcaagagctcccagtccctgctgtactccgaaaacaagaagaattatctcgcctggta ccagcagaagcctggacagtccccgaagctcctgatcttttgggcgtcgaccagggaatccg gcgtgcccgatcgcttcattggctccggttccggcaccgacttcaccctgaccattagcagcgt ccaggcggaggacctggctgtgtactactgccaacagtactacaacttccccactttcggatcg gggaccaagctggagatcaagggcggtggaggctcaggggggggcggctcgggagggg gtggaagcggaggaggaggctccgaagtgcagcttgtggagtctggcggcggtctggtgca gccgggaagatccctgaagctgtcatgcgccgcgtccgggtttaccttccgcgattactacatg gcctgggtcagacaggcacctaagaaggggctggaatgggtggcatccatctcatatgaagg aaacccgtactacggagactcggtgaaaggccgcttcactatctcacggaacaacgctaaga gcacgctgtacttgcaaatgaactccctccggtcggaggacacagccacttactactgtgccc ggcacgaccataacaacgtcgattggttcgcctactggggtcaaggaaccctcgtgaccgtgt cctcc
CAR20-9 - scFv - nt Soluble	850	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg acatcgtgatgactcagactccaagcagccaggccgtgtccgccggagagaaagtcaccat gtcgtgcaagagctcccagtccctgctgtactccgaaaacaagaagaattatctcgcctggtac cagcagaagcctggacagtccccgaagctcctgatcttttgggcgtcgaccagggaatccgg cgtgcccgatcgcttcattggctccggttccggcaccgacttcaccctgaccattagcagcgtc caggcggaggacctggctgtgtactactgccaacagtactacaacttccccactttcggatcg gggaccaagctggagatcaagggcggtggaggctcaggggggggcggctcgggagggg gtggaagcggaggaggaggctccgaagtgcagcttgtggagtctggcggcggtctggtgca gccgggaagatccctgaagctgtcatgcgccgcgtccgggtttaccttccgcgattactacatg gcctgggtcagacaggcacctaagaaggggctggaatgggtggcatccatctcatatgaagg aaacccgtactacggagactcggtgaaaggccgcttcactatctcacggaacaacgctaaga gcacgctgtacttgcaaatgaactccctccggtcggaggacacagccacttactactgtgccc ggcacgaccataacaacgtcgattggttcgcctactggggtcaaggaaccctcgtgaccgtgt cctccggatcgcaccaccatcaccatcatcatcac
CAR20-9 - scFv - aa Soluble	851	malpvtalllplalllhaarpdivmtqtpssqavsagekvtmsckssqsllysenkknylaw yqqkpgqspkllifwastresgvpdrfigsgsgtdftltissvqaedlavyycqqyynfptfg sgtkleikggggsggggsggggsggggsevqlvesggglvqpgrslklscaasgftfrdyy mawvrqapkkglewvasisyegnpyygdsvkgrftisrnnakstlylqmnslrsedtaty ycarhdhnnvdwfaywgqgtlvtvssgshhhhhhhh
CAR20- 9 – Completo - nt	852	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg acatcgtgatgactcagactccaagcagccaggccgtgtccgccggagagaaagtcaccat gtcgtgcaagagctcccagtccctgctgtactccgaaaacaagaagaattatctcgcctggtac cagcagaagcctggacagtccccgaagctcctgatcttttgggcgtcgaccagggaatccgg cgtgcccgatcgcttcattggctccggttccggcaccgacttcaccctgaccattagcagcgtc caggcggaggacctggctgtgtactactgccaacagtactacaacttccccactttcggatcg gggaccaagctggagatcaagggcggtggaggctcaggggggggcggctcgggagggg gtggaagcggaggaggaggctccgaagtgcagcttgtggagtctggcggcggtctggtgca

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CAR20- 9 – Completo - aa	853	malpvtalllplalllhaarpdivmtqtpssqavsagekvtmsckssqsllysenkknylaw yqqkpgqspkllifwastresgvpdrfigsgsgtdftltissvqaedlavyycqqyynfptfg sgtkleikggggsggggsggggsggggsevqlvesggglvqpgrslklscaasgftfrdyy mawvrqapkkglewvasisyegnpyygdsvkgrftisrnnakstlylqmnslrsedtaty ycarhdhnnvdwfaywgqgtlvtvsstttpaprpptpaptiasqplslrpeacrpaaggav htrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscr fpeeeeggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkp rrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqa lppr
dominio CAR20-10 scFv	854	diqmtqsppslsaslgdkvtitcqasqninkyiawyqqkpgkaprllirytstlesgtpsrfsg sgsgrdysfsisnvesgdvasyyclqyddlpytfgpgtklelkggggsggggsggggsgg ggsevqlvesggglvqpgtslklscvasgftfsssgmqwirqapkkglewisgiyydsyk ksyadsvkgrftisrdnsknt lylemnslrsedtatyycaksayygykdyfdywgqgvm vtvss
dominio CAR20-10 scFv nt	855	gacatccaaatgacacagtcacccccttctctttccgcgagcctgggagataaggtcaccatta cgtgccaagcgtcccagaacatcaacaagtacatcgcctggtaccagcagaaaccgggaaa ggccccgcggctgctgattagatacacctcgactctggaatccggcactccatcaagattcag cggctccggcagcgggagggactactcgttctccatctccaatgtggagtccggggacgtgg ccagctactattgcctgcaatacgacgatctgccctacaccttcggacctggaaccaagctgg aactcaagggcggtggaggctcagggggggcggctcgggaggggtggaagcggagg aggaggctccgaggtccagcttgtggaatcaggaggcggactcgtccagccgggtactagc ctgaagctcagctgtgtggccagcggttttaccttctcgtcctccgggatgcagtggattcggc aggctcccaagaagggactggaatggatctcgggcatctactacgactcgtacaagaagtcct acgccgattccgtgaaaggtcgcttcaccatctcccgggacaacagcaagaacactctgtacc tcgagatgaactccttgcgctccgaggataccgcaacctattactgcgccaagtcggcctacta cggctacaaggactacttcgactattggggccagggagtgatggtgaccgtgtcctcc
CAR20-10 - scFv - nt Soluble	856	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg acatccaaatgacacagtcacccccttctctttccgcgagcctgggagataaggtcaccattac gtgccaagcgtcccagaacatcaacaagtacatcgcctggtaccagcagaaaccgggaaag gccccgcggctgctgattagatacacctcgactctggaatccggcactccatcaagattcagc ggctccggcagcgggagggactactcgttctccatctccaatgtggagtccggggacgtggc

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CAR20-10 - scFv - aa Soluble	857	malpvtalllplalllhaarpdiqmtqsppslsaslgdkvtitcqasqninkyiawyqqkpg kaprllirytstlesgtpsrfsgsgsgrdysfsisnvesgdvasyyclqyddlpytfgpgtklel kggggsggggsggggsggggsevqlvesggglvqpgtslklscvasgftfsssgmqwir qapkkglewisgiyydsykksyadsvkgrftisrdnsknt lylemnslrsedtatyycaksa yygykdyfdywgqgvmvtvssgshhhhhhhh
194181 CAR20- 10 – Completo - nt	858	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg acatccaaatgacacagtcacccccttctctttccgcgagcctgggagataaggtcaccattac gtgccaagcgtcccagaacatcaacaagtacatcgcctggtaccagcagaaaccgggaaag gccccgcggctgctgattagatacacctcgactctggaatccggcactccatcaagattcagc ggctccggcagcgggagggactactcgttctccatctccaatgtggagtccggggacgtggc cagctactattgcctgcaatacgacgatctgccctacaccttcggacctggaaccaagctgga actcaagggcggtggaggctcaggggggggcggctcgggaggggtggaagcggagga ggaggctccgaggtccagcttgtggaatcaggaggcggactcgtccagccgggtactagcc tgaagctcagctgtgtggccagcggttttaccttctcgtcctccgggatgcagtggattcggca ggctcccaagaagggactggaatggatctcgggcatctactacgactcgtacaagaagtccta cgccgattccgtgaaaggtcgcttcaccatctcccgggacaacagcaagaacactctgtacct cgagatgaactccttgcgctccgaggataccgcaacctattactgcgccaagtcggcctacta cggctacaaggactacttcgactattggggccagggagtgatggtgaccgtgtcctccaccac taccccagcaccgaggccacccaccccggctcctaccatcgcctcccagcctctgtccctgc gtccggaggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcc tgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatc actctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcc tgtgcagactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggc ggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggc agaaccagctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaag cggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagaggg gcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaa ggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccgccac caaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
194181 CAR20- 10 – Completo - aa	859	malpvtalllplalllhaarpdiqmtqsppslsaslgdkvtitcqasqninkyiawyqqkpg kaprllirytstlesgtpsrfsgsgsgrdysfsisnvesgdvasyyclqyddlpytfgpgtklel kggggsggggsggggsggggsevqlvesggglvqpgtslklscvasgftfsssgmqwir qapkkglewisgiyydsykksyadsvkgrftisrdnsknt lylemnslrsedtatyycaksa yygykdyfdywgqgvmvtvsstttpaprpptpaptiasqplslrpeacrpaaggavhtrgl dfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpee eeggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrkn pqeglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr
dominio	860	divmtqtpssqavsagekvtmsckssqsllysenkknylawyqqkpgqspklliywastr

CAR20-11 scFv		esgvpdrfigsgsgtdftltissvqaedlavyycqqyynfppwtfgggtklelkggggsggg gsggggsggggsqiqlvqsgpelkkpgesvkiscktseytftdyafhwvkqapgkglkw mgwintysgkptyaddfkgrfvfsledsartanlqisnlknedtatyfcargayygyrdwft ywgqgtlvtvss
dominio CAR20-11 scFv nt	861	gatattgtgatgacccagaccccgtcgagccaggcagtgtccgctggagaaaaggtcaccat gtcctgcaagagctcacagtccctgttgtactccgaaaacaagaagaattacctggcctggtac cagcagaagcccggacagtcccctaaactgctgatctactgggcctcgactagggaatctgg cgtgcccgaccgctttatcggaagcggttcagggactgacttcaccctgaccattagcagcgt gcaggccgaggacctggcggtgtactactgtcaacagtactacaacttcccgccctggacttt cggcggtggaacgaagctcgaactcaagggcggtggaggctcagggggggcggctcgg gaggggtggaagcggaggaggaggctcccaaattcaactggtccagtccggccctgagct gaagaagccgggagaatccgtgaagatctcctgcaagacctcggagtacaccttcactgact acgccttccactgggtcaagcaggcacctgggaaaggcctgaagtggatgggctggatcaa cacttactcggggaagccaacctacgccgatgatttcaagggaagattcgtgtttagcctggag gactccgcccggacagctaacctccaaatctccaaccttaagaacgaggacactgcgaccta cttctgcgcgcggggagcctattacggttatcgcgactggttcacctactggggacagggcac cctcgtgaccgtgtcctcc
CAR20-11 -Soluble scFv - nt	862	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg atattgtgatgacccagaccccgtcgagccaggcagtgtccgctggagaaaaggtcaccatg tcctgcaagagctcacagtccctgttgtactccgaaaacaagaagaattacctggcctggtacc agcagaagcccggacagtcccctaaactgctgatctactgggcctcgactagggaatctggc gtgcccgaccgctttatcggaagcggttcagggactgacttcaccctgaccattagcagcgtg caggccgaggacctggcggtgtactactgtcaacagtactacaacttcccgccctggactttc ggcggtggaacgaagctcgaactcaagggcggtggaggctcagggggggcggctcggg aggggtggaagcggaggaggaggctcccaaattcaactggtccagtccggccctgagctg aagaagccgggagaatccgtgaagatctcctgcaagacctcggagtacaccttcactgacta cgccttccactgggtcaagcaggcacctgggaaaggcctgaagtggatgggctggatcaac acttactcggggaagccaacctacgccgatgatttcaagggaagattcgtgtttagcctggag gactccgcccggacagctaacctccaaatctccaaccttaagaacgaggacactgcgaccta cttctgcgcgcggggagcctattacggttatcgcgactggttcacctactggggacagggcac cctcgtgaccgtgtcctccggatcgcaccaccatcaccatcatcatcac
CAR20-11 -Soluble scFv - aa	863	malpvtalllplalllhaarpdivmtqtpssqavsagekvtmsckssqsllysenkknylaw yqqkpgqspklliywastresgvpdrfigsgsgtdftltissvqaedlavyycqqyynfpp wtfgggtklelkggggsggggsggggsggggsqiqlvqsgpelkkpgesvkiscktseyt ftdyafhwvkqapgkglkwmgwintysgkptyaddfkgrfvfsledsartanlqisnlkn edtatyfcargayygyrdwftywgqgtlvtvssgshhhhhhhh
CAR20- 11 – Completo - nt	864	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg atattgtgatgacccagaccccgtcgagccaggcagtgtccgctggagaaaaggtcaccatg tcctgcaagagctcacagtccctgttgtactccgaaaacaagaagaattacctggcctggtacc agcagaagcccggacagtcccctaaactgctgatctactgggcctcgactagggaatctggc gtgcccgaccgctttatcggaagcggttcagggactgacttcaccctgaccattagcagcgtg caggccgaggacctggcggtgtactactgtcaacagtactacaacttcccgccctggactttc ggcggtggaacgaagctcgaactcaagggcggtggaggctcagggggggcggctcggg aggggtggaagcggaggaggaggctcccaaattcaactggtccagtccggccctgagctg aagaagccgggagaatccgtgaagatctcctgcaagacctcggagtacaccttcactgacta cgccttccactgggtcaagcaggcacctgggaaaggcctgaagtggatgggctggatcaac acttactcggggaagccaacctacgccgatgatttcaagggaagattcgtgtttagcctggag

		gactccgcccggacagctaacctccaaatctccaaccttaagaacgaggacactgcgaccta cttctgcgcgcggggagcctattacggttatcgcgactggttcacctactggggacagggcac cctcgtgaccgtgtcctccaccactaccccagcaccgaggccacccaccccggctcctacca tcgcctcccagcctctgtccctgcgtccggaggcatgtagacccgcagctggtggggccgtg catacccggggtcttgacttcgcctgcgatatctacatttgggcccctctggctggtacttgcgg ggtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcggaagaagctgctgtacat ctttaagcaacccttcatgaggcctgtgcagactactcaagaggaggacggctgttcatgccg gttcccagaggaggaggaaggcggctgcgaactgcgcgtgaaattcagccgcagcgcaga tgctccagcctacaagcaggggcagaaccagctctacaacgaactcaatcttggtcggagag aggagtacgacgtgctggacaagcggagaggacgggacccagaaatgggcgggaagcc gcgcagaaagaatccccaagagggcctgtacaacgagctccaaaaggataagatggcaga agcctatagcgagattggtatgaaaggggaacgcagaagaggcaaaggccacgacggact gtaccagggactcagcaccgccaccaaggacacctatgacgctcttcacatgcaggccctgc cgcctcgg
CAR20-11 – Completo - aa	865	malpvtalllplalllhaarpdivmtqtpssqavsagekvtmsckssqsllysenkknylaw yqqkpgqspklliywastresgvpdrfigsgsgtdftltissvqaedlavyycqqyynfpp wtfgggtklelkggggsggggsggggsggggsqiqlvqsgpelkkpgesvkiscktseyt ftdyafhwvkqapgkglkwmgwintysgkptyaddfkgrfvfsledsartanlqisnlkn edtatyfcargayygyrdwftywgqgtlvtvsstttpaprpptpaptiasqplslrpeacrpa aggavhtrgldfacdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqee dgcscrfpeeeeggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpe mggkprrknpqeglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtyd alhmqalppr
dominio CAR20-12 scFv	866	qvvltqpksvstslestvklsckinsgnigsyfihwyqqhegrspttmiyrddkrphgvpdr fsgsidsssnsafltinnvqtedeaiyfchsydsginivfgggtkltvlggggsggggsgggg sggggsevqlvesggglvqpgrslklsclasgftfskygmnwirqapgkglewvasissts iyiyyadtvkgrftisrenakntlylqmtslrsedtalyycarhdyssysywgqgvmvtvss
dominio CAR20-12 scFv nt	867	caagtcgtgctgacgcaacccaagtccgtgagcaccagcctggagagcaccgtgaagctca gctgcaagattaactcgggcaacattgggtcctacttcatccattggtaccagcagcacgaag gacggtcccctaccactatgatctaccgggacgacaagcggccgcacggagtgccggaca gattctcgggttcaatcgattcctcatctaactcggcgtttctcaccatcaacaacgtgcagacc gaggacgaagcgatctacttctgccactcctacgactcgggtattaacattgtgttcggcggcg ggactaagctgacagtgctgggcggtggaggctcaggggggggcggctcgggaggggggt ggaagcggaggaggaggctccgaggtgcagctcgtcgaatccggtggaggactggtgcag ccaggaagatccctgaagctgtcctgtctcgcctcgggcttcactttctccaaatacggcatga attggattcgccaggcacccggaaaggggctggaatgggtggccagcatcagctcgactag catctacatctactatgccgataccgtcaagggccgcttcactatctcccgcgagaacgctaag aacacccctttacttgcaaatgacctccctgaggtccgaagataccgccctgtactattgcgccc ggcacgactactcatcctactcctactggggacagggagtcatggtgaccgtgtcctcc
CAR20-12 -Soluble scFv - nt	868	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccc aagtcgtgctgacgcaacccaagtccgtgagcaccagcctggagagcaccgtgaagctcag ctgcaagattaactcgggcaacattgggtcctacttcatccattggtaccagcagcacgaagga cggtcccctaccactatgatctaccgggacgacaagcggccgcacggagtgccggacagat tctcgggttcaatcgattcctcatctaactcggcgtttctcaccatcaacaacgtgcagaccgag gacgaagcgatctacttctgccactcctacgactcgggtattaacattgtgttcggcggcggga ctaagctgacagtgctgggcggtggaggctcaggggggggcggctcgggaggggggtgga agcggaggaggaggctccgaggtgcagctcgtcgaatccggtggaggactggtgcagcca

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CAR20-12 -Soluble scFv - aa	869	malpvtalllplalllhaarpqvvltqpksvstslestvklsckinsgnigsyfihwyqqhegr sptmiyrddkrphgvpdrfsgsidsssnsafltinnvqtedeaiyfchsydsginivfgggt kltvlggggsggggsggggsggggsevqlvesggglvqpgrslklsclasgftfskygmn wirqapgkglewvasisstsiyiyyadtvkgrftisrenakntlylqmtslrsedtalyycarh dyssysywgqgvmvtvssgshhhhhhhh
CAR20- 12 – Completo - nt	870	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccc aagtcgtgctgacgcaacccaagtccgtgagcaccagcctggagagcaccgtgaagctcag ctgcaagattaactcgggcaacattgggtcctacttcatccattggtaccagcagcacgaagga cggtcccctaccactatgatctaccgggacgacaagcggccgcacggagtgccggacagat tctcgggttcaatcgattcctcatctaactcggcgtttctcaccatcaacaacgtgcagaccgag gacgaagcgatctacttctgccactcctacgactcgggtattaacattgtgttcggcggcggga ctaagctgacagtgctgggcggtggaggctcaggggggggcggctcgggaggggtggga agcggaggaggaggctccgaggtgcagctcgtcgaatccggtggaggactggtgcagcca ggaagatccctgaagctgtcctgtctcgcctcgggcttcactttctccaaatacggcatgaattg gattcgccaggcacccggaaaggggctggaatgggtggccagcatcagctcgactagcatc tacatctactatgccgataccgtcaagggccgcttcactatctcccgcgagaacgctaagaaca ccctttacttgcaaatgacctccctgaggtccgaagataccgccctgtactattgcgcccggca cgactactcatcctactcctactggggacagggagtcatggtgaccgtgtcctccaccactacc ccagcaccgaggccacccaccccggctcctaccatcgcctcccagcctctgtccctgcgtcc ggaggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcg atatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactct ttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtg cagactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggct gcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcaga accagctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcgg agaggacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcct gtacaacgagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggg gaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaa ggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR20- 12 – Completo - aa	871	malpvtalllplalllhaarpqvvltqpksvstslestvklsckinsgnigsyfihwyqqhegr sptmiyrddkrphgvpdrfsgsidsssnsafltinnvqtedeaiyfchsydsginivfgggt kltvlggggsggggsggggsggggsevqlvesggglvqpgrslklsclasgftfskygmn wirqapgkglewvasisstsiyiyyadtvkgrftisrenakntlylqmtslrsedtalyycarh dyssysywgqgvmvtvssttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfac diyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeegg celrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeg lynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr
dominio CAR20-13 scFv	872	dvqmtqspsllsasvgdavtinckasqninrylnwyqqklgegprlliysanslqtgipsrfs gsgsgadftltitspqpedvatyfclqhnswpltfgsgtkleikggggsggggsggggsggg gsqvtlkesgpgilqpsqtlsltctftrfslstygmsvgwirqpsgkglewladiwwdddkh ynpslknrltiskdtsknqaflkitnvdtadtatyycarssttdgivtyvmdvwgqgasvtvs

		s
dominio CAR20-13 scFv nt	873	gacgtgcagatgactcagtccccgtcgctcctgtccgcctccgtcggcgacgccgtgactatt aactgcaaggcgtcccagaacatcaatcggtacctgaactggtaccagcaaaaactgggaga agggccgagacttctcatctactccgccaactccctgcaaactggcatcccgtcgaggttcag cggatcaggctctggtgccgacttcactttgaccatcacgagccctcagcccgaagatgtggc cacctacttctgcctccaacacaactcctggcccctgacctttggttcgggcaccaagctggag atcaagggcggtggaggctcagggggggggcggctcgggaggggggtggaagcggaggag gaggctcccaagtcacgctgaaggaatcgggccctggaattctgcagccaagccagaccct ctcgcttacttgcaccttcacccgcttctcactgtccacttacggaatgtccgtgggatggattcg gcagcccagcggaaagggtttggagtggctggccgacatttggtgggatgacgacaagcatt acaaccctagcctgaagaatcggctcaccatcagcaaagacacctccaagaaccaggcgttc ctgaagatcaccaacgtggataccgccgacactgcaacatactattgtgcccgctcctcaacc accgatgggatcgtgacctacgtgatggacgtctggggccagggagcttccgtgaccgtgtc ctcc
CAR20-13 -Soluble scFv - nt	874	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg acgtgcagatgactcagtccccgtcgctcctgtccgcctccgtcggcgacgccgtgactatta actgcaaggcgtcccagaacatcaatcggtacctgaactggtaccagcaaaaactgggagaa gggccgagacttctcatctactccgccaactccctgcaaactggcatcccgtcgaggttcagc ggatcaggctctggtgccgacttcactttgaccatcacgagccctcagcccgaagatgtggcc acctacttctgcctccaacacaactcctggcccctgacctttggttcgggcaccaagctggaga tcaagggcggtggaggctcagggggggggcggctcgggaggggggtggaagcggaggagg aggctcccaagtcacgctgaaggaatcgggccctggaattctgcagccaagccagaccctct cgcttacttgcaccttcacccgcttctcactgtccacttacggaatgtccgtgggatggattcgg cagcccagcggaaagggtttggagtggctggccgacatttggtgggatgacgacaagcatta caaccctagcctgaagaatcggctcaccatcagcaaagacacctccaagaaccaggcgttcc tgaagatcaccaacgtggataccgccgacactgcaacatactattgtgcccgctcctcaacca ccgatgggatcgtgacctacgtgatggacgtctggggccagggagcttccgtgaccgtgtcct ccggatcgcaccaccatcaccatcatcatcac
CAR20-13 -Soluble scFv - aa	875	malpvtalllplalllhaarpdvqmtqspsllsasvgdavtinckasqninrylnwyqqklg egprlliysanslqtgipsrfsgsgsgadftltitspqpedvatyfclqhnswpltfgsgtkleik ggggsggggsggggsggggsqvtlkesgpgilqpsqtlsltctftrfslstygmsvgwirqp sgkglewladiwwdddkhynpslknrltiskdtsknqaflkitnvdtadtatyycarssttd givtyvmdvwgqgasvtvssgshhhhhhhh
CAR20-13 – Completo nt	876	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg acgtgcagatgactcagtccccgtcgctcctgtccgcctccgtcggcgacgccgtgactatta actgcaaggcgtcccagaacatcaatcggtacctgaactggtaccagcaaaaactgggagaa gggccgagacttctcatctactccgccaactccctgcaaactggcatcccgtcgaggttcagc ggatcaggctctggtgccgacttcactttgaccatcacgagccctcagcccgaagatgtggcc acctacttctgcctccaacacaactcctggcccctgacctttggttcgggcaccaagctggaga tcaagggcggtggaggctcagggggggggcggctcgggaggggggtggaagcggaggagg aggctcccaagtcacgctgaaggaatcgggccctggaattctgcagccaagccagaccctct cgcttacttgcaccttcacccgcttctcactgtccacttacggaatgtccgtgggatggattcgg cagcccagcggaaagggtttggagtggctggccgacatttggtgggatgacgacaagcatta caaccctagcctgaagaatcggctcaccatcagcaaagacacctccaagaaccaggcgttcc tgaagatcaccaacgtggataccgccgacactgcaacatactattgtgcccgctcctcaacca ccgatgggatcgtgacctacgtgatggacgtctggggccagggagcttccgtgaccgtgtcct ccaccactaccccagcaccgaggccacccaccccggctcctaccatcgcctcccagcctctg

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CAR20-13 –Completo aa	877	malpvtalllplalllhaarpdvqmtqspsllsasvgdavtinckasqninrylnwyqqklg egprlliysanslqtgipsrfsgsgsgadftltitspqpedvatyfclqhnswpltfgsgtkleik ggggsggggsggggsggggsqvtlkesgpgilqpsqtlsltctftrfslstygmsvgwirqp sgkglewladiwwdddkhynpslknrltiskdtsknqaflkitnvdtadtatyycarssttd givtyvmdvwgqgasvtvsstttpaprpptpaptiasqplslrpeacrpaaggavhtrgldf acdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeee ggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpq eglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr
dominio CAR20-14 scFv	878	diqmtqspsflsasvgdrvtinckasqninrylnwyqqklgeapklliynanslqtgipsrfs gsgsgtdftltisslqpadvatyfclqhnsrpltfgsgtileikggggsggggsggggsggggs qvtlkesgpgllqpsqtlsltctfagfslnthgmgvgwirqpsgkglewlaniwwdddky ynpslknrltmskdtsnnqaflkitnvdtadtatyycariegspvvttvfdywgqgvmvtv ss
dominio CAR20-14 scFv nt	879	gacatccaaatgacccagtcacctagctttctgtcggcctcggtcggcgacagagtgaccatta actgcaaagcgtcccagaacatcaaccgctacctgaattggtaccagcagaagctgggggaa gccccgaagctgctgatctacaacgcgaacagcctccagactggtattccttcccggttctccg ggagcggctcgggtaccgatttcaccctcaccatctcctcccttcaacccgctgacgtggcca cctacttctgcttgcaacataattctcggcctctgaccttcggaagcggcactatcctcgagatc aagggcggtggaggctcagggggggggcggctcgggaggggtggaagcggaggagga ggctcccaagtcactcttaaggaatccgggccaggactgttgcagccgagccagaccctgtc cctcacttgtaccttcgccggcttttcactgaacacccacggaatgggcgtgggatggattagg cagccctcgggaaagggactggagtggctggccaacatttggtgggacgacgacaagtatta caacccgagcctcaagaaccgcctgactatgtccaaggatacctccaacaaccaggccttcct gaaaatcactaacgtggataccgctgacaccgcaacgtactactgcgcccggatcgaaggtt cccccgtcgtgacaactgtgttcgactactggggacagggcgtgatggtgaccgtgtcctcc
CAR20-14 -Soluble scFv - nt	880	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg acatccaaatgacccagtcacctagctttctgtcggcctcggtcggcgacagagtgaccattaa ctgcaaagcgtcccagaacatcaaccgctacctgaattggtaccagcagaagctgggggaa gccccgaagctgctgatctacaacgcgaacagcctccagactggtattccttcccggttctccg ggagcggctcgggtaccgatttcaccctcaccatctcctcccttcaacccgctgacgtggcca cctacttctgcttgcaacataattctcggcctctgaccttcggaagcggcactatcctcgagatc aagggcggtggaggctcagggggggggcggctcgggaggggtggaagcggaggagga ggctcccaagtcactcttaaggaatccgggccaggactgttgcagccgagccagaccctgtc cctcacttgtaccttcgccggcttttcactgaacacccacggaatgggcgtgggatggattagg cagccctcgggaaagggactggagtggctggccaacatttggtgggacgacgacaagtatta caacccgagcctcaagaaccgcctgactatgtccaaggatacctccaacaaccaggccttcct gaaaatcactaacgtggataccgctgacaccgcaacgtactactgcgcccggatcgaaggtt

		cccccgtcgtgacaactgtgttcgactactggggacagggcgtgatggtgaccgtgtcctccg gatcgcaccaccatcaccatcatcatcac
CAR20-14 -Soluble scFv - aa	881	malpvtalllplalllhaarpdiqmtqspsflsasvgdrvtinckasqninrylnwyqqklge apklliynanslqtgipsrfsgsgsgtdftltisslqpadvatyfclqhnsrpltfgsgtileikgg ggsggggsggggsggggsqvtlkesgpgllqpsqtlsltctfagfslnthgmgvgwirqps gkglewlaniwwdddkyynpslknrltmskdtsnnqaflkitnvdtadtatyycariegsp vvttvfdywgqgvmvtvssgshhhhhhhh
CAR20-14 – Completo nt	882	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggcccg acatccaaatgacccagtcacctagctttctgtcggcctcggtcggcgacagagtgaccattaa ctgcaaagcgtcccagaacatcaaccgctacctgaattggtaccagcagaagctgggggaa gccccgaagctgctgatctacaacgcgaacagcctccagactggtattccttcccggttctccg ggagcggctcgggtaccgatttcaccctcaccatctcctcccttcaacccgctgacgtggcca cctacttctgcttgcaacataattctcggcctctgaccttcggaagcggcactatcctcgagatc aagggcggtggaggctcaggggggggcggctcgggaggggtggaagcggaggagga ggctcccaagtcactcttaaggaatccgggccaggactgttgcagccgagccagaccctgtc cctcacttgtaccttcgccggcttttcactgaacacccacggaatgggcgtgggatggattagg cagccctcgggaaagggactggagtggctggccaacatttggtgggacgacgacaagtatta caacccgagcctcaagaaccgcctgactatgtccaaggatacctccaacaaccaggccttcct gaaaatcactaacgtggataccgctgacaccgcaacgtactactgcgcccggatcgaaggtt cccccgtcgtgacaactgtgttcgactactggggacagggcgtgatggtgaccgtgtcctcca ccactaccccagcaccgaggccacccaccccggctcctaccatcgcctcccagcctctgtcc ctgcgtccggaggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgactt cgcctgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcactcgt gatcactctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatga ggcctgtgcagactactcaagaggaggacggctgttcatgccggttcccagaggaggagga aggcggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcag gggcagaaccagctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctgg acaagcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaatcccca agagggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagattggta tgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcacc gccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR20-14 –Completo aa	883	malpvtalllplalllhaarpdiqmtqspsflsasvgdrvtinckasqninrylnwyqqklge apklliynanslqtgipsrfsgsgsgtdftltisslqpadvatyfclqhnsrpltfgsgtileikgg ggsggggsggggsggggsqvtlkesgpgllqpsqtlsltctfagfslnthgmgvgwirqps gkglewlaniwwdddkyynpslknrltmskdtsnnqaflkitnvdtadtatyycariegsp vvttvfdywgqgvmvtvsstttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfa cdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeeg gcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqe glynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr
dominio CAR20-15 scFv	884	kivltqsptitaaspgekvtitclassrvsniywyqqksgaspkllivstsslasgvpyrfsgsg sgtsysltintmeaedaatyychqwssnpwtfgggtklelkggggsggggsggggsggg gsqvtlkesgpgmlqpsktlsltcsfsgfslstsgmvvswirqpsgkslewlaaiawdgdk yynpslksrvtvskdtsntqvflritsvdiadtatyyctrrdydvgyyyfdfwgqgvmvtvs s
dominio CAR20-15 scFv nt	885	aagattgtgctgacccagagccccactattaccgccgcctccccgggggaaaaggtcaccat cacttgtctggcgtcctcacgcgtgtcgaatatctactggtatcagcagaagtccggcgccagc cccaagctgctgatctactcgacctcctccctcgcgtcgggagtgccttaccggttttctggctc

		gggaagcggaaccagctactccttgaccatcaacaccatggaagccgaggacgctgccactt actactgccaccagtggtcgagcaacccttggactttcggtggaggcaccaaactcgagctca agggcggtggaggctcagggggggggcggctcgggaggggggtggaagcggaggaggag gctcccaagtcaccctgaaagaatcgggtcccggaatgctgcagccatccaagacgctgtcc cttacatgctccttctccgggttcagcctctcaacttccgggatggtggtgtcatggatcagaca gccgagcggaaagtccctggagtggctggcggccatcgcatgggatggcgataagtactac aacccgagcctgaagtcaagggtcactgtgtccaaggacacctccaacacccaagtgttcctt cggatcacctccgtggacattgctgacaccgccacctattactgcactcgccgggactacgac gtgggctactactacttcgatttctggggacagggtgtcatggtgaccgtgtcctcc
CAR20-15 -Soluble scFv - nt	886	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggccca agattgtgctgacccagagccccactattaccgccgcctccccgggggaaaaggtcaccatc acttgtctggcgtcctcacgcgtgtcgaatatctactggtatcagcagaagtccggcgccagcc ccaagctgctgatctactcgacctcctccctcgcgtcgggagtgccttaccggttttctggctcg ggaagcggaaccagctactccttgaccatcaacaccatggaagccgaggacgctgccactta ctactgccaccagtggtcgagcaacccttggactttcggtggaggcaccaaactcgagctcaa gggcggtggaggctcagggggggggcggctcgggaggggggtggaagcggaggaggagg ctcccaagtcaccctgaaagaatcgggtcccggaatgctgcagccatccaagacgctgtccct tacatgctccttctccgggttcagcctctcaacttccgggatggtggtgtcatggatcagacagc cgagcggaaagtccctggagtggctggcggccatcgcatgggatggcgataagtactacaa cccgagcctgaagtcaagggtcactgtgtccaaggacacctccaacacccaagtgttccttcg gatcacctccgtggacattgctgacaccgccacctattactgcactcgccgggactacgacgt gggctactactacttcgatttctggggacagggtgtcatggtgaccgtgtcctccggatcgcac caccatcaccatcatcatcac
CAR20-15 -Soluble scFv - aa	887	malpvtalllplalllhaarpkivltqsptitaaspgekvtitclassrvsniywyqqksgaspk lliystsslasgvpyrfsgsgsgtsysltintmeaedaatyychqwssnpwtfgggtklelkg gggsggggsggggsggggsqvtlkesgpgmlqpsktlsltcsfsgfslstsgmvvswirq psgkslewlaaiawdgdkyynpslksrvtvskdtsntqvflritsvdiadtatyyctrrdydv gyyyfdfwgqgvmvtvssgshhhhhhhh
CAR20-15 – Completo nt	888	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggccca agattgtgctgacccagagccccactattaccgccgcctccccgggggaaaaggtcaccatc acttgtctggcgtcctcacgcgtgtcgaatatctactggtatcagcagaagtccggcgccagcc ccaagctgctgatctactcgacctcctccctcgcgtcgggagtgccttaccggttttctggctcg ggaagcggaaccagctactccttgaccatcaacaccatggaagccgaggacgctgccactta ctactgccaccagtggtcgagcaacccttggactttcggtggaggcaccaaactcgagctcaa gggcggtggaggctcagggggggggcggctcgggaggggggtggaagcggaggaggagg ctcccaagtcaccctgaaagaatcgggtcccggaatgctgcagccatccaagacgctgtccct tacatgctccttctccgggttcagcctctcaacttccgggatggtggtgtcatggatcagacagc cgagcggaaagtccctggagtggctggcggccatcgcatgggatggcgataagtactacaa cccgagcctgaagtcaagggtcactgtgtccaaggacacctccaacacccaagtgttccttcg gatcacctccgtggacattgctgacaccgccacctattactgcactcgccgggactacgacgt gggctactactacttcgatttctggggacagggtgtcatggtgaccgtgtcctccaccactacc ccagcaccgaggccacccaccccggctcctaccatcgcctcccagcctctgtccctgcgtcc ggaggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcg atatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactct ttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtg cagactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggct gcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcaga

		accagctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcgg agaggacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcct gtacaacgagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggg gaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaa ggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR20-15 –Completo aa	889	malpvtalllplalllhaarpkivltqsptitaaspgekvtitclassrvsniywyqqksgaspk lliystsslasgvpyrfsgsgsgtsysltintmeaedaatyychqwssnpwtfgggtklelkg gggsggggsggggsggggsqvtlkesgpgmlqpsktlsltcsfsgfslstsgmvvswirq psgkslewlaaiawdgdkyynpslksrvtvskdtsntqvflritsvdiadtatyyctrrdydv gyyyfdfwgqgvmvtvssttpaprpptpaptiasqplslrpeacrpaaggavhtrgldfac diyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeeegg celrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpqeg lynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr
dominio CAR20-16 scFv	890	niqltqspsrlsasvgdrvtlsckgsqninnylawyqqklgeapklliyntnnlqtgipsrfsg sgsgtdytftisglqpedvatyfccqynngntfgagtklelkggggsggggsggggsgggg sqiqlvqsgpelkkpgesvkisckasgntvtgyamhwvrqapgkglkwmgwintysg kptyaddfkgrcvfsleasastahlqisnlknedtatyfcarstyygykdwfaywgqgtlvt vss
dominio CAR20-16 scFv nt	891	aacatccaactgactcagagccccagccggctgtccgcctccgtgggggacagggtcacac tgagctgcaagggttctcagaacatcaacaactacctcgcgtggtaccagcagaagctggga gaggcccccaagctgctcatctacaacaccaacaatctgcaaactggcattccatcgagattct caggatcagggtccggtaccgactacaccttcacgatttcgggacttcagcctgaggatgtgg ccacctacttctgctgtcagtacaacaacggcaacaccttcggtgctggcaccaagctggaac tcaaaggcggtggaggctcagggggggggcggctcgggaggggggtggaagcggaggagg aggctcccaaattcagttggtgcagtccggcccggagctgaagaagcctggagaatccgtga agatctcgtgcaaagcttccgggaacaccgtgaccggatacgcaatgcactgggtccgccag gcaccgggaaagggactgaagtggatggggtggatcaacacctacagcggaaagccgact tacgccgatgactttaagggacgctgtgtgttctccctggaagcgtccgcctcgactgcccatc ttcaaatctccaacctgaagaatgaggacaccgccacttacttctgcgcccggagcacctatta cggctacaaggactggttcgcgtattggggccagggcactctcgtgaccgtgtcctcc
CAR20-16 - scFv - nt Soluble	892	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggccca acatccaactgactcagagccccagccggctgtccgcctccgtgggggacagggtcacact gagctgcaagggttctcagaacatcaacaactacctcgcgtggtaccagcagaagctgggag aggcccccaagctgctcatctacaacaccaacaatctgcaaactggcattccatcgagattctc aggatcagggtccggtaccgactacaccttcacgatttcgggacttcagcctgaggatgtggc cacctacttctgctgtcagtacaacaacggcaacaccttcggtgctggcaccaagctggaact caaaggcggtggaggctcagggggggggcggctcgggaggggggtggaagcggaggagg aggctcccaaattcagttggtgcagtccggcccggagctgaagaagcctggagaatccgtga agatctcgtgcaaagcttccgggaacaccgtgaccggatacgcaatgcactgggtccgccag gcaccgggaaagggactgaagtggatggggtggatcaacacctacagcggaaagccgact tacgccgatgactttaagggacgctgtgtgttctccctggaagcgtccgcctcgactgcccatc ttcaaatctccaacctgaagaatgaggacaccgccacttacttctgcgcccggagcacctatta cggctacaaggactggttcgcgtattggggccagggcactctcgtgaccgtgtcctccggatc gcaccaccatcaccatcatcatcac
CAR20-16 - scFv - aa Soluble	893	malpvtalllplalllhaarpniqltqspsrlsasvgdrvtlsckgsqninnylawyqqklgea pklliyntnnlqtgipsrfsgsgsgtdytftisglqpedvatyfccqynngntfgagtklelkg gggsggggsggggsggggsqiqlvqsgpelkkpgesvkisckasgntvtgyamhwvrq

		apgkglkwmgwintysgkptyaddfkgrcvfsleasastahlqisnlknedtatyfcarsty ygykdwfaywgqgtlvtvssgshhhhhhhh
CAR20-16 – Completo nt	894	atggccctccctgtcaccgccctgctgcttccgctggctcttctgctccacgccgctcggccca acatccaactgactcagagccccagccggctgtccgcctccgtgggggacagggtcacact gagctgcaagggttctcagaacatcaacaactacctcgcgtggtaccagcagaagctgggag aggcccccaagctgctcatctacaacaccaacaatctgcaaactggcattccatcgagattctc aggatcagggtccggtaccgactacaccttcacgatttcgggacttcagcctgaggatgtggc cacctacttctgctgtcagtacaacaacggcaacaccttcggtgctggcaccaagctggaact caaaggcggtggaggctcaggggggggcggctcgggaggggtggaagcggaggagg aggctcccaaattcagttggtgcagtccggcccggagctgaagaagcctggagaatccgtga agatctcgtgcaaagcttccgggaacaccgtgaccggatacgcaatgcactgggtccgccag gcaccgggaaagggactgaagtggatggggtggatcaacacctacagcggaaagccgact tacgccgatgactttaagggacgctgtgtgttctccctggaagcgtccgcctcgactgcccatc ttcaaatctccaacctgaagaatgaggacaccgccacttacttctgcgcccggagcacctatta cggctacaaggactggttcgcgtattggggccagggcactctcgtgaccgtgtcctccaccac taccccagcaccgaggccacccaccccggctcctaccatcgcctcccagcctctgtccctgc gtccggaggcatgtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcc tgcgatatctacatttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatc actctttactgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcc tgtgcagactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggc ggctgcgaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggc agaaccagctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaag cggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagg gcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaa ggggaacgcagaagaggcaaaggccacgacggactgtaccagggactcagcaccgccac caaggacacctatgacgctcttcacatgcaggccctgccgcctcgg
CAR20-16 –Completo aa	895	malpvtalllplalllhaarpniqltqspsrlsasvgdrvtlsckgsqninnylawyqqklgea pklliyntnnlqtgipsrfsgsgsgtdytftisglqpedvatyfccqynngntfgagtklelkg gggsggggsggggsggggsqiqlvqsgpelkkpgesvkisckasgntvtgyamhwvrq apgkglkwmgwintysgkptyaddfkgrcvfsleasastahlqisnlknedtatyfcarsty ygykdwfaywgqgtlvtvssttpaprpptpaptiasqplslrpeacrpaaggavhtrgldf acdiyiwaplagtcgvlllslvitlyckrgrkkllyifkqpfmrpvqttqeedgcscrfpeeee ggcelrvkfsrsadapaykqgqnqlynelnlgrreeydvldkrrgrdpemggkprrknpq eglynelqkdkmaeayseigmkgerrrgkghdglyqglstatkdtydalhmqalppr

Tabla 11B. Constructos CAR CD20 humanizados

Nombre	SEQ ID NO:	Secuencia
CD20-3m scFv	691	QVQLVESGGGVVQPGRSLRLSCAASGFTFRDYYMAWVRQAPGKGL EWVASISYEGNPYYGDSVKGRFTISRDNAKSTLYLQMSSLRAEDTAV YYCARHDHNNVDWFAYWGQGTLVTVSSGGGGSGGGGSGGGGSGG GGSDIVMTQTPLSLSVTPGQPVSMSCKSSQSLLYSENKKNYLAWYL QKPGQSPQLLIFWASTRESGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCQQYYNFPTFGQGTKLEIK
CD20-3J scFv	692	QVQLVQSGAEVKKPGASVKVSCKASGFTFRDYYMAWVRQAPGQRL EWMGSISYEGNPYYGDSVKGRVTITRDNSASTLYMELSSLRSEDTAV

		YYCARHDHNNVDWFAYWGQGTLVTVSSGGGGSGGGGSGGGGSGG GGSDIQMTQSPSSLSASVGDRVTITCKSSQSLLYSENKKNYLAWYQQ KPGKVPKLLIFWASTRESGVPSRFSGSGSGTDFTLTISSLQPEDVATY YCQQYYNFPTFGQGTKLEIK
CD20-3H5k3 scFv	693	EVQLVQSGAEVKKPGESLKISCKGSGFTFRDYYMAWVRQMPGKGL EWMGSISYEGNPYYGDSVKGQVTISRDNSISTLYLQWSSLKASDTA MYYCARHDHNNVDWFAYWGQGTLVTVSSGGGGSGGGGSGGGGS GGGGSEIVMTQSPATLSLSPGERATLSCKSSQSLLYSENKKNYLAWY QQKPGQAPRLLIFWASTRESGIPARFSGSGSGTDFTLTISSLQPEDLAV YYCQQYYNFPTFGQGTKLEIK
CD20-3H5k1 scFv	694	EVQLVQSGAEVKKPGESLKISCKGSGFTFRDYYMAWVRQMPGKGL EWMGSISYEGNPYYGDSVKGQVTISRDNSISTLYLQWSSLKASDTA MYYCARHDHNNVDWFAYWGQGTLVTVSSGGGGSGGGGSGGGGS GGGGSDIQMTQSPSSLSASVGDRVTITCKSSQSLLYSENKKNYLAWY QQKPGKVPKLLIFWASTRESGVPSRFSGSGSGTDFTLTISSLQPEDVA TYYCQQYYNFPTFGQGTKLEIK
CD20-3H1k3 scFv	695	QVQLVQSGAEVKKPGASVKVSCKASGFTFRDYYMAWVRQAPGQG LEWMGSISYEGNPYYGDSVKGRVTMTRDNSTSTLYMELSSLRSEDT AVYYCARHDHNNVDWFAYWGQGTLVTVSSGGGGSGGGGSGGGGS GGGGSEIVMTQSPATLSLSPGERATLSCKSSQSLLYSENKKNYLAWY QQKPGQAPRLLIFWASTRESGIPARFSGSGSGTDFTLTISSLQPEDLAV YYCQQYYNFPTFGQGTKLEIK
CD20-3H1k1 scFv	696	QVQLVQSGAEVKKPGASVKVSCKASGFTFRDYYMAWVRQAPGQG LEWMGSISYEGNPYYGDSVKGRVTMTRDNSTSTLYMELSSLRSEDT AVYYCARHDHNNVDWFAYWGQGTLVTVSSGGGGSGGGGSGGGGS GGGGSDIQMTQSPSSLSASVGDRVTITCKSSQSLLYSENKKNYLAWY QQKPGKVPKLLIFWASTRESGVPSRFSGSGSGTDFTLTISSLQPEDVA TYYCQQYYNFPTFGQGTKLEIK

En algunas modalidades, el dominio de unión a antígeno comprende una HC CDR1, una HC CDR2, y una HC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada listadas en la **Tabla 11A y 11B**. En modalidades, el dominio de unión al antígeno comprende adicionalmente una LC CDR1, una LC CDR2, y una LC CDR3. En modalidades, el dominio de union a antígeno comprende una LC CDR1, una LC CDR2, y una LC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera listadas en la **Tabla 11A y 11B**.

En algunas modalidades, el dominio de unión a antígeno cmoprende una, dos o todas de las LC CDR1, LC CDR2, y LC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera listadas en la **Tabla 11A y 11B**, y una, dos o todas de las HC CDR1, HC CDR2, y HC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada listadas en la **Tabla 11A y 11B**.

En algunas modalidades, las CDRs están definidas de acuerdo con el esquema de

numeración de Kabat, el esquema de numeración de Chothia, o una combinación de los mismos.

Las secuencias de las secuencias de las CDR humanas de los dominios de scFv se muestran en la **Tabla 12** para los dominios variables de la cadena pesada y en la **Tabla 13** para los dominios variables de la cadena ligera. Las "ID" aparecen para su respectivo SEQ ID NO para cada CDR.

Tabla 12A. CDRs del dominio variable de la cadena pesada de los CARs CD20. Las CDRs están definidas de acuerdo con la definición "combinada".

Candidato	**HCDR1**	**SEQ ID NO:**	**HCDR2**	**SEQ ID NO:**	**HCDR3**	**SEQ ID NO:**
CAR20-1	EYTFTDYAFH	697	WINTYSGKPTYADDFKG	791	DWFTY	903
CAR20-2	GFTFSKYGMN	698	SISSTSIYIYYADTVKG	792	HDYSSYSY	904
CAR20-3	GFTFRDYYMA	699	SISYEGNPYYGDSVKG	793	HDHNNVDWFAY	905
CAR20-4	RFSLSTYGMSVG	778	DIWWDDDKHYNPSLKN	794	SSTTDGIVTYVMDV	906
CAR20-5	GFTFSSSGMQ	779	GIYYDSYKKSYADSVKG	795	SAYYGYKDYFDY	907
CAR20-6	GFSLNTHGMGVG	780	NIWWDDDKYYNPSLKN	796	IEGSPVVTTVFDY	908
CAR20-7	GFSLSTSGMVVS	781	AIAWDGDKYYNPSLKS	797	RDYDVGYYYFDF	909
CAR20-8	GNTVTGYAMH	782	WINTYSGKPTYADDFKG	798	DWFAY	910
CAR20-9	GFTFRDYYMA	783	SISYEGNPYYGDSVKG	799	HDHNNVDWFAY	911
CAR20-10	GFTFSSSGMQ	784	GIYYDSYKKSYADSVKG	896	SAYYGYKDYFDY	912
CAR20-11	EYTFTDYAFH	785	WINTYSGKPTYADDFKG	897	GAYYGYRDWFTY	913
CAR20-12	GFTFSKYGMN	786	SISSTSIYIYYADTVKG	898	HDYSSYSY	914
CAR20-13	RFSLSTYGMSVG	787	DIWWDDDKHYNPSLKN	899	SSTTDGIVTYVMDV	915
CAR20-14	GFSLNTHGMGVG	788	NIWWDDDKYYNPSLKN	900	IEGSPVVTTVFDY	916
CAR20-15	GFSLSTSGMVVS	789	AIAWDGDKYYNPSLKS	901	RDYDVGYYYFDF	917
CAR20-16	GNTVTGYAMH	790	WINTYSGKPTYADDFKG	902	STYYGYKDWFAY	918

Tabla 12B. CDRs del dominio variable de la cadena pesada de los CARs CD20. Las CDRs están definidas de acuerdo con la definición de Kabat.

Candidato	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:
CAR20-1	DYAFH		WINTYSGKPTYADDFKG		GAYYGYRDWFTY	
CAR20-2	KYGMN		SISSTSIYIYYADTVKG		HDYSSYSY	
CAR20-3	DYYMA		SISYEGNPYYGDSVKG		HDHNNVDWFAY	
CAR20-4	TYGMSVG		DIWWDDDKHYNPSLKN		SSTTDGIVTYVMDV	
CAR20-5	SSGMQ		GIYYDSYKKSYADSVKG		SAYYGYKDYFDY	
CAR20-6	THGMGVG		NIWWDDDKYYNPSLKN		IEGSPVVTTVFDY	
CAR20-7	TSGMVVS		AIAWDGDKYYNPSLKS		RDYDVGYYYFDF	
CAR20-8	GYAMH		WINTYSGKPTYADDFKG		STYYGYKDWFAY	
CAR20-9	DYYMA		SISYEGNPYYGDSVKG		HDHNNVDWFAY	
CAR20-10	SSGMQ		GIYYDSYKKSYADSVKG		SAYYGYKDYFDY	
CAR20-11	DYAFH		WINTYSGKPTYADDFKG		GAYYGYRDWFTY	
CAR20-12	KYGMN		SISSTSIYIYYADTVKG		HDYSSYSY	
CAR20-13	TYGMSVG		DIWWDDDKHYNPSLKN		SSTTDGIVTYVMDV	
CAR20-14	THGMGVG		NIWWDDDKYYNPSLKN		IEGSPVVTTVFDY	
CAR20-15	TSGMVVS		AIAWDGDKYYNPSLKS		RDYDVGYYYFDF	
CAR20-16	GYAMH		WINTYSGKPTYADDFKG		STYYGYKDWFAY	

Tabla 13. CDRs del dominio variable de la cadena ligera de los CARs CD20. Las secuencias de LC CDR en esta tabla tienen la misma secuencia bajo las definiciones de Kabat y combinada.

Candidato	LCDR1	SEQ ID NO:	LCDR2	SEQ ID NO:	LCDR3	SEQ ID NO:
CAR20-1	KSSQSLLYSENKKNYLA	919	WASTRES	935	QQYYNFPPWT	951

CAR20-2	KINSGNIGSYFIH	920	RDDKRPH	936	HSYDSGINIV	952
CAR20-3	KSSQSLLYSENKKNYLA	921	WASTRES	937	QQYYNFPT	953
CAR20-4	KASQNINRYLN	922	SANSLQT	938	LQHNSWPLT	954
CAR20-5	QASQNINKYIA	923	YTSTLES	939	LQYDDLPYT	955
CAR20-6	KASQNINRYLN	924	NANSLQT	940	LQHNSRPLT	956
CAR20-7	LASSRVSNIY	925	STSSLAS	941	HQWSSNPWT	957
CAR20-8	KGSQNINNYLA	926	NTNNLQT	942	CQYNNGNT	958
CAR20-9	KSSQSLLYSENKKNYLA	927	WASTRES	943	QQYYNFPT	959
CAR20-10	QASQNINKYIA	928	YTSTLES	944	LQYDDLPYT	960
CAR20-11	KSSQSLLYSENKKNYLA	929	WASTRES	945	QQYYNFPPWT	961
CAR20-12	KINSGNIGSYFIH	930	RDDKRPH	946	HSYDSGINIV	962
CAR20-13	KASQNINRYLN	931	SANSLQT	947	LQHNSWPLT	963
CAR20-14	KASQNINRYLN	932	NANSLQT	948	LQHNSRPLT	964
CAR20-15	LASSRVSNIY	933	STSSLAS	949	HQWSSNPWT	965
CAR20-16	KGSQNINNYLA	934	NTNNLQT	950	CQYNNGNT	966

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Tabla 14A. Regiones variables de la cadena pesada de las moléculas de anticuerpo CD20

Candidato	**SEQ ID NO:**	**Región Variable de la Cadena Pesada**
CAR-1	967	QIQLVQSGPELKKPGESVKISCKTSEYTFTDYAFHWVKQAPGK GLKWMGWINTYSGKPTYADDFKGRFVFSLEDSARTANLQISN LKNEDTATYFCARGAYYGYRDWFTYWGQGTLVTV
CAR20-2	968	EVQLVESGGGLVQPGRSLKLSCLASGFTFSKYGMNWIRQAPG KGLEWVASISSTSIYIYYADTVKGRFTISRENAKNTLYLQMTSL RSEDTALYYCARHDYSSYSYWGQGVMVTV
CAR20-3	969	EVQLVESGGGLVQPGRSLKLSCAASGFTFRDYYMAWVRQAPK KGLEWVASISYEGNPYYGDSVKGRFTISRNNAKSTLYLQMNSL

		RSEDTATYYCARHDHNNVDWFAYWGQGTLVTV
CAR20-4	970	QVTLKESGPGILQPSQTLSLTCTFTRFSLSTYGMSVGWIRQPSG KGLEWLADIWWDDDKHYNPSLKNRLTISKDTSKNQAFLKITN VDTADTATYYCARSSTTDGIVTYVMDVWGQGASVTV
CAR20-5	971	EVQLVESGGGLVQPGTSLKLSCVASGFTFSSSGMQWIRQAPKK GLEWISGIYYDSYKKSYADSVKGRFTISRDNSKNTLYLEMNSL RSEDTATYYCAKSAYYGYKDYFDYWGQGVMVTV
CAR20-6	972	QVTLKESGPGLLQPSQTLSLTCTFAGFSLNTHGMGVGWIRQPS GKGLEWLANIWWDDDKYYNPSLKNRLTMSKDTSNNQAFLKI TNVDTADTATYYCARIEGSPVVTTVFDYWGQGVMVTV
CAR20-7	973	QVTLKESGPGMLQPSKTLSLTCSFSGFSLSTSGMVVSWIRQPSG KSLEWLAAIAWDGDKYYNPSLKSRVTVSKDTSNTQVFLRITSV DIADTATYYCTRRDYDVGYYYFDFWGQGVMVTV
CAR20-8	974	QIQLVQSGPELKKPGESVKISCKASGNTVTGYAMHWVRQAPG KGLKWMGWINTYSGKPTYADDFKGRCVFSLEASASTAHLQIS NLKNEDTATYFCARSTYYGYKDWFAYWGQGTLVTV
CAR20-9	975	EVQLVESGGGLVQPGRSLKLSCAASGFTFRDYYMAWVRQAPK KGLEWVASISYEGNPYYGDSVKGRFTISRNNAKSTLYLQMNSL RSEDTATYYCARHDHNNVDWFAYWGQGTLVTV
CAR20-10	976	EVQLVESGGGLVQPGTSLKLSCVASGFTFSSSGMQWIRQAPKK GLEWISGIYYDSYKKSYADSVKGRFTISRDNSKNTLYLEMNSL RSEDTATYYCAKSAYYGYKDYFDYWGQGVMVTV
CAR20-11	977	QIQLVQSGPELKKPGESVKISCKTSEYTFTDYAFHWVKQAPGK GLKWMGWINTYSGKPTYADDFKGRFVFSLEDSARTANLQISN LKNEDTATYFCARGAYYGYRDWFTYWGQGTLVTV
CAR20-12	978	EVQLVESGGGLVQPGRSLKLSCLASGFTFSKYGMNWIRQAPG KGLEWVASISSTSIYIYYADTVKGRFTISRENAKNTLYLQMTSL RSEDTALYYCARHDYSSYSYWGQGVMVTV

CAR20-13	979	QVTLKESGPGILQPSQTLSLTCTFTRFSLSTYGMSVGWIRQPSG KGLEWLADIWWDDDKHYNPSLKNRLTISKDTSKNQAFLKITN VDTADTATYYCARSSTTDGIVTYVMDVWGQGASVTV
CAR20-14	980	QVTLKESGPGLLQPSQTLSLTCTFAGFSLNTHGMGVGWIRQPS GKGLEWLANIWWDDDKYYNPSLKNRLTMSKDTSNNQAFLKI TNVDTADTATYYCARIEGSPVVTTVFDYWGQGVMVTV
CAR20-15	981	QVTLKESGPGMLQPSKTLSLTCSFSGFSLSTSGMVVSWIRQPSG KSLEWLAAIAWDGDKYYNPSLKSRVTVSKDTSNTQVFLRITSV DIADTATYYCTRRDYDVGYYYFDFWGQGVMVTV
CAR20-16	982	QIQLVQSGPELKKPGESVKISCKASGNTVTGYAMHWVRQAPG KGLKWMGWINTYSGKPTYADDFKGRCVFSLEASASTAHLQIS NLKNEDTATYFCARSTYYGYKDWFAYWGQGTLVTV

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Tabla 14B. Regiones variables de la cadena pesada de la smoléculas humanizadas de anticuerpo CD20.

Candidato	**SEQ ID NO:**	**Región variable de la cadena pesada**
CD20-3_VH1_1-46	983	QVQLVQSGAEVKKPGASVKVSCKASGFTFRDYYMAWVRQAPGQG LEWMGSISYEGNPYYGDSVKGRVTMTRDNSTSTLYMELSSLRSED TAVYYCARHDHNNVDWFAYWGQGTLVTVSS
CD20-3_VH5_5-51	984	EVQLVQSGAEVKKPGESLKISCKGSGFTFRDYYMAWVRQMPGKG LEWMGSISYEGNPYYGDSVKGQVTISRDNSISTLYLQWSSLKASDT AMYYCARHDHNNVDWFAYWGQGTLVTVSS
CD20-3_VH M	985	QVQLVESGGGVVQPGRSLRLSCAASGFTFRDYYMAWVRQAPGKG LEWVASISYEGNPYYGDSVKGRFTISRDNAKSTLYLQMSSLRAEDT AVYYCARHDHNNVDWFAYWGQGTLVTVSS
CD20-3_VH J	986	QVQLVQSGAEVKKPGASVKVSCKASGFTFRDYYMAWVRQAPGQR LEWMGSISYEGNPYYGDSVKGRVTITRDNSASTLYMELSSLRSEDT

		AVYYCARHDHNNVDWFAYWGQGTLVTVSS

Tabla 15A. Regiones variables de la cadena ligera de las moléculas de anticuerpo CD20

Candidato	**ID**	**Región variable de la cadena ligera**
CAR20-1	987	DIVMTQTPSSQAVSAGEKVTMSCKSSQSLLYSENKKNYLAWY QQKPGQSPKLLIYWASTRESGVPDRFIGSGSGTDFTLTISSVQA EDLAVYYCQQYYNFPPWTFGGGTKLELK
CAR20-2	988	QVVLTQPKSVSTSLESTVKLSCKINSGNIGSYFIHWYQQHEGRS PTTMIYRDDKRPHGVPDRFSGSIDSSSNSAFLTINNVQTEDEAIY FCHSYDSGINIVFGGGTKLTVL
CAR20-3	989	DIVMTQTPSSQAVSAGEKVTMSCKSSQSLLYSENKKNYLAWY QQKPGQSPKLLIFWASTRESGVPDRFIGSGSGTDFTLTISSVQAE DLAVYYCQQYYNFPTFGSGTKLEIK
CAR20-4	990	DVQMTQSPSLLSASVGDAVTINCKASQNINRYLNWYQQKLGE GPRLLIYSANSLQTGIPSRFSGSGSGADFTLTITSPQPEDVATYF CLQHNSWPLTFGSGTKLEIK
CAR20-5	991	DIQMTQSPPSLSASLGDKVTITCQASQNINKYIAWYQQKPGKA PRLLIRYTSTLESGTPSRFSGSGSGRDYSFSISNVESGDVASYYC LQYDDLPYTFGPGTKLELK
CAR20-6	992	DIQMTQSPSFLSASVGDRVTINCKASQNINRYLNWYQQKLGEA PKLLIYNANSLQTGIPSRFSGSGSGTDFTLTISSLQPADVATYFC LQHNSRPLTFGSGTILEIK
CAR20-7	993	KIVLTQSPTITAASPGEKVTITCLASSRVSNIYWYQQKSGASPKL LIYSTSSLASGVPYRFSGSGSGTSYSLTINTMEAEDAATYYCHQ WSSNPWTFGGGTKLELK
CAR20-8	994	NIQLTQSPSRLSASVGDRVTLSCKGSQNINNYLAWYQQKLGEA PKLLIYNTNNLQTGIPSRFSGSGSGTDYTFTISGLQPEDVATYFC

		CQYNNGNTFGAGTKLELK
CAR20-9	995	DIVMTQTPSSQAVSAGEKVTMSCKSSQSLLYSENKKNYLAWY QQKPGQSPKLLIFWASTRESGVPDRFIGSGSGTDFTLTISSVQAE DLAVYYCQQYYNFPTFGSGTKLEIK
CAR20-10	996	DIQMTQSPPSLSASLGDKVTITCQASQNINKYIAWYQQKPGKA PRLLIRYTSTLESGTPSRFSGSGSGRDYSFSISNVESGDVASYYC LQYDDLPYTFGPGTKLELK
CAR20-11	997	DIVMTQTPSSQAVSAGEKVTMSCKSSQSLLYSENKKNYLAWY QQKPGQSPKLLIYWASTRESGVPDRFIGSGSGTDFTLTISSVQA EDLAVYYCQQYYNFPPWTFGGGTKLELK
CAR20-12	998	QVVLTQPKSVSTSLESTVKLSCKINSGNIGSYFIHWYQQHEGRS PTTMIYRDDKRPHGVPDRFSGSIDSSSNSAFLTINNVQTEDEAIY FCHSYDSGINIVFGGGTKLTVL
CAR20-13	999	DVQMTQSPSLLSASVGDAVTINCKASQNINRYLNWYQQKLGE GPRLLIYSANSLQTGIPSRFSGSGSGADFTLTITSPQPEDVATYF CLQHNSWPLTFGSGTKLEIK
CAR20-14	1000	DIQMTQSPSFLSASVGDRVTINCKASQNINRYLNWYQQKLGEA PKLLIYNANSLQTGIPSRFSGSGSGTDFTLTISSLQPADVATYFC LQHNSRPLTFGSGTILEIK
CAR20-15	1001	KIVLTQSPTITAASPGEKVTITCLASSRVSNIYWYQQKSGASPKL LIYSTSSLASGVPYRFSGSGSGTSYSLTINTMEAEDAATYYCHQ WSSNPWTFGGGTKLELK
CAR20-16	1002	NIQLTQSPSRLSASVGDRVTLSCKGSQNINNYLAWYQQKLGEA PKLLIYNTNNLQTGIPSRFSGSGSGTDYTFTISGLQPEDVATYFC CQYNNGNTFGAGTKLELK

Tabla 15B. Regiones variables de la cadena ligera de las moléculas de anticuerpo CD20 humanizado

Candidato	SEQ ID NO:	Región variable de la cadena ligera
CD20-3_VK1_A20	1003	DIQMTQSPSSLSASVGDRVTITCKSSQSLLYSENKKNYLAWYQQKPGKVPKLLIFWASTRESGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQQYYNFPTFGQGTKLEIK
CD20-3_VK3_L25	1004	EIVMTQSPATLSLSPGERATLSCKSSQSLLYSENKKNYLAWYQQKPGQAPRLLIFWASTRESGIPARFSGSGSGTDFTLTISSLQPEDLAVYYCQQYYNFPTFGQGTKLEIK
CD20-3_VL M and CD20-3_VL J	1005	DIVMTQTPLSLSVTPGQPVSMSCKSSQSLLYSENKKNYLAWYLQKPGQSPQLLIFWASTRESGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQYYNFPTFGQGTKLEIK

En algunas modalidades, el dominio de unión a antígeno comprende una HC CDR1, una HC CDR2, y una HC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada listadas en la **Tabla 14A o 14B**. En modalidades, el dominio de unión al antígeno comprende adicionalmente una LC CDR1, una LC CDR2, y una LC CDR3. En modalidades, el dominio de union a antígeno comprende una LC CDR1, una LC CDR2, y una LC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera listadas en la **Tabla 15A o 15B**.

En algunas modalidades, el dominio de unión a antígeno cmoprende una, dos o todas de las LC CDR1, LC CDR2, y LC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera listadas en la **Tabla 15A o 15B**, y una, dos o todas de las HC CDR1, HC CDR2, y HC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada listadas en la **Tabla 14A o 14B**.

En algunas modalidades, las CDRs están definidas de acuerdo con el esquema de numeración de Kabat, el esquema de numeración de Chothia, o una combinación de los mismos.

constructos CAR123

Se aislaron los fragmentos de cadena única anti-CD23. Los scFvs anti-CD23 fueron clonados en vectores de expression lentivirales de CAR con la cadena CD3zeta y la molécula coestimuladora 4-1BB. Los plásmidos que contienen el CAR fueron amplificados mediante transformación bacteriana en células STBL3, seguido de Maxiprep usando el kit Qiagen Plasmid Maki libre de endotoxina. El sobrenadante lentiviral fue producido en células 293T usando técnicas estándar.

Las secuencias de los CARs se proporcionan a continuación en la **Tabla 16**. Los components adicionales de los CARs (por ejemplo, los dominios líder, bisagra, transmembrana, y de señalización) se describen en el presente documento.

El orden en el cual aparecen los dominios VL y VH en el scFv puedeser variado (es decir, orientación VL-VH, o VH-VL), y en donde, ya sea tres o cuatro copias de la subunidad "G4S" (SEQ ID NO:18), en la cual cada subunidad comprende la secuencia GGGGS (SEQ ID NO:18) (por ejemplo, $(G4S)_3$ (SEQ ID NO:107) o $(G4S)_4$(SEQ ID NO:106)), conectan los dominios variables para crear la totalidad del dominio scFv.

Las secuencias de los CARs humanos se proporcionan a continuación en la **Tabla 16.**

Todos estos clones contenían un cambio de residuo Q/K en el dominio señal del dominio coestimulatorio derivado de la cadena CD3zeta.

Tabla 16: Constructos CAR CD123 Humanos

Nombre	**SEQ ID**	**Secuencia**
CAR123-1 NT	1123	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggccccaagtccaactcgtccagtcaggagcggaag tcaagaagcccggagcgtcagtcaaagtgtcatgcaaagcctcgggc tacactttcactgggtactacatgcactgggtgcgccaggctccagg acagggactggaatggatgggatggatcaacccgaactccggtggca ccaattacgcccagaagttccaggggagggtgaccatgactcgcgac acgtcgatcagcaccgcatacatggagctgtcaagactccggtccga cgatactgccgtgtactactgcgcacgggacatgaacattctggcca

		ccgtgccttttgacatctggggtcagggaactatggttaccgtgtcc tctggtggaggcggctccggcgggggggggaagcggaggcggtggaag cgacattcagatgacccagtcgccttcatccctttcggcgagcgtgg gagatcgcgtcactatcacttgtcgggcctcgcagtccatctccacc tacctcaattggtaccagcagaagccaggaaaagcaccgaatctgct gatctacgccgcgttttccttgcaatcgggagtgccaagcagattca gcggatcgggatcaggcactgatttcaccctcaccatcaactcgctg caaccggaggatttcgctacgtactattgccaacaaggagacagcgt gccgctcaccttcggcggagggactaagctggaaatcaagaccacta ccccagcaccgaggccacccaccccggctcctaccatcgcctcccag cctctgtccctgcgtccggaggcatgtagacccgcagctggtggggc cgtgcatacccggggtcttgacttcgcctgcgatatctacatttggg cccctctggctggtacttgcggggtcctgctgctttcactcgtgatc actctttactgtaagcgcggtcggaagaagctgctgtacatctttaa gcaacccttcatgaggcctgtgcagactactcaagaggaggacggct gttcatgccggttcccagaggaggaggaaggcggctgcgaactgcgc gtgaaattcagccgcagcgcagatgctccagcctacaagcaggggca gaaccagctctacaacgaactcaatcttggtcggagagaggagtacg acgtgctggacaagcggagaggacgggacccagaaatgggcgggaag ccgcgcagaaagaatccccaagagggcctgtacaacgagctccaaaa ggataagatggcagaagcctatagcgagattggtatgaaaggggaac gcagaagaggcaaaggccacgacggactgtaccagggactcagcacc gccaccaaggacacctatgacgctcttcacatgcaggccctgccgcc tcgg
CAR123-1 AA	1124	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASG YTFTGYYMHWVRQAPGQGLEWMGWINPNSGGTNYAQKFQGRVTMTRD TSISTAYMELSRLRSDDTAVYYCARDMNILATVPFDIWGQGTMVTVS SGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSIST YLNWYQQKPGKAPNLLIYAAFSLQSGVPSRFSGSGSGTDFTLTINSL QPEDFATYYCQQGDSVPLTFGGGTKLEIKTTTPAPRPPTPAPTIASQ PLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVI TLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELR

		VKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST ATKDTYDALHMQALPPR
CAR123-1 scFv	1125	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASG YTFTGYYMHWVRQAPGQGLEWMGWINPNSGGTNYAQKFQGRVTMTRD TSISTAYMELSRLRSDDTAVYYCARDMNILATVPFDIWGQGTMVTVS SGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSIST YLNWYQQKPGKAPNLLIYAAFSLQSGVPSRFSGSGSGTDFTLTINSL QPEDFATYYCQQGDSVPLTFGGGTKLEIK
CAR123-1 VH	1126	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEW MGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVY YCARDMNILATVPFDIWGQGTMVTVSS
CAR123-1 VL	1127	DIQMTQSPSSLSASVGDRVTITCRASQSISTYLNWYQQKPGKAPNLL IYAAFSLQSGVPSRFSGSGSGTDFTLTINSLQPEDFATYYCQQGDSV PLTFGGGTKLEIK
CAR123-2 NT	1128	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggccccaagtgcaactcgtccaaagcggagcggaag tcaagaaacccggagcgagcgtgaaagtgtcctgcaaagcctccggc tacacctttacgggctactacatgcactgggtgcgccaggcaccagg acagggtcttgaatggatgggatggatcaaccctaattcgggcggaa ctaactacgcacagaagttccaggggagagtgactctgactcgggat acctccatctcaactgtctacatggaactctcccgcttgcggtcaga tgatacggcagtgtactactgcgcccgcgacatgaatatcctggcta ccgtgccgttcgacatctggggacaggggactatggttactgtctca tcgggcggtggaggttcaggaggaggcggctcgggaggcggaggttc ggacattcagatgacccagtccccatcctctctgtcggccagcgtcg gagatagggtgaccattacctgtcgggcctcgcaaagcatctcctcg tacctcaactggtatcagcaaaagccgggaaaggcgcctaagctgct gatctacgccgcttcgagcttgcaaagcggggtgccatccagattct cgggatcaggctcaggaaccgacttcaccctgaccgtgaacagcctc cagccggaggactttgccacttactactgccagcagggagactccgt gccgcttactttcgggggggtacccgcctggagatcaagaccacta

		ccccagcaccgaggccacccaccccggctcctaccatcgcctcccag cctctgtccctgcgtccggaggcatgtagacccgcagctggtggggc cgtgcatacccggggtcttgacttcgcctgcgatatctacatttggg cccctctggctggtacttgcggggtcctgctgctttcactcgtgatc actctttactgtaagcgcggtcggaagaagctgctgtacatctttaa gcaacccttcatgaggcctgtgcagactactcaagaggaggacggct gttcatgccggttcccagaggaggaggaaggcggctgcgaactgcgc gtgaaattcagccgcagcgcagatgctccagcctacaagcaggggca gaaccagctctacaacgaactcaatcttggtcggagagaggagtacg acgtgctggacaagcggagaggacgggacccagaaatgggcgggaag ccgcgcagaaagaatccccaagagggcctgtacaacgagctccaaaa ggataagatggcagaagcctatagcgagattggtatgaaaggggaac gcagaagaggcaaaggccacgacggactgtaccagggactcagcacc gccaccaaggacacctatgacgctcttcacatgcaggccctgccgcc tcgg
CAR123-2 AA	1129	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASG YTFTGYYMHWVRQAPGQGLEWMGWINPNSGGTNYAQKFQGRVTLTRD TSISTVYMELSRLRSDDTAVYYCARDMNILATVPFDIWGQGTMVTVS SGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSISS YLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTVNSL QPEDFATYYCQQGDSVPLTFGGGTRLEIKTTTPAPRPPTPAPTIASQ PLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVI TLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELR VKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST ATKDTYDALHMQALPPR
CAR123-2 scFv	1130	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASG YTFTGYYMHWVRQAPGQGLEWMGWINPNSGGTNYAQKFQGRVTLTRD TSISTVYMELSRLRSDDTAVYYCARDMNILATVPFDIWGQGTMVTVS SGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSISS YLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTVNSL QPEDFATYYCQQGDSVPLTFGGGTRLEIK

CAR123-2 VH	1131	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEW MGWINPNSGGTNYAQKFQGRVTLTRDTSISTVYMELSRLRSDDTAVY YCARDMNILATVPFDIWGQGTMVTVSS
CAR123-2 VL	1132	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTVNSLQPEDFATYYCQQGDSV PLTFGGGTRLEIK
CAR123-3 NT	1133	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggccccaagtccaactcgttcaatccggcgcagaag tcaagaagccaggagcatcagtgaaagtgtcctgcaaagcctcaggc tacatcttcacgggatactacatccactgggtgcgccaggctccggg ccagggccttgagtggatgggctggatcaaccctaactctgggggaa ccaactacgctcagaagttccaggggagggtcactatgactcgcgat acctccatctccactgcgtacatggaactctcgggactgagatccga cgatcctgccgtgtactactgcgcccgggacatgaacatcttggcga ccgtgccgtttgacatttggggacagggcaccctcgtcactgtgtcg agcggtggaggaggctcgggggtggcggatcaggaggggaggaag cgacatccagctgactcagagcccatcgtcgttgtccgcgtcggtgg gggatagagtgaccattacttgccgcgccagccagagcatctcatca tatctgaattggtaccagcagaagcccggaaaggccccaaaactgct gatctacgctgcaagcagcctccaatcgggagtgccgtcacggttct ccgggtccggttcgggaactgactttaccctgaccgtgaattcgctg caaccggaggatttcgccacgtactactgtcagcaaggagactccgt gccgctgaccttcggtggaggcaccaaggtcgaaatcaagaccacta ccccagcaccgaggccacccaccccggctcctaccatcgcctcccag cctctgtccctgcgtccggaggcatgtagacccgcagctggtggggc cgtgcatacccggggtcttgacttcgcctgcgatatctacatttggg cccctctggctggtacttgcggggtcctgctgctttcactcgtgatc actctttactgtaagcgcggtcggaagaagctgctgtacatctttaa gcaacccttcatgaggcctgtgcagactactcaagaggaggacggct gttcatgccggttcccagaggaggaggaaggcggctgcgaactgcgc gtgaaattcagccgcagcgcagatgctccagcctacaagcaggggca gaaccagctctacaacgaactcaatcttggtcggagagaggagtacg

		acgtgctggacaagcggagaggacgggacccagaaatgggcgggaag ccgcgcagaaagaatccccaagagggcctgtacaacgagctccaaaa ggataagatggcagaagcctatagcgagattggtatgaaaggggaac gcagaagaggcaaaggccacgacggactgtaccagggactcagcacc gccaccaaggacacctatgacgctcttcacatgcaggccctgccgcc tcgg
CAR123-3 AA	1134	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASG YIFTGYYIHWVRQAPGQGLEWMGWINPNSGGTNYAQKFQGRVTMTRD TSISTAYMELSGLRSDDPAVYYCARDMNILATVPFDIWGQGTLVTVS SGGGGSGGGGSGGGGSDIQLTQSPSSLSASVGDRVTITCRASQSISS YLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTVNSL QPEDFATYYCQQGDSVPLTFGGGTKVEIKTTTPAPRPPTPAPTIASQ PLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVI TLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELR VKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGK PRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST ATKDTYDALHMQALPPR
CAR123-3 scFv	1135	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASG YIFTGYYIHWVRQAPGQGLEWMGWINPNSGGTNYAQKFQGRVTMTRD TSISTAYMELSGLRSDDPAVYYCARDMNILATVPFDIWGQGTLVTVS SGGGGSGGGGSGGGGSDIQLTQSPSSLSASVGDRVTITCRASQSISS YLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTVNSL QPEDFATYYCQQGDSVPLTFGGGTKVEIK
CAR123-3 VH	1136	QVQLVQSGAEVKKPGASVKVSCKASGYIFTGYYIHWVRQAPGQGLEW MGWINPNSGGTNYAQKFQGRVTMTRDTSISTAYMELSGLRSDDPAVY YCARDMNILATVPFDIWGQGTLVTVSS
CAR123-3 VL	1137	DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTVNSLQPEDFATYYCQQGDSV PLTFGGGTKVEIK
CAR123-4 NT	1138	atggccctccctgtcaccgccctgctgcttccgctggctcttctgct ccacgccgctcggccccaagtccaactccaacagtcaggcgcagaag tgaaaaagagcggtgcatcggtgaaagtgtcatgcaaagcctcgggc

		tacaccttcactgactactatatgcactggctgcggcaggcaccggg acagggacttgagtggatgggatggatcaacccgaattcaggggaca ctaactacgcgcagaagttccaggggagagtgaccctgacgagggac acctcaatttcgaccgtctacatggaattgtcgcgcctgagatcgga cgatactgctgtgtactactgtgcccgcgacatgaacatcctcgcga ctgtgccttttgatatctggggacaggggactatggtcaccgtttcc tccgcttccggtggcggaggctcgggaggccgggcctccggtggagg aggcagcgacatccagatgactcagagcccttcctcgctgagcgcct cagtgggagatcgcgtgaccatcacttgccgggccagccagtccatt tcgtcctacctcaattggtaccagcagaagccgggaaaggcgcccaa gctcttgatctacgctgcgagctccctgcaaagcggggtgccgagcc gattctcgggttccggctcgggaaccgacttcactctgaccatctca tccctgcaaccagaggactttgccacctactactgccaacaaggaga ttctgtcccactgacgttcggcggaggaaccaaggtcgaaatcaaga ccactaccccagcaccgaggccacccaccccggctcctaccatcgcc tcccagcctctgtccctgcgtccggaggcatgtagacccgcagctgg tggggccgtgcatacccggggtcttgacttcgcctgcgatatctaca tttgggcccctctggctggtacttgcggggtcctgctgctttcactc gtgatcactctttactgtaagcgcggtcggaagaagctgctgtacat ctttaagcaacccttcatgaggcctgtgcagactactcaagaggagg acggctgttcatgccggttcccagaggaggaggaaggcggctgcgaa ctgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagca ggggcagaaccagctctacaacgaactcaatcttggtcggagagagg agtacgacgtgctggacaagcggagaggacgggacccagaaatgggc gggaagccgcgcagaaagaatccccaagagggcctgtacaacgagct ccaaaaggataagatggcagaagcctatagcgagattggtatgaaag gggaacgcagaagaggcaaaggccacgacggactgtaccagggactc agcaccgccaccaaggacacctatgacgctcttcacatgcaggccct gccgcctcgg
CAR123-4 AA	1139	MALPVTALLLPLALLLHAARPQVQLQQSGAEVKKSGASVKVSCKASG YTFTDYYMHWLRQAPGQGLEWMGWINPNSGDTNYAQKFQGRVTLTRD TSISTVYMELSRLRSDDTAVYYCARDMNILATVPFDIWGQGTMVTVS

		SASGGGGSGGRASGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSI SSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQGDSVPLTFGGGTKVEIKTTTPAPRPPTPAPTIA SQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSL VITLYCK
CAR123-4 scFv	1140	MALPVTALLLPLALLLHAARPQVQLQQSGAEVKKSGASVKVSCKASG YTFTDYYMHWLRQAPGQGLEWMGWINPNSGDTNYAQKFQGRVTLTRD TSISTVYMELSRLRSDDTAVYYCARDMNILATVPFDIWGQGTMVTVS SASGGGGSGGRASGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSI SSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQGDSVPLTFGGGTKVEIK
CAR123-4 VH	1141	QVQLQQSGAEVKKSGASVKVSCKASGYTFTDYYMHWLRQAPGQGLEW MGWINPNSGDTNYAQKFQGRVTLTRDTSISTVYMELSRLRSDDTAVY YCARDMNILATVPFD**I**WGQGTMVTVSS
CAR123-4 VL	1142	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGDSV PLTFGGGTKVEIK

En algunas modalidades, el dominio de unión a antígeno comprende una HC CDR1, una HC CDR2, y una HC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada listadas en la **Tabla 16**. En modalidades, el dominio de unión al antígeno comprende adicionalmente una LC CDR1, una LC CDR2, y una LC CDR3. En modalidades, el dominio de union a antígeno comprende una LC CDR1, una LC CDR2, y una LC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera listadas en la **Tabla 16**.

En algunas modalidades, el dominio de unión a antígeno cmoprende una, dos o todas de las LC CDR1, LC CDR2, y LC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera listadas en la **Tabla 16**, y una, dos o todas de las HC CDR1, HC CDR2, y HC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada listadas en la **Tabla 16**.

En algunas modalidades, las CDRs están definidas de acuerdo con el esquema de

numeración de Kabat, el esquema de numeración de Chothia, o una combinación de los mismos.

Las secuencias de las secuencias de las CDR humanas de los dominios de scFv se muestran en la **Tabla 17** para los dominios variables de la cadena pesada y en la **Tabla 18** para los dominios variables de la cadena ligera. Las "ID" aparecen para su respectivo SEQ ID NO para cada CDR.

Tabla 17. CDRs de dominio variable de la cadena pesada

Candidato	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQID NO:
CAR123-1	GYTFTDYYMH	1006	WINPNSGDTNYAQKFQG	1010	DMNILATVPFDI	1014
CAR123-2	GYTFTGYYMH	1007	WINPNSGGTNYAQKFQG	1011	DMNILATVPFDI	1015
CAR123-3	GYTFTGYYMH	1008	WINPNSGGTNYAQKFQG	1012	DMNILATVPFDI	1016
CAR123-4	GYIFTGYYIH	1009	WINPNSGGTNYAQKFQG	1013	DMNILATVPFDI	1017

Tabla 18. CDRs de dominio variable de la cadena pesada

Candidato	LCDR1	SEQ ID NO:	LCDR2	SEQ ID NO:	LCDR3	SEQ ID NO:
CAR123-1	RASQSISSYLN	1018	AASSLQS	1022	QQGDSVPLT	1026
CAR123-2	RASQSISTYLN	1019	AAFSLQS	1023	QQGDSVPLT	1027
CAR123-3	RASQSISSYLN	1020	AASSLQS	1024	QQGDSVPLT	1028
CAR123-4	RASQSISSYLN	1021	AASSLQS	1025	QQGDSVPLT	1029

En una modalidad, el inhibidor de la célula B comprende un CAR CD123 que comprende un anticuerpo o fragment de anticuerpo que incluye un dominio de unión a CD123, en donde dicho dominio de unión a CD123 comprende una o más de la secuencia de aminoácidos de la región 1 determinante de la complementariedad de la cadena ligera (LC

CDR1), región 2 determinante de la complementariedad de la cadena ligera (LC CDR2), y la región 3 determinante de la complementariedad de la cadena ligera (LC CDR3) listada en la **Tabla 18**, y una o más de la región 1 determinante de la complementariedad de la cadena pesada (HC CDR1), región 2 determinante de la complementariedad de la cadena pesada (HC CDR2), y la región 3 determinante de la complementariedad de la cadena pesada (HC CDR3) de cualquier secuencia de aminoácidos del dominio de unión a CD123 de la cadena pesada listada en la **Tabla 17**.

Las secuencias adicionales de CDR CD123 de los dominios scFv se muetsran en las Tablas **19, 21 y 23** para los dominios variables de la cadena pesada y en las Tablas **20, 22, y 24** para los dominios variables de la cadena ligera. Las "ID" aparecen para la respective SEQ ID NO para cada CDR.

Las CDRs proporcionadas en las **Tablas 19 y 20** están de acuerdo a la combinación d elos esuqemas de numeración de Kabat y Chothia.

Tabla 19. CDRs de dominio variable de la cadena pesada

Candidato	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:
CAR123-1	GYTFTDYYMH	1030	WINPNSGDTNYAQKFQG	1034	DMNILATVPFDI	1038
CAR123-2	GYTFTGYYMH	1031	WINPNSGGTNYAQKFQG	1035	DMNILATVPFDI	1039
CAR123-3	GYIFTGYYIH	1032	WINPNSGGTNYAQKFQG	1036	DMNILATVPFDI	1040
CAR123-4	GYTFTGYYMH	1033	WINPNSGGTNYAQKFQG	1037	DMNILATVPFDI	1041

Tabla 20. CDRs de dominio variable de la cadena ligera

Candidato	LCDR1	SEQ ID NO:	LCDR2	SEQ ID NO:	LCDR3	SEQ ID NO:
CAR123-1	RASQSISTYLN	1042	AASSLQS	1046	QQGDSVPLT	1050
CAR123-2	RASQSISSYLN	1043	AAFSLQS	1047	QQGDSVPLT	1051
CAR123-3	RASQSISSYLN	1044	AASSLQS	1048	QQGDSVPLT	1052
CAR123-4	RASQSISSYLN	1045	AASSLQS	1049	QQGDSVPLT	1053

En una modalidad, el inhibidor de la célula B comprende un CAR CD123 que comprende un anticuerpo o fragment de anticuerpo que incluye un dominio de unión a CD123, en donde dicho dominio de unión a CD123 comprende una o más de la secuencia de aminoácidos de la región 1 determinante de la complementariedad de la cadena ligera (LC CDR1), región 2 determinante de la complementariedad de la cadena ligera (LC CDR2), y la región 3 determinante de la complementariedad de la cadena ligera (LC CDR3) listada en la **Tabla 20**, y una o más de la región 1 determinante de la complementariedad de la cadena pesada (HC CDR1), región 2 determinante de la complementariedad de la cadena pesada (HC CDR2), y la región 3 determinante de la complementariedad de la cadena pesada (HC CDR3) de cualquier secuencia de aminoácidos del dominio de unión a CD123 de la cadena pesada listada en la **Tabla 19**.

Tabla 21. CDRs del dominio variable de la cadena pesada de acuerdo con el esquema de numeración de Kabat (Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD)

Candidato	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:
CAR123-1	GYYMH	1054	WINPNSGGTNYAQKFQG	1058	DMNILATVPFDI	1062
CAR123-2	GYYMH	1055	WINPNSGGTNYAQKFQG	1059	DMNILATVPFDI	1063
CAR123-3	GYYIH	1056	WINPNSGGTNYAQKFQG	1060	DMNILATVPFDI	1064
CAR123-4	DYYMH	1057	WINPNSGDTNYAQKFQG	1061	DMNILATVPFDI	1065

Tabla 26. CDRs del dominio variable de la cadena ligera de acuerdo con el esquema de numeración de Kabat (Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD)

Candidate	LCDR1	SEQ ID NO:	LCDR2	SEQ ID NO:	LCDR3	SEQ ID NO:
CAR123-1	RASQSISTYLN	1066	AAFSLQS	1070	QQGDSVPLT	1074
CAR123-2	RASQSISSYLN	1067	AASSLQS	1071	QQGDSVPLT	1075
CAR123-3	RASQSISSYLN	1068	AASSLQS	1072	QQGDSVPLT	1076

CAR123-4	RASQSISSYLN	1069	AASSLQS	1073	QQGDSVPLT	1077

En una modalidad, el inhibidor de la célula B comprende un CAR CD123 que comprende un anticuerpo o fragment de anticuerpo que incluye un dominio de unión a CD123, en donde dicho dominio de unión a CD123 comprende una o más de la secuencia de aminoácidos de la región 1 determinante de la complementariedad de la cadena ligera (LC CDR1), región 2 determinante de la complementariedad de la cadena ligera (LC CDR2), y la región 3 determinante de la complementariedad de la cadena ligera (LC CDR3) listada en la **Tabla 22**, y una o más de la región 1 determinante de la complementariedad de la cadena pesada (HC CDR1), región 2 determinante de la complementariedad de la cadena pesada (HC CDR2), y la región 3 determinante de la complementariedad de la cadena pesada (HC CDR3) de cualquier secuencia de aminoácidos del dominio de unión a CD123 de la cadena pesada listada en la **Tabla 21**.

Tabla 23. CDRs del dominio variable de la cadena pesada de acuerdo con el esquema de numeración de Chothia (Al-Lazikani et al., (1997) JMB 273,927-948)

Candidato	**HCDR1**	**SEQ ID NO:**	**HCDR2**	**SEQ ID NO:**	**HCDR3**	**SEQ ID NO:**
CAR123-1	GYTFTGY	1078	NPNSGG	1082	DMNILATVPFDI	1086
CAR123-2	GYTFTGY	1079	NPNSGG	1083	DMNILATVPFDI	1087
CAR123-3	GYIFTGY	1080	NPNSGG	1084	DMNILATVPFDI	1088
CAR123-4	GYTFTDY	1081	NPNSGD	1085	DMNILATVPFDI	1089

Tabla 24. CDRs del dominio variable de la cadena ligera de acuerdo con el esquema de numeración de Chothia (Al-Lazikani et al., (1997) JMB 273,927-948)

Candidato	**LCDR1**	**SEQ ID NO:**	**LCDR2**	**SEQ ID NO:**	**LCDR3**	**SEQ ID NO:**
CAR123-1	SQSISTY	1090	AAF	1094	GDSVPL	1098
CAR123-2	SQSISSY	1091	AAS	1095	GDSVPL	1099
CAR123-3	SQSISSY	1092	AAS	1096	GDSVPL	1100
CAR123-4	SQSISSY	1093	AAS	1097	GDSVPL	1101

En una modalidad, el inhibidor de la célula B comprende un CAR CD123 que

comprende un anticuerpo o fragment de anticuerpo que incluye un dominio de unión a CD123, en donde dicho dominio de unión a CD123 comprende una o más de la secuencia de aminoácidos de la región 1 determinante de la complementariedad de la cadena ligera (LC CDR1), región 2 determinante de la complementariedad de la cadena ligera (LC CDR2), y la región 3 determinante de la complementariedad de la cadena ligera (LC CDR3) listada en la **Tabla 24**, y una o más de la región 1 determinante de la complementariedad de la cadena pesada (HC CDR1), región 2 determinante de la complementariedad de la cadena pesada (HC CDR2), y la región 3 determinante de la complementariedad de la cadena pesada (HC CDR3) de cualquier secuencia de aminoácidos del dominio de unión a CD123 de la cadena pesada listada en la **Tabla 23**.

Se proporciona una descripción adicional de tales CARs CD123, por ejemplo, en PCT/CN2014/090508, cuya solicitud se incorpora como referencia en la presente en su totalidad.

Se evaluó la actividad de los constructos CAR anti-CD123 humanos usando una línea celular Jurkat que contiene un reportero de luciferasa inducido por el promotor NFAT (denominadas células JNL). La actividad del CAR CD123 fue medida para cuatro constructos humanos de CAR descritos en el presente documento (CD123 CAR1-4) y los constructos CAR CD123 murinos 1172 y 1176. La actividad del CAR fue medida como la activación del reportero inducido por NFAT. Los sobrenadadntes lentivirales que contienen los constructos CART fueron añadidos a las células JNL para su transducción. 4-6 días después de la transducción, las células JNL fueron evaluadas para medir la expression de CAR mediante FACS como se describe a continuación o fueron mezcladas con líneas celulares positivas para el blanco (MOLM3, K562 células modificadas para expresar CD123 (CD123-K562)) o negativas para el blanco (K562) en un efector (JNL) para dirigirse a una línea celular proporción (E:T) de 3:1 para desencadenar la activación (Figura 41). Después de 20 horas de co-incubación, se midió la señal de luciferasa usando el ensayo de luciferasa Bright-Glo™ Luciferase Assay en el instrumento EnVision como se muestra en la Figura 42.

Se seleccionaron los constructos CAR anti-CD123 óptimos en base a la cantidad y calidad de las respuestas de las células T efectoras de las células T CAR CD123transducidas ("CAR-CD123" o "células TCAR-CD123") en respuesta a blancos que expresan CD123 ("CD123 +"). Las respuestas de células T efectoras incluyen, pero no se limitan a, la expansión,

la proliferación, la duplicación, la producción celular de citocinas y la destrucción de las células blanco o la actividad citolítica (degranulación).

Generación del CART-CD123

Los vectores lentivirales de transferencia que codifican el scFv humanos se utilizaron para producir el material genómico empaquetado en las partículas lentivirales VSVG pseudotipadas. El ADN del vector lentiviral de transferencia se mezcló con los tres componentes del embalaje de VSVG, gag/pol y rev en combinación con el reactivo de lipofectamina para transfectar juntos en a las células Lenti-X 293T (Clontech).

Después de 30 horas, se recogió el medio, se filtra y se almacena a -80ºC. Los CAR-CD123 terapéuticos fueron generados con la sangre de un donante normal cuyas células T inalteradas se obtuvieron mediante la selección negativa para las células T, linfocitos CD4 + y CD8 +. Estas células se activaron por perlas CD3x28 (Dynabeads® Human T-Expander CD3 / CD28, Invitrogen) en una proporción de 1: 3en RPMI 1640 10% de suero de fetal bovino, inactivado por calor (FCS), 2 mM L-glutamina, 1x penicilina/estreptomicina, 100 mM de aminoácidos no esenciales, 1 mM piruvato de soido, mM Hepes 10, y 55 mM 2-mercaptoetanol a 37 °C, 5% de CO_2. Las células T se cultivaron a $1x10^6$ células T en 0,5 ml de medio por pozo de una placa de 24 pozos. Después de 24 horas, las células T estaban proliferando y se añadieron 0,5 ml de sobrenadante viral. Las células T comenzaron entonces a dividirse en un patrón de crecimiento logarítmico, que se controló midiendo los recuentos de células por ml, y se diluyeron las células T en medio fresco cada dos días. Como las células T comenzaron a descansar después de aproximadamente 10 días, el crecimiento logarítmico disminuyó. La combinación de la tasa de desaceleración del crecimiento y el tamaño de las células T se aproxima ~300 fl determinó el estado de las células T para ser criopreservados para su posterior análisis.

Antes de la crioconservación, el porcentaje de células transducidas (que expresan el CAR anti-CD123 en la superficie celular), y su intensidad de fluorescencia relativa de expresión se determinaron mediante análisis de citometría de flujo en un LSRFortessa BD o BD-FACSCanto utilizando proteína L como reactivo de detección. Las gráficas del histograma de diferenciamiento de intensidad de fluorescencia relativa de que FACS para la señal superior de las células no teñidas demostraron el porcentaje de células T transducidas. La transducción

resultó en una serie de células positivas en un rango de 12 hasta 42% como se muestra en la Figura 42.

La evaluación de la actividad citolítica de las células T CAR-CD123 redirigidas.

Para evaluar las capacidades funcionales de las células TCAR-CD123 para matar las células que expresan al blanco, las células se descongelaron y se dejaron recuperar durante la noche.

La muerte de células T se dirige hacia líneas celulares MOLM13 de *leucemia mielógena aguda* que expresan CD123 que expresan luciferasa de forma estable. Se utilizaron las células T no transducidas para determinar los niveles de fondo no específicos de muerte. Las actividades citolíticas de CART-CD123 se midieron como una titulación de proporciones de efector: célula diana de 4:1 y diluciones de 2 veces a la baja de células T en los que se definen los efectores como las células T que expresan el receptor quimérico anti-CD123. Los ensayos se iniciaron mediante la mezcla de un número adecuado de células T con un número constante de células diana. Después de 20 horas se midió la señal de luciferasa usando el ensayo de luciferasa Bright Glo-™ en el instrumento EnVision. A medida que se incrementó la proporción de células T que expresan CAR-CD123 las células T no transducidas, se incrementó de manera similar la destrucción de las células CD123. Los datos presentados en este documento sugieren que esas células que expresan CD123 se destruyen solamente por las células T que expresan el CAR-CD23 y no por las células T no transducidas. Figura 43.

Transducción de células T

Los clones humanos NVS 2 anti-CD123 humanos (que expresan CAR123-2), NVS 3 (que expresan CAR123-3), NVS 4 (que expresan CAR123-4) fueron seleccionados para el estudio adicional. Todos estos clones tenían una reacción cruzada contra CD123 de cynomolgus. Su actividad se comparó con los clones 1172 y 1176de ratones, que comprenden los Dominios VH y VL en una orientación ligera a pesado con un Dominio bisagra CD8, dominio transmembrana CD8 y un dominio co-estimulador 41BB. 1176 también tiene una reacción cruzada contra CD123cynomolgus. 1172 no la tiene.

Los plásmidos se transformaron en células competentes, cultivadas en 500cc de caldo, aislado por maxiprep, y transducidas utilizando métodos estándar en células 293T. El

sobrenadante lentiviral se recogió a las 24 y 48 horas, se concentró mediante ultracentrifugación, y se congeló.

El lentivirus se tituló en células SupT1 y se determinó la cantidad adecuada de virus para una transducción de células T primarias a una MOI de 3. Las células CD4 + CD8 primarias de un donante normal se estimularon usando perlas anti-CD3/CD28 (Dynal, Invitrogen) y interleucina-2 100 U/ml durante 6 días, seguido del desprendimiento de las perlas y fueron congelados una vez. El volumen celular de las células T disminuye a <300fL (después de aproximadamente 10-12 días).

La eficacia de la transducción de células T era prácticamente 100% para todos los clones (Fig. 44a y 44b). CD4: CD8 fueron de aproximadamente 1: 1 en los clones NVS, y 3: 2 en los 1172 y 1176 clones (Fig 45).

Degranulación

Para evaluar la desgranulación, las células de CART (clones NVS 2-4, 1172 y 1176) fueron descongeladas, reposadas durante la noche a una concentración de células $2e^6$/ ml en medio de células T. Las células se contaron y se resuspendieron a $1e^6$ células / ml al día siguiente. Las células diana tumorales (TCM, PMA / iono, MOLM14 o Jurkat) se resuspendieron a $5e^6$ células / ml. Las células se sembraron en una relación de células T $1e^5$: $5e^5$células tumorales en placas de 48 pozos y se incubaron durante 2 horas en presencia de anti-CD107a PECy7, el anti-CD49d se purificó, y anticuerpos purificados anti-CD28. Las células se recogieron a continuación, se tiñeron con CPA anti-CD3 y adquiridas usando BD LSR Fortessa (Fig. 46).

La desgranulación de las células T se indica en el cuadrante superior derecho de cada gráfica de la Figura 46. Los resultados presentados en este documento demuestran el reconocimiento similar de células T de los blancos CD123 +, que se manifiesta por la desgranulación similar durante un ensayo in vitro de 2-hr. C1176 tenía desgranulación inferior de 65% en comparación con aproximadamente 80% en los otros clones.

Citotoxicidad

Para evaluar la citotoxicidad, las células de CART (clones NVS 2-4, 1172 y 1176) se descongelaron y reposaron durante la noche a $2e^6$ células/ ml en medio de células T. Las células se contaron y se resuspendieron a $1e^6$ células / ml al día siguiente. Las células diana tumorales

(MOLM14) se resuspendieron a $1e^6$ células / ml. Las células se sembraron en una placa negra de fondo plano de 96 pozos a una disminución de las proporciones E: T como se indica (figura 47), por duplicado. Después de 20 horas de incubación, se añadió luciferina y la placa fue fotografiada para determinar flujo de fotones como una medida de las células vivas residuales. La destrucción de las células MOLM14 fue equivalente entre todos los clones en la mayoría de las proporciones efector: diana a las 20 horas.

Modelo de ratón in vivo

Los ratones GSN fueron inyectados iv con $1e^6$ células MOLM14 que expresan luciferasa en D0. En D6 los ratones fueron registrados (IVIS Spectrum) para la carga tumoral y asignados al azar en grupos de tratamiento. Los ratones con la carga tumoral más baja fueron asignados al grupo control (células T no transducidas, UTD). Las células TCAR (clones NVS 2-4, 1172 y 1176) o las células T de control ($1e^6$) fueron inyectadas por vía intravenosa en el D7. Los datos de formación de imágenes en realizadas en el D13 se muestran en la Figura 48. Seis días después de la inyección, todas los constructos anti-CD123 proporcionados presentaron un efecto anti-tumor igual, consistente con los datos in vitro.

Se generan los fragmentos variables de cadena sencilla anti-CD123 humanizados (scFv) basado en murino 1176 que tiene reacción cruzada contra CD123 de cynomolgus y se clonaron en un vector de expresión lentiviral con la cadena CD3zeta intracelular y el dominio co-estimulador intracelular de 4-1BB.

El orden en que los Dominios VL y VH aparecen en el scFv se varió (es decir, orientación VL-VH, o VH-VL), y en donde ya sea que tres o cuatro copias de la subunidad "G4S", (SEQ ID NO: 18), en el que cada subunidad comprende la secuencia de GGGGS (SEQ ID NO: 18) (por ejemplo, $(G4S)_3$ (SEQ ID NO: 107) o $(G4S)_4$ (SEQ ID NO: 106)), conectan los Dominios variables para crear la totalidad del Dominio scFv, como se muestra en la Tabla 25.

Las secuencias de los CARs humanizados se proporcionan a continuación en la Tabla 25.

Todos estos clones contenían un cambio de residuo Q / K en el dominio señal del dominio co-estimulador derivado de la cadena CD3zeta.

Tabla 25: Constructos CAR CD123 Humanizados

Nombre	SEQ ID	Secuencia
hzCAR123-1 NT	1143	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGC TCGGCCCCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGGCGCTA GCGTGAAAGTGTCCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAAT TGGGTCAGACAGGCGCCCGGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTA CGACTCCGAAACCCATTACAACCAGAAGTTCAAGGACCGCGTGACCATGACTGTGG ATAAGTCCACTTCCACCGCTTACATGGAGCTGTCCAGCCTGCGCTCCGAGGATACC GCAGTGTACTACTGCGCCCGGGGAAACTGGGACGACTATTGGGGACAGGGAACTAC CGTGACCGTGTCAAGCGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCG GCTCAGGGGGCGGAGGAAGCGACGTGCAGCTCACCCAGTCGCCCTCATTTCTGTCG GCCTCAGTGGGAGACAGAGTGACCATTACTTGTCGGGCCTCCAAGAGCATCTCCAA GGACCTGGCCTGGTATCAGCAGAAGCCAGGAAAGGCGCCTAAGTTGCTCATCTACT CGGGGTCGACCCTGCAATCTGGCGTGCCGTCCCGGTTCTCCGGTTCGGGAAGCGGT ACCGAATTCACCCTTACTATCTCCTCCCTGCAACCGGAGGACTTCGCCACCTACTA CTGCCAACAGCACAACAAGTACCCGTACACTTTCGGGGGTGGCACGAAGGTCGAAA TCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCC CAGCCTCTGTCCCTGCGTCCGGAggcatgtagacccgcagctggtggggccgtgca tacccggggtcttgacttcgcctgcgatatctacatttgggcccctctggctggta cttgcggggtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcgg aagaagctgctgtacatctttaagcaacccttcatgaggcctgtgcagactactca agaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgcgaac tgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaac cagctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaa gcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaag agggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagatt ggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggact cagcaccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctc gg
hzCAR123-1 AA	1144	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMN WVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDT AVYYCARGNWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLS ASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSG TEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIAS QPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGR KKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQN QLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEI GMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
hzCAR123-1	1145	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAP

scFv		GQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDD YWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCRASKSIS KDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHN KYPYTFGGGTKVEIK
hzCAR123-1 VH	1146	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-1 VL	1147	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRF SGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-2 NT	1148	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGC TCGGCCCCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGGCGCTA GCGTGAAAGTGTCCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAAT TGGGTCAGACAGGCGCCCGGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTA CGACTCCGAAACCCATTACAACCAGAAGTTCAAGGACCGCGTGACCATGACTGTGG ATAAGTCCACTTCCACCGCTTACATGGAGCTGTCCAGCCTGCGCTCCGAGGATACC GCAGTGTACTACTGCGCCCGGGGAAACTGGGACGACTATTGGGGACAGGGAACTAC CGTGACCGTGTCAAGCGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCG GCTCAGGGGGCGGAGGAAGCGAAGTGGTGCTGACCCAGTCGCCCGCAACCCTCTCT CTGTCGCCGGGAGAACGCGCCACTCTTTCCTGTCGGGCGTCCAAGAGCATCTCAAA GGACCTCGCCTGGTACCAGCAGAAGCCTGGTCAAGCCCCGCGGCTGCTGATCTACT CCGGCTCCACGCTGCAATCAGGAATCCCAGCCAGATTTTCCGGTTCGGGGTCGGGG ACTGACTTCACCTTGACCATTAGCTCGCTGGAACCTGAGGACTTCGCCGTGTATTA CTGCCAGCAGCACAACAAGTACCCGTACACCTTCGGAGGCGGTACTAAGGTCGAGA TCAAGACCACTACCCCAGCACCGAGGCCACCCACCCCGGCTCCTACCATCGCCTCC CAGCCTCTGTCCCTGCGTCCGGAggcatgtagacccgcagctggtggggccgtgca tacccggggtcttgacttcgcctgcgatatctacatttgggcccctctggctggta cttgcggggtcctgctgctttcactcgtgatcactctttactgtaagcgcggtcgg aagaagctgctgtacatctttaagcaacccttcatgaggcctgtgcagactactca agaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgcgaac tgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaac cagctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaa gcggagaggacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaag agggcctgtacaacgagctccaaaaggataagatggcagaagcctatagcgagatt ggtatgaaaggggaacgcagaagaggcaaaggccacgacggactgtaccagggact cagcaccgccaccaaggacacctatgacgctcttcacatgcaggccctgccgcctc gg
hzCAR123-2 AA	1149	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA

		VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-2 scFv	1150	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-2 VH	1151	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-2 VL	1152	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARF SGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-3 NT	1153	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGGCGCTAGCGTGAAAGTGT CCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAATTGGGTCAGACAGGCGCCC GGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTACGACTCCGAAACCCATTACAACCA GAAGTTCAAGGACCGCGTGACCATGACTGTGGATAAGTCCACTTCCACCGCTTACATGGAGC TGTCCAGCCTGCGCTCCGAGGATACCGCAGTGTACTACTGCGCCCGGGGAAACTGGGACGAC TATTGGGGACAGGGAACTACCGTGACCGTGTCAAGCGGGGGTGGCGGTAGCGGAGGAGGGGG CTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTCGTGATGACCCAGTCACCGGCAT TCCTGTCCGTGACTCCCGGAGAAAAGGTCACGATTACTTGCCGGGCGTCCAAGAGCATCTCC AAGGACCTCGCCTGGTACCAACAGAAGCCGGACCAGGCCCCTAAGCTGTTGATCTACTCGGG GTCCACCCTTCAATCGGGAGTGCCATCGCGGTTTAGCGGTTCGGGTTCTGGGACCGACTTCA CTTTCACCATCTCCTCACTGGAAGCCGAGGATGCCGCCACTTACTACTGTCAGCAGCACAAC AAGTATCCGTACACCTTCGGAGGCGGTACCAAAGTGGAGATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-3 AA	1154	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA

		TYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-3 scFv	1155	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-3 VH	1156	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-3 VL	1157	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRF SGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-4 NT	1158	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGGCGCTAGCGTGAAAGTGT CCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAATTGGGTCAGACAGGCGCCC GGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTACGACTCCGAAACCCATTACAACCA GAAGTTCAAGGACCGCGTGACCATGACTGTGGATAAGTCCACTTCCACCGCTTACATGGAGC TGTCCAGCCTGCGCTCCGAGGATACCGCAGTGTACTACTGCGCCCGGGGAAACTGGGACGAC TATTGGGGACAGGGAACTACCGTGACCGTGTCAAGCGGGGGTGGCGGTAGCGGAGGAGGGGG CTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGGTCATGACTCAGTCCCCGGACT CACTCGCGGTGTCGCTTGGAGAGAGAGCGACCATCAACTGTCGGGCCTCAAAGAGCATCAGC AAGGACCTGGCCTGGTACCAGCAGAAGCCGGGACAGCCGCCAAAGCTGCTGATCTACTCCGG GTCCACCTTGCAATCTGGTGTCCCTGACCGGTTCTCCGGTTCCGGGTCGGGTACCGACTTCA CGCTCACTATTTCGTCGCTGCAAGCCGAAGATGTGGCCGTGTACTATTGCCAACAGCACAAC AAGTACCCCTACACTTTTGGCGGAGGCACCAAGGTGGAAATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-4 AA	1159	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA

		VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-4 scFv	1160	MALPVTALLLPLALLLHAARPQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-4 VH	1161	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-4 VL	1162	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRF SGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-5 NT	1163	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGACGTGCAGCTCACCCAGTCGCCCTCATTTCTGTCGGCCTCAGTGGGAGACAGAGTGACCA TTACTTGTCGGGCCTCCAAGAGCATCTCCAAGGACCTGGCCTGGTATCAGCAGAAGCCAGGA AAGGCGCCTAAGTTGCTCATCTACTCGGGGTCGACCCTGCAATCTGGCGTGCCGTCCCGGTT CTCCGGTTCGGGAAGCGGTACCGAATTCACCCTTACTATCTCCTCCCTGCAACCGGAGGACT TCGCCACCTACTACTGCCAACAGCACAACAAGTACCCGTACACTTTCGGGGGTGGCACGAAG GTCGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGGCGCTAGCG TGAAAGTGTCCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAATTGGGTCAGA CAGGCGCCCGGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTACGACTCCGAAACCCA TTACAACCAGAAGTTCAAGGACCGCGTGACCATGACTGTGGATAAGTCCACTTCCACCGCTT ACATGGAGCTGTCCAGCCTGCGCTCCGAGGATACCGCAGTGTACTACTGCGCCCGGGGAAAC TGGGACGACTATTGGGGACAGGGAACTACCGTGACCGTGTCAAGCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-5 AA	1164	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA

		VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-5 scFv	1165	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-5 VH	1166	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-5 VL	1167	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRF SGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-6 NT	1168	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGAAGTGGTGCTGACCCAGTCGCCCGCAACCCTCTCTCTGTCGCCGGGAGAACGCGCCACTC TTTCCTGTCGGGCGTCCAAGAGCATCTCAAAGGACCTCGCCTGGTACCAGCAGAAGCCTGGT CAAGCCCCGCGGCTGCTGATCTACTCCGGCTCCACGCTGCAATCAGGAATCCCAGCCAGATT TTCCGGTTCGGGGTCGGGGACTGACTTCACCTTGACCATTAGCTCGCTGGAACCTGAGGACT TCGCCGTGTATTACTGCCAGCAGCACAACAAGTACCCGTACACCTTCGGAGGCGGTACTAAG GTCGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGGCGCTAGCG TGAAAGTGTCCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAATTGGGTCAGA CAGGCGCCCGGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTACGACTCCGAAACCCA TTACAACCAGAAGTTCAAGGACCGCGTGACCATGACTGTGGATAAGTCCACTTCCACCGCTT ACATGGAGCTGTCCAGCCTGCGCTCCGAGGATACCGCAGTGTACTACTGCGCCCGGGGAAAC TGGGACGACTATTGGGGACAGGGAACTACCGTGACCGTGTCAAGCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-6 AA	1169	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA

		VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-6 scFv	1170	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-6 VH	1171	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-6 VL	1172	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARF SGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-7 NT	1173	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGACGTCGTGATGACCCAGTCACCGGCATTCCTGTCCGTGACTCCCGGAGAAAAGGTCACGA TTACTTGCCGGGCGTCCAAGAGCATCTCCAAGGACCTCGCCTGGTACCAACAGAAGCCGGAC CAGGCCCCTAAGCTGTTGATCTACTCGGGGTCCACCCTTCAATCGGGAGTGCCATCGCGGTT TAGCGGTTCGGGTTCTGGGACCGACTTCACTTTCACCATCTCCTCACTGGAAGCCGAGGATG CCGCCACTTACTACTGTCAGCAGCACAACAAGTATCCGTACACCTTCGGAGGCGGTACCAAA GTGGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGGCGCTAGCG TGAAAGTGTCCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAATTGGGTCAGA CAGGCGCCCGGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTACGACTCCGAAACCCA TTACAACCAGAAGTTCAAGGACCGCGTGACCATGACTGTGGATAAGTCCACTTCCACCGCTT ACATGGAGCTGTCCAGCCTGCGCTCCGAGGATACCGCAGTGTACTACTGCGCCCGGGGAAAC TGGGACGACTATTGGGGACAGGGAACTACCGTGACCGTGTCAAGCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-7 AA	1174	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA

		VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-7 scFv	1175	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-7 VH	1176	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-7 VL	1177	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRF SGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-8 NT	1178	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGACGTGGTCATGACTCAGTCCCCGGACTCACTCGCGGTGTCGCTTGGAGAGAGAGCGACCA TCAACTGTCGGGCCTCAAAGAGCATCAGCAAGGACCTGGCCTGGTACCAGCAGAAGCCGGGA CAGCCGCCAAAGCTGCTGATCTACTCCGGGTCCACCTTGCAATCTGGTGTCCCTGACCGGTT CTCCGGTTCCGGGTCGGGTACCGACTTCACGCTCACTATTTCGTCGCTGCAAGCCGAAGATG TGGCCGTGTACTATTGCCAACAGCACAACAAGTACCCCTACACTTTTGGCGGAGGCACCAAG GTGGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCCAAGTGCAGCTGGTCCAGTCGGGAGCCGAAGTCAAGAAGCCCGGCGCTAGCG TGAAAGTGTCCTGCAAAGCCTCCGGGTACACATTCACCTCCTACTGGATGAATTGGGTCAGA CAGGCGCCCGGCCAGGGACTCGAGTGGATGGGAAGGATTGATCCTTACGACTCCGAAACCCA TTACAACCAGAAGTTCAAGGACCGCGTGACCATGACTGTGGATAAGTCCACTTCCACCGCTT ACATGGAGCTGTCCAGCCTGCGCTCCGAGGATACCGCAGTGTACTACTGCGCCCGGGGAAAC TGGGACGACTATTGGGGACAGGGAACTACCGTGACCGTGTCAAGCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-8 AA	1179	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA

		VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-8 scFv	1180	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRVTMTVDKSTSTAYMELSSLRSEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-8 VH	1181	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRVTMTVDKSTSTAYMELSSLRSEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-8 VL	1182	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRF SGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-9 NT	1183	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGGAGCCTCCGTCAAAGTGT CCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAACTGGGTCCGCCAGGCACCT GGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATTCCGAAACCCATTACAATCA GAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGTGTCCACCGCCTACCTCCAAA TTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGCGCTCGCGGAAACTGGGATGAC TATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAGGAGGGGG CTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGCAGCTCACCCAGTCGCCCTCAT TTCTGTCGGCCTCAGTGGGAGACAGAGTGACCATTACTTGTCGGGCCTCCAAGAGCATCTCC AAGGACCTGGCCTGGTATCAGCAGAAGCCAGGAAAGGCGCCTAAGTTGCTCATCTACTCGGG GTCGACCCTGCAATCTGGCGTGCCGTCCCGGTTCTCCGGTTCGGGAAGCGGTACCGAATTCA CCCTTACTATCTCCTCCCTGCAACCGGAGGACTTCGCCACCTACTACTGCCAACAGCACAAC AAGTACCCGTACACTTTCGGGGGTGGCACGAAGGTCGAAATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-9 AA	1184	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA

		TYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-9 scFv	1185	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-9 VH	1186	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-10 VL	1187	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRF SGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-10 NT	1188	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGGAGCCTCCGTCAAAGTGT CCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAACTGGGTCCGCCAGGCACCT GGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATTCCGAAACCCATTACAATCA GAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGTGTCCACCGCCTACCTCCAAA TTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGCGCTCGCGGAAACTGGGATGAC TATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAGGAGGGGG CTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGAAGTGGTGCTGACCCAGTCGCCCGCAA CCCTCTCTCTGTCGCCGGGAGAACGCGCCACTCTTTCCTGTCGGGCGTCCAAGAGCATCTCA AAGGACCTCGCCTGGTACCAGCAGAAGCCTGGTCAAGCCCCGCGGCTGCTGATCTACTCCGG CTCCACGCTGCAATCAGGAATCCCAGCCAGATTTTCCGGTTCGGGGTCGGGGACTGACTTCA CCTTGACCATTAGCTCGCTGGAACCTGAGGACTTCGCCGTGTATTACTGCCAGCAGCACAAC AAGTACCCGTACACCTTCGGAGGCGGTACTAAGGTCGAGATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-10 AA	1189	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA

		VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-10 scFv	1190	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-10 VH	1191	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-10 VL	1192	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARF SGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-11 NT	1193	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGGAGCCTCCGTCAAAGTGT CCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAACTGGGTCCGCCAGGCACCT GGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATTCCGAAACCCATTACAATCA GAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGTGTCCACCGCCTACCTCCAAA TTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGCGCTCGCGGAAACTGGGATGAC TATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAGGAGGGGG CTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTCGTGATGACCCAGTCACCGGCAT TCCTGTCCGTGACTCCCGGAGAAAAGGTCACGATTACTTGCCGGGCGTCCAAGAGCATCTCC AAGGACCTCGCCTGGTACCAACAGAAGCCGGACCAGGCCCCTAAGCTGTTGATCTACTCGGG GTCCACCCTTCAATCGGGAGTGCCATCGCGGTTTAGCGGTTCGGGTTCTGGGACCGACTTCA CTTTCACCATCTCCTCACTGGAAGCCGAGGATGCCGCCACTTACTACTGTCAGCAGCACAAC AAGTATCCGTACACCTTCGGAGGCGGTACCAAAGTGGAGATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-11 AA	1194	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA

		TYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-11 scFv	1195	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-11 VH	1196	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-11 VL	1197	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRF SGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-12 NT	1198	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGGAGCCTCCGTCAAAGTGT CCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAACTGGGTCCGCCAGGCACCT GGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATTCCGAAACCCATTACAATCA GAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGTGTCCACCGCCTACCTCCAAA TTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGCGCTCGCGGAAACTGGGATGAC TATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAGGAGGGGG CTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGGTCATGACTCAGTCCCCGGACT CACTCGCGGTGTCGCTTGGAGAGAGAGCGACCATCAACTGTCGGGCCTCAAAGAGCATCAGC AAGGACCTGGCCTGGTACCAGCAGAAGCCGGGACAGCCGCCAAAGCTGCTGATCTACTCCGG GTCCACCTTGCAATCTGGTGTCCCTGACCGGTTCTCCGGTTCCGGGTCGGGTACCGACTTCA CGCTCACTATTTCGTCGCTGCAAGCCGAAGATGTGGCCGTGTACTATTGCCAACAGCACAAC AAGTACCCCTACACTTTTGGCGGAGGCACCAAGGTGGAAATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-12 AA	1199	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA

		VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-12 scFv	1200	MALPVTALLLPLALLLHAARPQVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQ APGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-12 VH	1201	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-12 VL	1202	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRF SGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-13 NT	1203	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGACGTGCAGCTCACCCAGTCGCCCTCATTTCTGTCGGCCTCAGTGGGAGACAGAGTGACCA TTACTTGTCGGGCCTCCAAGAGCATCTCCAAGGACCTGGCCTGGTATCAGCAGAAGCCAGGA AAGGCGCCTAAGTTGCTCATCTACTCGGGGTCGACCCTGCAATCTGGCGTGCCGTCCCGGTT CTCCGGTTCGGGAAGCGGTACCGAATTCACCCTTACTATCTCCTCCCTGCAACCGGAGGACT TCGCCACCTACTACTGCCAACAGCACAACAAGTACCCGTACACTTTCGGGGGTGGCACGAAG GTCGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGGAGCCTCCG TCAAAGTGTCCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAACTGGGTCCGC CAGGCACCTGGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATTCCGAAACCCA TTACAATCAGAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGTGTCCACCGCCT ACCTCCAAATTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGCGCTCGCGGAAAC TGGGATGACTATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-13 AA	1204	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA

		VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-13 scFv	1205	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-13 VH	1206	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-13 VL	1207	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRF SGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-14 NT	1208	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGAAGTGGTGCTGACCCAGTCGCCCGCAACCCTCTCTCTGTCGCCGGGAGAACGCGCCACTC TTTCCTGTCGGGCGTCCAAGAGCATCTCAAAGGACCTCGCCTGGTACCAGCAGAAGCCTGGT CAAGCCCCGCGGCTGCTGATCTACTCCGGCTCCACGCTGCAATCAGGAATCCCAGCCAGATT TTCCGGTTCGGGGTCGGGGACTGACTTCACCTTGACCATTAGCTCGCTGGAACCTGAGGACT TCGCCGTGTATTACTGCCAGCAGCACAACAAGTACCCGTACACCTTCGGAGGCGGTACTAAG GTCGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGGAGCCTCCG TCAAAGTGTCCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAACTGGGTCCGC CAGGCACCTGGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATTCCGAAACCCA TTACAATCAGAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGTGTCCACCGCCT ACCTCCAAATTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGCGCTCGCGGAAAC TGGGATGACTATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-14 AA	1209	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA

		VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-14 scFv	1210	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-14 VH	1211	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-14 VL	1212	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARF SGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-15 NT	1213	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGACGTCGTGATGACCCAGTCACCGGCATTCCTGTCCGTGACTCCCGGAGAAAAGGTCACGA TTACTTGCCGGGCGTCCAAGAGCATCTCCAAGGACCTCGCCTGGTACCAACAGAAGCCGGAC CAGGCCCCTAAGCTGTTGATCTACTCGGGGTCCACCCTTCAATCGGGAGTGCCATCGCGGTT TAGCGGTTCGGGTTCTGGGACCGACTTCACTTTCACCATCTCCTCACTGGAAGCCGAGGATG CCGCCACTTACTACTGTCAGCAGCACAACAAGTATCCGTACACCTTCGGAGGCGGTACCAAA GTGGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGGAGCCTCCG TCAAAGTGTCCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAACTGGGTCCGC CAGGCACCTGGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATTCCGAAACCCA TTACAATCAGAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGTGTCCACCGCCT ACCTCCAAATTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGCGCTCGCGGAAAC TGGGATGACTATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-15 AA	1214	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA

		VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-15 scFv	1215	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-15 VH	1216	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-15 VL	1217	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRF SGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-16 NT	1218	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGACGTGGTCATGACTCAGTCCCCGGACTCACTCGCGGTGTCGCTTGGAGAGAGAGCGACCA TCAACTGTCGGGCCTCAAAGAGCATCAGCAAGGACCTGGCCTGGTACCAGCAGAAGCCGGGA CAGCCGCCAAAGCTGCTGATCTACTCCGGGTCCACCTTGCAATCTGGTGTCCCTGACCGGTT CTCCGGTTCCGGGTCGGGTACCGACTTCACGCTCACTATTTCGTCGCTGCAAGCCGAAGATG TGGCCGTGTACTATTGCCAACAGCACAACAAGTACCCCTACACTTTTGGCGGAGGCACCAAG GTGGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCCAAGTGCAGCTGGTGCAGTCAGGCAGCGAACTGAAGAAGCCCGGAGCCTCCG TCAAAGTGTCCTGCAAAGCCTCGGGATACACCTTCACCTCCTACTGGATGAACTGGGTCCGC CAGGCACCTGGACAGGGGCTGGAGTGGATGGGAAGGATCGATCCCTACGATTCCGAAACCCA TTACAATCAGAAGTTCAAGGACCGGTTTGTGTTCTCCGTGGACAAGTCCGTGTCCACCGCCT ACCTCCAAATTAGCAGCCTGAAGGCGGAGGATACAGCTGTCTACTACTGCGCTCGCGGAAAC TGGGATGACTATTGGGGCCAGGGAACTACCGTGACTGTGTCCTCCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-16 AA	1219	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA

		VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-16 scFv	1220	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSQVQLVQSGSELKKPGASVKVSCKASGYTFTSY WMNWVRQAPGQGLEWMGRIDPYDSETHYNQKFKDRFVFSVDKSVSTAYLQISSLKAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-16 VH	1221	QVQLVQSGSELKKPGASVKVSCKASGYTFTSYWMNWVRQAPGQGLEWMGRIDPYDSETHYNQ KFKDRFVFSVDKSVSTAYLQISSLKAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-16 VL	1222	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRF SGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-17 NT	1223	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGGAGAATCCCTGAGGATCA GCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAATTGGGTCCGCCAGATGCCC GGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACTCGGAAACCCATTACAACCA GAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCATTTCCACTGCGTACCTCCAGT GGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGCGCACGCGGAAACTGGGATGAT TACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAGGAGGGGG CTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGCAGCTCACCCAGTCGCCCTCAT TTCTGTCGGCCTCAGTGGGAGACAGAGTGACCATTACTTGTCGGGCCTCCAAGAGCATCTCC AAGGACCTGGCCTGGTATCAGCAGAAGCCAGGAAAGGCGCCTAAGTTGCTCATCTACTCGGG GTCGACCCTGCAATCTGGCGTGCCGTCCCGGTTCTCCGGTTCGGGAAGCGGTACCGAATTCA CCCTTACTATCTCCTCCCTGCAACCGGAGGACTTCGCCACCTACTACTGCCAACAGCACAAC AAGTACCCGTACACTTTCGGGGGTGGCACGAAGGTCGAAATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-17 AA	1224	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA

		TYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-17 scFv	1225	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-17 VH	1226	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYNQ KFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR123-17 VL	1227	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRF SGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-18 NT	1228	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGGAGAATCCCTGAGGATCA GCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAATTGGGTCCGCCAGATGCCC GGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACTCGGAAACCCATTACAACCA GAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCATTTCCACTGCGTACCTCCAGT GGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGCGCACGCGGAAACTGGGATGAT TACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAGGAGGGGG CTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGAAGTGGTGCTGACCCAGTCGCCCGCAA CCCTCTCTCTGTCGCCGGGAGAACGCGCCACTCTTTCCTGTCGGGCGTCCAAGAGCATCTCA AAGGACCTCGCCTGGTACCAGCAGAAGCCTGGTCAAGCCCCGCGGCTGCTGATCTACTCCGG CTCCACGCTGCAATCAGGAATCCCAGCCAGATTTTCCGGTTCGGGGTCGGGGACTGACTTCA CCTTGACCATTAGCTCGCTGGAACCTGAGGACTTCGCCGTGTATTACTGCCAGCAGCACAAC AAGTACCCGTACACCTTCGGAGGCGGTACTAAGGTCGAGATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-18 AA	1229	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA

		VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-18 scFv	1230	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-18 VH	1231	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYNQ KFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR123-18 VL	1232	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARF SGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-19 NT	1233	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGGAGAATCCCTGAGGATCA GCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAATTGGGTCCGCCAGATGCCC GGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACTCGGAAACCCATTACAACCA GAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCATTTCCACTGCGTACCTCCAGT GGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGCGCACGCGGAAACTGGGATGAT TACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAGGAGGGGG CTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTCGTGATGACCCAGTCACCGGCAT TCCTGTCCGTGACTCCCGGAGAAAAGGTCACGATTACTTGCCGGGCGTCCAAGAGCATCTCC AAGGACCTCGCCTGGTACCAACAGAAGCCGGACCAGGCCCCTAAGCTGTTGATCTACTCGGG GTCCACCCTTCAATCGGGAGTGCCATCGCGGTTTAGCGGTTCGGGTTCTGGGACCGACTTCA CTTTCACCATCTCCTCACTGGAAGCCGAGGATGCCGCCACTTACTACTGTCAGCAGCACAAC AAGTATCCGTACACCTTCGGAGGCGGTACCAAAGTGGAGATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-19 AA	1234	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA

		TYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-19 scFv	1235	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-19 VH	1236	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYNQ KFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR123-19 VL	1237	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRF SGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-20 NT	1238	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGGAGAATCCCTGAGGATCA GCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAATTGGGTCCGCCAGATGCCC GGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACTCGGAAACCCATTACAACCA GAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCATTTCCACTGCGTACCTCCAGT GGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGCGCACGCGGAAACTGGGATGAT TACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCGGGGGTGGCGGTAGCGGAGGAGGGGG CTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGGTCATGACTCAGTCCCCGGACT CACTCGCGGTGTCGCTTGGAGAGAGAGCGACCATCAACTGTCGGGCCTCAAAGAGCATCAGC AAGGACCTGGCCTGGTACCAGCAGAAGCCGGGACAGCCGCCAAAGCTGCTGATCTACTCCGG GTCCACCTTGCAATCTGGTGTCCCTGACCGGTTCTCCGGTTCCGGGTCGGGTACCGACTTCA CGCTCACTATTTCGTCGCTGCAAGCCGAAGATGTGGCCGTGTACTATTGCCAACAGCACAAC AAGTACCCCTACACTTTTGGCGGAGGCACCAAGGTGGAAATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-20 AA	1239	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA

		VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-20 scFv	1240	MALPVTALLLPLALLLHAARPEVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQ MPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-20 VH	1241	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYNQ KFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR123-20 VL	1242	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRF SGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-21 NT	1243	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGACGTGCAGCTCACCCAGTCGCCCTCATTTCTGTCGGCCTCAGTGGGAGACAGAGTGACCA TTACTTGTCGGGCCTCCAAGAGCATCTCCAAGGACCTGGCCTGGTATCAGCAGAAGCCAGGA AAGGCGCCTAAGTTGCTCATCTACTCGGGGTCGACCCTGCAATCTGGCGTGCCGTCCCGGTT CTCCGGTTCGGGAAGCGGTACCGAATTCACCCTTACTATCTCCTCCCTGCAACCGGAGGACT TCGCCACCTACTACTGCCAACAGCACAACAAGTACCCGTACACTTTCGGGGGTGGCACGAAG GTCGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGGAGAATCCC TGAGGATCAGCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAATTGGGTCCGC CAGATGCCCGGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACTCGGAAACCCA TTACAACCAGAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCATTTCCACTGCGT ACCTCCAGTGGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGCGCACGCGGAAAC TGGGATGATTACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-21 AA	1244	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA

		MYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-21 scFv	1245	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSS
hzCAR123-21 VH	1246	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYNQ KFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR123-21 VL	1247	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRF SGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-22 NT	1248	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGAAGTGGTGCTGACCCAGTCGCCCGCAACCCTCTCTCTGTCGCCGGGAGAACGCGCCACTC TTTCCTGTCGGGCGTCCAAGAGCATCTCAAAGGACCTCGCCTGGTACCAGCAGAAGCCTGGT CAAGCCCCGCGGCTGCTGATCTACTCCGGCTCCACGCTGCAATCAGGAATCCCAGCCAGATT TTCCGGTTCGGGGTCGGGGACTGACTTCACCTTGACCATTAGCTCGCTGGAACCTGAGGACT TCGCCGTGTATTACTGCCAGCAGCACAACAAGTACCCGTACACCTTCGGAGGCGGTACTAAG GTCGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGGAGAATCCC TGAGGATCAGCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAATTGGGTCCGC CAGATGCCCGGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACTCGGAAACCCA TTACAACCAGAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCATTTCCACTGCGT ACCTCCAGTGGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGCGCACGCGGAAAC TGGGATGATTACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-22 AA	1249	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA

		MYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-22 scFv	1250	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSS
hzCAR123-22 VH	1251	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYNQ KFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR123-22 VL	1252	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARF SGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-23 NT	1253	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGACGTCGTGATGACCCAGTCACCGGCATTCCTGTCCGTGACTCCCGGAGAAAAGGTCACGA TTACTTGCCGGGCGTCCAAGAGCATCTCCAAGGACCTCGCCTGGTACCAACAGAAGCCGGAC CAGGCCCCTAAGCTGTTGATCTACTCGGGGTCCACCCTTCAATCGGGAGTGCCATCGCGGTT TAGCGGTTCGGGTTCTGGGACCGACTTCACTTTCACCATCTCCTCACTGGAAGCCGAGGATG CCGCCACTTACTACTGTCAGCAGCACAACAAGTATCCGTACACCTTCGGAGGCGGTACCAAA GTGGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGGAGAATCCC TGAGGATCAGCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAATTGGGTCCGC CAGATGCCCGGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACTCGGAAACCCA TTACAACCAGAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCATTTCCACTGCGT ACCTCCAGTGGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGCGCACGCGGAAAC TGGGATGATTACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-23 AA	1254	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA

		MYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-23 scFv	1255	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSS
hzCAR123-23 VH	1256	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYNQ KFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR123-23 VL	1257	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRF SGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-24 NT	1258	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGACGTGGTCATGACTCAGTCCCCGGACTCACTCGCGGTGTCGCTTGGAGAGAGAGCGACCA TCAACTGTCGGGCCTCAAAGAGCATCAGCAAGGACCTGGCCTGGTACCAGCAGAAGCCGGGA CAGCCGCCAAAGCTGCTGATCTACTCCGGGTCCACCTTGCAATCTGGTGTCCCTGACCGGTT CTCCGGTTCCGGGTCGGGTACCGACTTCACGCTCACTATTTCGTCGCTGCAAGCCGAAGATG TGGCCGTGTACTATTGCCAACAGCACAACAAGTACCCCTACACTTTTGGCGGAGGCACCAAG GTGGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCGAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTCAAGAAGCCTGGAGAATCCC TGAGGATCAGCTGCAAAGGCAGCGGGTATACCTTCACCTCCTACTGGATGAATTGGGTCCGC CAGATGCCCGGAAAAGGCCTGGAGTGGATGGGACGGATTGACCCCTACGACTCGGAAACCCA TTACAACCAGAAGTTCAAGGATCACGTGACCATCTCCGTGGACAAGTCCATTTCCACTGCGT ACCTCCAGTGGTCAAGCCTGAAGGCCTCCGACACTGCTATGTACTACTGCGCACGCGGAAAC TGGGATGATTACTGGGGACAGGGAACAACCGTGACTGTGTCCTCCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-24 AA	1259	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA

		MYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-24 scFv	1260	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGESLRISCKGSGYTFTSY WMNWVRQMPGKGLEWMGRIDPYDSETHYNQKFKDHVTISVDKSISTAYLQWSSLKASDTA MYYCARGNWDDYWGQGTTVTVSS
hzCAR123-24 VH	1261	EVQLVQSGAEVKKPGESLRISCKGSGYTFTSYWMNWVRQMPGKGLEWMGRIDPYDSETHYNQ KFKDHVTISVDKSISTAYLQWSSLKASDTAMYYCARGNWDDYWGQGTTVTVSS
hzCAR123-24 VL	1262	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRF SGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-25 NT	1263	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGGAGGAAGCCTGAGGCTGT CCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAACTGGGTCAGACAGGCACCT GGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACTCCGAAACCCATTACAATCA GAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAAGAGCACCGCGTACCTCCAAA TGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGCGCCCGGGGAAACTGGGATGAT TACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCGGGGGTGGCGGTAGCGGAGGAGGGGG CTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGCAGCTCACCCAGTCGCCCTCAT TTCTGTCGGCCTCAGTGGGAGACAGAGTGACCATTACTTGTCGGGCCTCCAAGAGCATCTCC AAGGACCTGGCCTGGTATCAGCAGAAGCCAGGAAAGGCGCCTAAGTTGCTCATCTACTCGGG GTCGACCCTGCAATCTGGCGTGCCGTCCCGGTTCTCCGGTTCGGGAAGCGGTACCGAATTCA CCCTTACTATCTCCTCCCTGCAACCGGAGGACTTCGCCACCTACTACTGCCAACAGCACAAC AAGTACCCGTACACTTTCGGGGGTGGCACGAAGGTCGAAATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-25 AA	1264	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA

		TYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-25 scFv	1265	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVQLTQSPSFLSASVGDRVTITCR ASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-25 VH	1266	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYNQ KFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-25 VL	1267	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRF SGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-26 NT	1268	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGGAGGAAGCCTGAGGCTGT CCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAACTGGGTCAGACAGGCACCT GGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACTCCGAAACCCATTACAATCA GAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAAGAGCACCGCGTACCTCCAAA TGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGCGCCCGGGGAAACTGGGATGAT TACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCGGGGGTGGCGGTAGCGGAGGAGGGGG CTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGAAGTGGTGCTGACCCAGTCGCCCGCAA CCCTCTCTCTGTCGCCGGGAGAACGCGCCACTCTTTCCTGTCGGGCGTCCAAGAGCATCTCA AAGGACCTCGCCTGGTACCAGCAGAAGCCTGGTCAAGCCCCGCGGCTGCTGATCTACTCCGG CTCCACGCTGCAATCAGGAATCCCAGCCAGATTTTCCGGTTCGGGGTCGGGGACTGACTTCA CCTTGACCATTAGCTCGCTGGAACCTGAGGACTTCGCCGTGTATTACTGCCAGCAGCACAAC AAGTACCCGTACACCTTCGGAGGCGGTACTAAGGTCGAGATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-26 AA	1269	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA

		VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-26 scFv	1270	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-26 VH	1271	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYNQ KFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-26 VL	1272	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARF SGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-27 NT	1273	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGGAGGAAGCCTGAGGCTGT CCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAACTGGGTCAGACAGGCACCT GGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACTCCGAAACCCATTACAATCA GAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAAGAGCACCGCGTACCTCCAAA TGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGCGCCCGGGGAAACTGGGATGAT TACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCGGGGGTGGCGGTAGCGGAGGAGGGGG CTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTCGTGATGACCCAGTCACCGGCAT TCCTGTCCGTGACTCCCGGAGAAAAGGTCACGATTACTTGCCGGGCGTCCAAGAGCATCTCC AAGGACCTCGCCTGGTACCAACAGAAGCCGGACCAGGCCCCTAAGCTGTTGATCTACTCGGG GTCCACCCTTCAATCGGGAGTGCCATCGCGGTTTAGCGGTTCGGGTTCTGGGACCGACTTCA CTTTCACCATCTCCTCACTGGAAGCCGAGGATGCCGCCACTTACTACTGTCAGCAGCACAAC AAGTATCCGTACACCTTCGGAGGCGGTACCAAAGTGGAGATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-27 AA	1274	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA

		TYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-27 scFv	1275	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPAFLSVTPGEKVTITCR ASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-27 VH	1276	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYNQ KFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-27 VL	1277	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRF SGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-28 NT	1278	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGGAGGAAGCCTGAGGCTGT CCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAACTGGGTCAGACAGGCACCT GGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACTCCGAAACCCATTACAATCA GAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAAGAGCACCGCGTACCTCCAAA TGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGCGCCCGGGGAAACTGGGATGAT TACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCGGGGGTGGCGGTAGCGGAGGAGGGGG CTCCGGCGGCGGCGGCTCAGGGGGCGGAGGAAGCGACGTGGTCATGACTCAGTCCCCGGACT CACTCGCGGTGTCGCTTGGAGAGAGAGCGACCATCAACTGTCGGGCCTCAAAGAGCATCAGC AAGGACCTGGCCTGGTACCAGCAGAAGCCGGGACAGCCGCCAAAGCTGCTGATCTACTCCGG GTCCACCTTGCAATCTGGTGTCCCTGACCGGTTCTCCGGTTCCGGGTCGGGTACCGACTTCA CGCTCACTATTTCGTCGCTGCAAGCCGAAGATGTGGCCGTGTACTATTGCCAACAGCACAAC AAGTACCCCTACACTTTTGGCGGAGGCACCAAGGTGGAAATCAAGACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-28 AA	1279	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA

		VYYCQQHNKYPYTFGGGTKVEIKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-28 scFv	1280	MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQ APGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARG NWDDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDVVMTQSPDSLAVSLGERATINCR ASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVA VYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-28 VH	1281	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYNQ KFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-28 VL	1282	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRF SGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-29 NT	1283	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGACGTGCAGCTCACCCAGTCGCCCTCATTTCTGTCGGCCTCAGTGGGAGACAGAGTGACCA TTACTTGTCGGGCCTCCAAGAGCATCTCCAAGGACCTGGCCTGGTATCAGCAGAAGCCAGGA AAGGCGCCTAAGTTGCTCATCTACTCGGGGTCGACCCTGCAATCTGGCGTGCCGTCCCGGTT CTCCGGTTCGGGAAGCGGTACCGAATTCACCCTTACTATCTCCTCCCTGCAACCGGAGGACT TCGCCACCTACTACTGCCAACAGCACAACAAGTACCCGTACACTTTCGGGGGTGGCACGAAG GTCGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGGAGGAAGCC TGAGGCTGTCCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAACTGGGTCAGA CAGGCACCTGGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACTCCGAAACCCA TTACAATCAGAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAAGAGCACCGCGT ACCTCCAAATGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGCGCCCGGGGAAAC TGGGATGATTACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-29 AA	1284	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA

		VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-29 scFv	1285	MALPVTALLLPLALLLHAARPDVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQK PGKAPKLLIYSGSTLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-29 VH	1286	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYNQ KFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-29 VL	1287	DVQLTQSPSFLSASVGDRVTITCRASKSISKDLAWYQQKPGKAPKLLIYSGSTLQSGVPSRF SGSGSGTEFTLTISSLQPEDFATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-30 NT	1288	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGAAGTGGTGCTGACCCAGTCGCCCGCAACCCTCTCTCTGTCGCCGGGAGAACGCGCCACTC TTTCCTGTCGGGCGTCCAAGAGCATCTCAAAGGACCTCGCCTGGTACCAGCAGAAGCCTGGT CAAGCCCCGCGGCTGCTGATCTACTCCGGCTCCACGCTGCAATCAGGAATCCCAGCCAGATT TTCCGGTTCGGGGTCGGGGACTGACTTCACCTTGACCATTAGCTCGCTGGAACCTGAGGACT TCGCCGTGTATTACTGCCAGCAGCACAACAAGTACCCGTACACCTTCGGAGGCGGTACTAAG GTCGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGGAGGAAGCC TGAGGCTGTCCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAACTGGGTCAGA CAGGCACCTGGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACTCCGAAACCCA TTACAATCAGAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAAGAGCACCGCGT ACCTCCAAATGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGCGCCCGGGGAAAC TGGGATGATTACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-30 AA	1289	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA

		VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-30 scFv	1290	MALPVTALLLPLALLLHAARPEVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQK PGQAPRLLIYSGSTLQSGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-30 VH	1291	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYNQ KFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-30 VL	1292	EVVLTQSPATLSLSPGERATLSCRASKSISKDLAWYQQKPGQAPRLLIYSGSTLQSGIPARF SGSGSGTDFTLTISSLEPEDFAVYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-31 NT	1293	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGACGTCGTGATGACCCAGTCACCGGCATTCCTGTCCGTGACTCCCGGAGAAAAGGTCACGA TTACTTGCCGGGCGTCCAAGAGCATCTCCAAGGACCTCGCCTGGTACCAACAGAAGCCGGAC CAGGCCCCTAAGCTGTTGATCTACTCGGGGTCCACCCTTCAATCGGGAGTGCCATCGCGGTT TAGCGGTTCGGGTTCTGGGACCGACTTCACTTTCACCATCTCCTCACTGGAAGCCGAGGATG CCGCCACTTACTACTGTCAGCAGCACAACAAGTATCCGTACACCTTCGGAGGCGGTACCAAA GTGGAGATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGGAGGAAGCC TGAGGCTGTCCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAACTGGGTCAGA CAGGCACCTGGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACTCCGAAACCCA TTACAATCAGAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAAGAGCACCGCGT ACCTCCAAATGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGCGCCCGGGGAAAC TGGGATGATTACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-31 AA	1294	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA

		VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-31 scFv	1295	MALPVTALLLPLALLLHAARPDVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQK PDQAPKLLIYSGSTLQSGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-31 VH	1296	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYNQ KFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-31 VL	1297	DVVMTQSPAFLSVTPGEKVTITCRASKSISKDLAWYQQKPDQAPKLLIYSGSTLQSGVPSRF SGSGSGTDFTFTISSLEAEDAATYYCQQHNKYPYTFGGGTKVEIK
hzCAR123-32 NT	1298	ATGGCCCTCCCTGTCACCGCCCTGCTGCTTCCGCTGGCTCTTCTGCTCCACGCCGCTCGGCC CGACGTGGTCATGACTCAGTCCCCGGACTCACTCGCGGTGTCGCTTGGAGAGAGAGCGACCA TCAACTGTCGGGCCTCAAAGAGCATCAGCAAGGACCTGGCCTGGTACCAGCAGAAGCCGGGA CAGCCGCCAAAGCTGCTGATCTACTCCGGGTCCACCTTGCAATCTGGTGTCCCTGACCGGTT CTCCGGTTCCGGGTCGGGTACCGACTTCACGCTCACTATTTCGTCGCTGCAAGCCGAAGATG TGGCCGTGTACTATTGCCAACAGCACAACAAGTACCCCTACACTTTTGGCGGAGGCACCAAG GTGGAAATCAAGGGGGGTGGCGGTAGCGGAGGAGGGGGCTCCGGCGGCGGCGGCTCAGGGGG CGGAGGAAGCGAAGTGCAGCTCGTCGAGAGCGGAGGGGGACTGGTGCAGCCCGGAGGAAGCC TGAGGCTGTCCTGCGCTGCCTCCGGCTACACCTTCACCTCCTACTGGATGAACTGGGTCAGA CAGGCACCTGGAAAGGGACTGGTCTGGGTGTCGCGCATTGACCCCTACGACTCCGAAACCCA TTACAATCAGAAATTCAAGGACCGCTTCACCATCTCCGTGGACAAAGCCAAGAGCACCGCGT ACCTCCAAATGAACTCCCTGCGCGCTGAGGATACAGCAGTGTACTATTGCGCCCGGGGAAAC TGGGATGATTACTGGGGCCAGGGAACTACTGTGACTGTGTCATCCACCACTACCCCAGCACC GAGGCCACCCACCCCGGCTCCTACCATCGCCTCCCAGCCTCTGTCCCTGCGTCCGGAggcat gtagacccgcagctggtggggccgtgcatacccggggtcttgacttcgcctgcgatatctac atttgggcccctctggctggtacttgcggggtcctgctgctttcactcgtgatcactcttta ctgtaagcgcggtcggaagaagctgctgtacatctttaagcaacccttcatgaggcctgtgc agactactcaagaggaggacggctgttcatgccggttcccagaggaggaggaaggcggctgc gaactgcgcgtgaaattcagccgcagcgcagatgctccagcctacaagcaggggcagaacca gctctacaacgaactcaatcttggtcggagagaggagtacgacgtgctggacaagcggagag gacgggacccagaaatgggcgggaagccgcgcagaaagaatccccaagagggcctgtacaac gagctccaaaaggataagatggcagaagcctatagcgagattggtatgaaaggggaacgcag aagaggcaaaggccacgacggactgtaccagggactcagcaccgccaccaaggacacctatg acgctcttcacatgcaggccctgccgcctcgg
hzCAR123-32 AA	1299	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA

		VYYCARGNWDDYWGQGTTVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGC SCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHM QALPPR
hzCAR123-32 scFv	1300	MALPVTALLLPLALLLHAARPDVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQK PGQPPKLLIYSGSTLQSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFG GGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGYTFTSY WMNWVRQAPGKGLVWVSRIDPYDSETHYNQKFKDRFTISVDKAKSTAYLQMNSLRAEDTA VYYCARGNWDDYWGQGTTVTVSS
hzCAR123-32 VH	1301	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMNWVRQAPGKGLVWVSRIDPYDSETHYNQ KFKDRFTISVDKAKSTAYLQMNSLRAEDTAVYYCARGNWDDYWGQGTTVTVSS
hzCAR123-32 VL	1302	DVVMTQSPDSLAVSLGERATINCRASKSISKDLAWYQQKPGQPPKLLIYSGSTLQSGVPDRF SGSGSGTDFTLTISSLQAEDVAVYYCQQHNKYPYTFGGGTKVEIK

Las secuencias de las secuencias CDR humanizadas de los dominios scFv los CARs hzCD123 1-32 se muestran en la **Tabla 26** para los dominios variables de la caena pesada **Tabla 27** para los dominios variablesde la cadena ligera. Las "ID" aparecen para su respectivo SEQ ID NO para cada CDR.

Tabla 26. CDR de dominio variable de la cadena pesada

	HCDR1	SEQ ID NO:	HCDR2	SEQ ID NO:	HCDR3	SEQ ID NO:
hzCAR123	GYTFTSYWMN	1102	RIDPYDSETHYNQKFKD	1103	GNWDDY	1104

Tabla 27. CDR de dominio variable para la cadena ligera

	LCDR1	SEQ ID NO:	LCDR2	SEQ ID NO:	LCDR3	SEQ ID NO:
hzCAR123	RASKSISKDLA	1105	SGSTLQS	1106	QQHNKYPYT	1107

Los fragmentos CAR scFv fueron clonados luego en vectores lentivirales para crear un constructo CAR de longitude completa en un único marco codificante, y usando el promotor EF1 alfa para la expresión.

Constructs CAR19/CAR22 biespecíficos y función de los mismos

Esta sección describe la producción y la función de los constructos CAR19/CAR22 biespecíficos. Se diseñaron dos fusiones biespecíficas de scFv en tandem: antiCD22 (HL)4G4S-antiCD19 (LH) y antiCD19-4G4S-antiCD22. La designación (HL) indica que la region variable de la cadena pesada se encuentra aguas arriba de la region variable d ela cadena pesada dentro del scFv indicado, y la designación (LH) indica que la region variable de la cadena ligera se encuentra aguas arriba de la region variable de la cadena pesada dentro del scFv indicado. La molecula de base anti-CD22 es hCD22-2, y usa la orientación HL. La molécula de base anti-CD19 e suna secuencia anti-CD19 humanizada, proporcionada en el presente document como un constructo de ID 104876 de la **Tabla 2,** el cual usa la orientación LH Los constructos se ilustran de manera esquemática en la FIG. 13.

Las secuencias de nucleótidos y aminoácidos de ambos constructos biespecíficos, así como de la sporciones scFv de los mismos, se dan a continuación en la **Tabla 28**.

Table 28. Constructos CAR19/CAR22 bispecíificos

Nombre	SEQ ID NO	Secuencia
antiCD22-4G4S-antiCD19 scFv secuencia de aminoácidos	1303	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQ SPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARDLGWIAVAGTFDYWGQGTLVTV SSGGGGSGGGGSGGGGSQSALTQPASVSGSPGQSITISCTG TSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVSNRFS GSKSGNTASLTISGLQAEDEADYYCSSYTSSSLNHVFGTGT KVTVLTGGGGSGGGGSGGGGSGGGGSEIVMTQSPATLSLSP GERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHS GIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYT FGQGTKLEIKGGGGSGGGGSGGGGSQVQLQESGPGLVKPSE TLSLTCTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGSETT YYQSSLKSRVTISKDNSKNQVSLKLSSVTAADTAVYYCAKH YYYGGSYAMDYWGQGTLVTVSS
antiCD22-CD19 CAR secuencia de	1304	EVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQ SPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQF SLQLNSVTPEDTAVYYCARDLGWIAVAGTFDYWGQGTLVTV SSGGGGSGGGGSGGGGSQSALTQPASVSGSPGQSITISCTG TSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVSNRFS

aminoácidos		GSKSGNTASLTISGLQAEDEADYYCSSYTSSSLNHVFGTGT KVTVLTGGGGSGGGGSGGGGSGGGGSEIVMTQSPATLSLSP GERATLSCRASQDISKYLNWYQQKPGQAPRLLIYHTSRLHS GIPARFSGSGSGTDYTLTISSLQPEDFAVYFCQQGNTLPYT FGQGTKLEIKGGGGSGGGGSGGGGSQVQLQESGPGLVKPSE TLSLTCTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGSETT YYQSSLKSRVTISKDNSKNQVSLKLSSVTAADTAVYYCAKH YYYGGSYAMDYWGQGTLVTVSSTTTPAPRPPTPAPTIASQP LSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLL LSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRF PEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREE YDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYS EIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
antiCD22- 4G4S- antiCD19 scFv secuencia nucléica	1305	gaagtgcagctccaacagtcaggaccaggactcgtcaaacc ctcccaaaccctcagccttacttgtgccatttccggggatt ccgtgtcgagcaattccgccgcctggaactggatcaggcag tccccgtcgcgcgggctcgaatggctgggacgcacttacta ccggtccaagtggtacaacgactacgccgtcagcgtgaagt cgcggatcaccattaaccccgacacctccaagaaccagttc agcctccaactgaactccgtgacccctgaggataccgcggt ctactattgtgcccgggacctgggttggattgccgtggccg ggaccttcgattactggggccagggaactctcgtcaccgtg tcctcgggaggggtggctcaggggtggtggatcgggtgg tggcggctcccagtccgctctgactcagcccgcgtccgtgt ccggttccccgggacagtcgatcacaatcagctgcactggc acctcctccgacgtcggcgggtacaactacgtgtcgtggta ccaacagcaccctggaaaagccccgaagctgatgatctacg acgtgtccaagaggccaagcggagtgtcaaatcgcttttcc ggctcgaagtcgggaaacaccgccagcctgactatctcggg actgcaggccgaggacgaggccgactactactgctcgtctt acacctcctcatccttgaaccacgtgttcggaaccggaacc aaggtcaccgtgctgactggaggggaggctccggtggcgg cggctctggaggaggagggtccggcggaggaggatcggaaa tcgtgatgacccagtcccccgcaaccctgtccctgagcccg ggcgaaagagctaccctgtcgtgccgggcgtcgcaggacat ctccaagtacctgaactggtaccagcagaagcccggccagg caccgagactgctgatctaccacactagccgcctgcattcc ggtatccccgcacggttcagcggcagcgggagcggaaccga ttacacgctcactatttcctcactgcaacccgaggatttcg ctgtgtacttctgccaacaaggaaacaccctgccttatacc ttcggacagggtacaaagctggagattaagggaggaggggg ctccggcggcgggggcagcgggggcggcggaagccaggtcc agctgcaggaatccggtccgggactcgtgaagccctccgaa actctctcccttacgtgcaccgtgtcaggggtgtccctgcc ggactacggagtgtcctggattcggcaacctccggggaagg gactggagtggatcggagtgatctggggctccgaaactacc tactaccagtcatcattgaagtcaagagtgaccatttcgaa ggacaacagcaagaaccaggtgtcccttaaactgtccagcg

		tgaccgcggcggatactgccgtctactactgcgccaagcac tattactacggcggaagctatgcgatggactactggggaca gggcaccttggtcactgtgtcctcc
antiCD22-CD19 CAR secuencia de ácido nucléico	1306	gaagtgcagctccaacagtcaggaccaggactcgtcaaacc ctcccaaaccctcagccttacttgtgccatttccggggatt ccgtgtcgagcaattccgccgcctggaactggatcaggcag tccccgtcgcgcgggctcgaatggctgggacgcacttacta ccggtccaagtggtacaacgactacgccgtcagcgtgaagt cgcggatcaccattaaccccgacacctccaagaaccagttc agcctccaactgaactccgtgacccctgaggataccgcggt ctactattgtgcccgggacctgggttggattgccgtggccg ggaccttcgattactggggccagggaactctcgtcaccgtg tcctcgggaggggtggctcaggggtggtggatcgggtgg tggcggctcccagtccgctctgactcagcccgcgtccgtgt ccggttccccgggacagtcgatcacaatcagctgcactggc acctcctccgacgtcggcgggtacaactacgtgtcgtggta ccaacagcaccctggaaaagccccgaagctgatgatctacg acgtgtccaagaggccaagcggagtgtcaaatcgcttttcc ggctcgaagtcgggaaacaccgccagcctgactatctcggg actgcaggccgaggacgaggccgactactactgctcgtctt acacctcctcatccttgaaccacgtgttcggaaccggaacc aaggtcaccgtgctgactggaggggaggctccggtggcgg cggctctggaggaggagggtccggcggaggaggatcggaaa tcgtgatgacccagtcccccgcaaccctgtccctgagcccg ggcgaaagagctaccctgtcgtgccgggcgtcgcaggacat ctccaagtacctgaactggtaccagcagaagcccggccagg caccgagactgctgatctaccacactagccgcctgcattcc ggtatccccgcacggttcagcggcagcgggagcggaaccga ttacacgctcactatttcctcactgcaacccgaggatttcg ctgtgtacttctgccaacaaggaaacaccctgccttatacc ttcggacagggtacaaagctggagattaagggaggaggggg ctccggcggcgggggcagcgggggcggcggaagccaggtcc agctgcaggaatccggtccgggactcgtgaagccctccgaa actctctcccttacgtgcaccgtgtcaggggtgtccctgcc ggactacggagtgtcctggattcggcaacctccggggaagg gactggagtggatcggagtgatctggggctccgaaactacc tactaccagtcatcattgaagtcaagagtgaccatttcgaa ggacaacagcaagaaccaggtgtcccttaaactgtccagcg tgaccgcggcggatactgccgtctactactgcgccaagcac tattactacggcggaagctatgcgatggactactggggaca gggcaccttggtcactgtgtcctccaccactaccccagcac cgaggccacccaccccggctcctaccatcgcctcccagcct ctgtccctgcgtccggaggcatgtagacccgcagctggtgg ggccgtgcatacccggggtcttgacttcgcctgcgatatct acatttgggcccctctggctggtacttgcggggtcctgctg ctttcactcgtgatcactctttactgtaagcgcggtcggaa gaagctgctgtacatctttaagcaacccttcatgaggcctg tgcagactactcaagaggaggacggctgttcatgccggttc

		ccagaggaggaggaaggcggctgcgaactgcgcgtgaaatt cagccgcagcgcagatgctccagcctacaagcaggggcaga accagctctacaacgaactcaatcttggtcggagagaggag tacgacgtgctggacaagcggagaggacgggacccagaaat gggcgggaagccgcgcagaaagaatccccaagagggcctgt acaacgagctccaaaaggataagatggcagaagcctatagc gagattggtatgaaaggggaacgcagaagaggcaaaggcca cgacggactgtaccagggactcagcaccgccaccaaggaca cctatgacgctcttcacatgcaggccctgccgcctcgg
antiCD19-4G4S-antiCD22 scFv secuencia de aminoácidos	1307	EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPG QAPRLLIYHTSRLHSGIPARFSGSGSGTDYTLTISSLQPED FAVYFCQQGNTLPYTFGQGTKLEIKGGGGSGGGGSGGGGSQ VQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPG KGLEWIGVIWGSETTYYQSSLKSRVTISKDNSKNQVSLKLS SVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSSGGGG SGGGGSGGGGSGGGGSEVQLQQSGPGLVKPSQTLSLTCAIS GDSVSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYAVS VKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARDLGWIA VAGTFDYWGQGTLVTVSSGGGGSGGGGSGGGGSQSALTQPA SVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM IYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYC SSYTSSSLNHVFGTGTKVTVLT
antiCD19-4G4S-antiCD22 CAR secuencia de aminoácidos	1308	EIVMTQSPATLSLSPGERATLSCRASQDISKYLNWYQQKPG QAPRLLIYHTSRLHSGIPARFSGSGSGTDYTLTISSLQPED FAVYFCQQGNTLPYTFGQGTKLEIKGGGGSGGGGSGGGGSQ VQLQESGPGLVKPSETLSLTCTVSGVSLPDYGVSWIRQPPG KGLEWIGVIWGSETTYYQSSLKSRVTISKDNSKNQVSLKLS SVTAADTAVYYCAKHYYYGGSYAMDYWGQGTLVTVSSGGGG SGGGGSGGGGSGGGGSEVQLQQSGPGLVKPSQTLSLTCAIS GDSVSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYAVS VKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARDLGWIA VAGTFDYWGQGTLVTVSSGGGGSGGGGSGGGGSQSALTQPA SVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM IYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYC SSYTSSSLNHVFGTGTKVTVLTTTTPAPRPPTPAPTIASQP LSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLL LSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRF PEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREE YDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYS EIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
antiCD19-4G4S-antiCD22 scFv	1309	gaaatcgtgatgacccagtcccccgcaaccctgtccctgag cccgggcgaaagagctaccctgtcgtgccgggcgtcgcagg acatctccaagtacctgaactggtaccagcagaagcccggc caggcaccgagactgctgatctaccacactagccgcctgca ttccggtatccccgcacggttcagcggcagcgggagcggaa ccgattacacgctcactatttcctcactgcaacccgaggat ttcgctgtgtacttctgccaacaaggaaacaccctgcctta

secuencia de ácido nucléico		taccttcggacagggtacaaagctggagattaagggaggag ggggctccggcggcgggggcagcgggggcggcggaagccag gtccagctgcaggaatccggtccgggactcgtgaagccctc cgaaactctctcccttacgtgcaccgtgtcaggggtgtccc tgccggactacggagtgtcctggattcggcaacctccgggg aagggactggagtggatcggagtgatctggggctccgaaac tacctactaccagtcatcattgaagtcaagagtgaccattt cgaaggacaacagcaagaaccaggtgtcccttaaactgtcc agcgtgaccgcggcggatactgccgtctactactgcgccaa gcactattactacggcggaagctatgcgatggactactggg gacagggcaccttggtcactgtgtcctccggaggggaggc tccggtggcggcggctctggaggaggagggtccggcggagg aggatcggaagtgcagctccaacagtcaggaccaggactcg tcaaaccctcccaaaccctcagccttacttgtgccatttcc ggggattccgtgtcgagcaattccgccgcctggaactggat caggcagtccccgtcgcgcgggctcgaatggctgggacgca cttactaccggtccaagtggtacaacgactacgccgtcagc gtgaagtcgcggatcaccattaaccccgacacctccaagaa ccagttcagcctccaactgaactccgtgacccctgaggata ccgcggtctactattgtgcccgggacctgggttggattgcc gtggccgggaccttcgattactggggccagggaactctcgt caccgtgtcctcgggaggggtggctcaggggtggtggat cgggtggtggcggctcccagtccgctctgactcagcccgcg tccgtgtccggttccccgggacagtcgatcacaatcagctg cactggcacctcctccgacgtcggcgggtacaactacgtgt cgtggtaccaacagcaccctggaaaagccccgaagctgatg atctacgacgtgtccaagaggccaagcggagtgtcaaatcg cttttccggctcgaagtcgggaaacaccgccagcctgacta tctcgggactgcaggccgaggacgaggccgactactactgc tcgtcttacacctcctcatccttgaaccacgtgttcggaac cggaaccaaggtcaccgtgctgact
antiCD19-4G4S-antiCD22 CAR secuencia de ácido nucléico	1310	gaaatcgtgatgacccagtcccccgcaaccctgtccctgag cccgggcgaaagagctaccctgtcgtgccgggcgtcgcagg acatctccaagtacctgaactggtaccagcagaagcccggc caggcaccgagactgctgatctaccacactagccgcctgca ttccggtatccccgcacggttcagcggcagcgggagcggaa ccgattacacgctcactatttcctcactgcaacccgaggat ttcgctgtgtacttctgccaacaaggaaacaccctgcctta taccttcggacagggtacaaagctggagattaagggaggag ggggctccggcggcgggggcagcgggggcggcggaagccag gtccagctgcaggaatccggtccgggactcgtgaagccctc cgaaactctctcccttacgtgcaccgtgtcaggggtgtccc tgccggactacggagtgtcctggattcggcaacctccgggg aagggactggagtggatcggagtgatctggggctccgaaac tacctactaccagtcatcattgaagtcaagagtgaccattt cgaaggacaacagcaagaaccaggtgtcccttaaactgtcc agcgtgaccgcggcggatactgccgtctactactgcgccaa gcactattactacggcggaagctatgcgatggactactggg

		gacagggcaccttggtcactgtgtcctccggaggggaggc tccggtggcggcggctctggaggaggagggtccggcggagg aggatcggaagtgcagctccaacagtcaggaccaggactcg tcaaaccctcccaaaccctcagccttacttgtgccatttcc ggggattccgtgtcgagcaattccgccgcctggaactggat caggcagtccccgtcgcgcgggctcgaatggctgggacgca cttactaccggtccaagtggtacaacgactacgccgtcagc gtgaagtcgcggatcaccattaaccccgacacctccaagaa ccagttcagcctccaactgaactccgtgacccctgaggata ccgcggtctactattgtgcccgggacctgggttggattgcc gtggccgggaccttcgattactggggccagggaactctcgt caccgtgtcctcgggaggggtggctcaggggtggtggat cgggtggtggcggctcccagtccgctctgactcagcccgcg tccgtgtccggttccccgggacagtcgatcacaatcagctg cactggcacctcctccgacgtcggcgggtacaactacgtgt cgtggtaccaacagcaccctggaaaagccccgaagctgatg atctacgacgtgtccaagaggccaagcggagtgtcaaatcg cttttccggctcgaagtcgggaaacaccgccagcctgacta tctcgggactgcaggccgaggacgaggccgactactactgc tcgtcttacacctcctcatccttgaaccacgtgttcggaac cggaaccaaggtcaccgtgctgactaccactaccccagcac cgaggccacccaccccggctcctaccatcgcctcccagcct ctgtccctgcgtccggaggcatgtagacccgcagctggtgg ggccgtgcatacccggggtcttgacttcgcctgcgatatct acatttgggcccctctggctggtacttgcggggtcctgctg ctttcactcgtgatcactctttactgtaagcgcggtcggaa gaagctgctgtacatctttaagcaacccttcatgaggcctg tgcagactactcaagaggaggacggctgttcatgccggttc ccagaggaggaggaaggcggctgcgaactgcgcgtgaaatt cagccgcagcgcagatgctccagcctacaagcaggggcaga accagctctacaacgaactcaatcttggtcggagagaggag tacgacgtgctggacaagcggagaggacgggacccagaaat gggcgggaagccgcgcagaaagaatccccaagagggcctgt acaacgagctccaaaaggataagatggcagaagcctatagc gagattggtatgaaaggggaacgcagaagaggcaaaggcca cgacggactgtaccagggactcagcaccgccaccaaggaca cctatgacgctcttcacatgcaggccctgccgcctcgg

En algunas modalidades, el dominio de unión a antígeno comprende una HC CDR1, una HC CDR2, y una HC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada listadas en la **Tabla 28**. En modalidades, el dominio de unión al antígeno comprende adicionalmente una LC CDR1, una LC CDR2, y una LC CDR3. En modalidades, el dominio de union a antígeno comprende una LC CDR1, una LC CDR2, y una LC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera listadas en

la **Tabla 28**.

En algunas modalidades, el dominio de unión a antígeno cmoprende una, dos o todas de las LC CDR1, LC CDR2, y LC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena ligera listadas en la **Tabla 28**, y una, dos o todas de las HC CDR1, HC CDR2, y HC CDR3 de cualquiera de las secuencias de aminoácidos del dominio de unión de la cadena pesada listadas en la **Tabla 28**.

En algunas modalidades, las CDRs están definidas de acuerdo con el esquema de numeración de Kabat, el esquema de numeración de Chothia, o una combinación de los mismos.

Los constructos CD19-CD22 y CD22-CD19 biespecíficos descritos anteriormente, fueron probados en un ensayo NFAT, como s eilustra en los ejemplos a continuación. Como controles se usaron un CAR anti-CD19 solo y un CAR anti-CD22 solo. Los resultados de este ensayo se muestran en la FIG. 14. Los datos indican que tanto el scFv anti-CD19 y el scFv anti-CD22 son activos frente a sus blancos.

EJEMPLOS

La invención se describe adicionalmente en detalle como referencia a los siguientes ejemplos experimentales. Estos ejemplos se proporcionan para los propósitos de ilustración solamente, y no pretenden ser limitantes a menos que se especifique lo contrario. Por lo tanto, la invención de ninguna manera debe interpretarse como limitada a los siguientes ejemplos, sino más bien, debe interpretarse que abarca cualquiera y todas las variaciones que se hacen evidentes como resultado de la enseñanza proporcionada en la presente.

Sin descripción adicional, se cree que un experto en la técnica puede, utilizando la descripción precedente y los siguientes ejemplos ilustrativos, fabricar y utilizar los compuestos de la presente invención y practicar los métodos reivindicados. Los siguientes ejemplos de trabajo señalan específicamente diversos aspectos de la presente invención, y no deben interpretarse como limitantes en ningún modo el resto de la divulgación.

Ejemplo 1: Células CART CD19 para uso en el tratamiento de mieloma múltiple.

Incluso con los regímenes actuales de quimioterapia, las terapias dirigidas, y el trasplante

de células madre autólogas, el mieloma se considera una enfermedad incurable. El presente ejemplo describe el tratamiento de mieloma múltiple con células T autólogas dirigidas a CD19 con un receptor quimérico de antígeno (lentivirus/CD19: 4-1BB: CD3zeta; también conocido como "CART19" o CTL019). Este ejemplo demuestra que las terapias CAR CD19 dirigidas tienen la posibilidad de establecer, remisiones duraderas profundas a largo plazo basadas en metas de los niveles de CD19 de células madre de mieloma y/o células tumorales que expresan en casntidades muy bajas (no detectable por la mayoría de los métodos).

Al tratar un paciente con una leucemia celular plasmática secundaria agresiva, se encontró que CART19 administrado dos días después de un trasplante de células tallo autólogas salvajes resultó en la rápida eliminación de la leucemia de células plasmáticas y una muy buena respuesta parcial en un paciente que había progresado a través de varias líneas de la quimioterapia. Este paciente fue dependiente de las transfusiones durante meses antes del tratamiento; a los dos meses después del tratamiento, se recuperaron sus recuentos de células sanguíneas (con recuentos de plaquetas y recuentos de glóbulos blancos de rango normal) y no ha requerido transfusiones puesto que el paciente fue dado de alta del hospital tras el tratamiento.

Dado que las células de mieloma no expresan naturalmente CD19, el hallazgo de que el tratamiento con CART19 indujo una respuesta tumoral rápida y significativa en este tumor fue sorprendente. Sin desear estar limitado por una teoría particular, se razonó que CART19 podría utilizarse para tratar mieloma porque: (1) mientras las células de mieloma se cree tradicionalmente son negativas para la expresión de CD19 por citometría de flujo, hay datos que indican que las células de mieloma pueden expresar niveles muy bajos de CD19, de tal manera que la expresión es detectable por el ARN pero no por citometría de flujo o inmunohistoquímica, y (2) el concepto de dirigirse a la célula B clonotípica de la célula B clonotipica, que se cree que es la célula tallo cancerosa que da lugar a mieloma múltiple, y es particularmente resistente a la quimioterapia. Existe una relación clonal entre las células B y las células tumorales de mieloma, pero la terapia de mieloma tradicional está dirigida a las células plasmáticas malignas en lugar de las células B. CART19 para el tratamiento de mieloma, por tanto dirige a una población de células diferente que la mayoría de terapias de mieloma.

En nuestra única experiencia con pacientes, el paciente tuvo células plasmáticas circulantes, y se pudo probar las células tumorales para la expresión de CD19.

Aproximadamente 1-2% de sus células tumorales expresaron el antígeno CD19. De este modo, se razonó que CART19 puede tener un efecto directo sobre una población muy pequeña de sus células tumorales, una respuesta parcial muy buena, la cual no pudo haber sido predicha a partir de marcar solamente a la muy pequeña población de células tumorales CD19+.

En este caso, CART19 se administró tras un rescate de trasplante de células tallo autólogas después de altas dosis de melfalán. Aunque esta es una terapia estándar en mieloma, no es curativa. Además, este paciente había sido sometido previamente a trasplantes de células tallo autólogas en tándem y tuvo una recaída temprana (<6 meses) después del trasplante. Sin desear estar limitado por una teoría particular, el uso de células CART19 como se describe en el presente ejemplo puede tener un mecanismo no traslapante en el tratamiento de mieloma cuando se combina con un trasplante de células tallo autólogas de salvamento.

Diez pacientes adicionales con mieloma múltiple serán tratados con CART19 en un ensayo de fase I Y al menos tres pacientes se han tratado hasta la fecha.

Justificación de Dosis y Riesgos / Beneficios

Se ha elegido utilizar la dosificación plana a través de la vía de administración intravenosa para este protocolo. El objetivo principal de este protocolo fue poner a prueba la seguridad y la viabilidad de administrar células CART-19 a pacientes con mieloma múltiple. Las toxicidades primarias que fueron anticipadas son (I) liberación de citoquinas cuando los CARs encuentran su antígeno CD19 sustituto en células B malignas o normales; (2) agotamiento de las células B normales, similar a la terapia con rituximab; (3) síndromes dérmicos y gastrointestinales sensibles a esteroides parecidos a la enfermedad de injerto contra huésped como se ha visto anteriormente cuando las células T autólogas expandidas/co-estimuladas se han acoplado con ASCT para MM. Una preocupación teórica fue si la transformación o proliferación incontrolada de las células T CART-19 podrían ocurrir en respuesta a los altos niveles de CD19. Esto era menos una preocupación en esta solicitud en comparación con otro estudio de pacientes con CLL, como la carga de células B clonotípicas en MM se espera que sea mucho menor que la carga de células B malignas en los pacientes con CLL refractaria tratados en ese estudio.

Justificación de la Dosis

Con los 3 primeros pacientes, hemos observado actividad clínica a dosis que van desde

1.4 x 10^7 a l.1 x 10^9 células CART-19. Esta observación demuestra, al menos en los 3 primeros pacientes tratados, que no hay una relación obvia de respuesta a la dosis. Se observó una respuesta completa en pacientes a quienes se administró una dosis diferente en dos órdenes. Por lo tanto, a diferencia de los medicamentos estándar que se metabolizan, las células T CAR pueden tener un amplio gama de respuestas a dosis. Esto es más probable puesto que las células T CAR son capaces de proliferarse extensivamente en los pacientes. Por lo tanto, establecemos un rango de dosis de l-5 x 10^8 células CART-19 para la infusión. En este estudio de un solo paciente que se ofrece sobre una base de uso compasivo, el paciente recibirá hasta 5 x $l0^8$ células CART19, sin límite inferior de dosis. Para el ensayo de diez pacientes, los pacientes se les ofrecerá 1-5 x 10^7 células CART-19.

Diseño General

Este fue un estudio de un solo paciente ofrecido sobre una base de uso compasivo, fue modelado después de un estudio de fase I para determinar si la infusión de células T autólogas transducidas para expresar CART-19 es segura. Los objetivos primarios del estudio fueron determinar la seguridad, tolerabilidad y el potencial injerto de células T -19 CART en pacientes sometidos a rescate con TACM tras una recidiva precoz tras la primera TACM. El protocolo consiste en un estudio piloto de etiqueta abierta.

En la entrada los sujetos serán sometidos a una biopsia de médula ósea y exámenes de laboratorio de rutina y evaluación de imágenes de su MM. Los sujetos elegibles serán sometidos a aféresis de estado estable para obtener grandes números de células mononucleares de sangre periférica (PBMC) para la fabricación de CART-19. Las células T se purificaron a partir de las PBMC, transducidas con TCRζ/4-1BB del vector lentiviral, se expandieron in vitro y después se congelan para la futura administración. El número de pacientes que tienen colecciones, expansión o fabricación de células T inadeacuadas en comparación con el número de pacientes que tienen células T exitosamente fabricadas serán registrados; la factibilidad de la fabricación del producto no se espera que sea problemática en esta población de pacientes.

Los sujetos han tenido células madre generalmente de sangre periférica adecuadas que han permanecido almacenados desde la movilización / colección realizada en preparación para su primera TACM para llevar a cabo dos TACM adicionales. Aquellos que no han experimentado un segundo procedimiento de movilización/colección, ya sea antes o después de su aféresis de estado estable con un régimen de acuerdo a la preferencia del médico tratante.

Aproximadamente dos semanas después de la leucoféresis inicial, los sujetos serán admitidos al hospital y recibir melfalán de dosis altas (día -2) seguido de una infusión de células madre autólogas, dos días después (día 0), y todos los sujetos recibirán infusión de células CART-19 de doce y catorce días más tarde (día +12-14). Hasta 10 pacientes se inscribirán.

A todos los sujetos se les realizarán análisis de sangre para evaluar la seguridad y el injerto y la persistencia de las células CART-19 a intervalos regulares hasta la semana 4 del estudio. El día +42 y el día +100, los sujetos se someten a aspirados/biopsias de médula ósea para evaluar la carga celular plasmática de médula ósea y el tráfico de células CART-19 a la médula ósea. Una evaluación de la respuesta formal se hará el día 100 de acuerdo con los criterios 136 del Grupo de Trabajo de Mieloma Internacional (IMWG) y la TTP será monitoreada de acuerdo a la práctica clínica de rutina para pacientes con mieloma múltiple. El principal resultado de eficacia medido en este estudio será una comparación de PTT después de una TACM inicial de un paciente para PTT después del TACM en este estudio.

A medida que el criterio de valoración principal de este estudio es la seguridad y la viabilidad de la infusión de células CART -19 con TACM, el estudio emplea una regla de interrupción temprana. Brevemente, si se producen menos de 2 eventos graves, adversos e inesperados entre los primeros cinco sujetos tratados, el estudio luego aumentará otros cinco sujetos a una inscripción objetivo de 10. Los sujetos tratados se observan durante 40 días después de la infusión de CART-19 (por ejemplo, a través de la medición oficial de la primera respuesta en el día 42) antes de reclutar al siguiente sujeto hasta que se reclutaron 5 sujetos y se observó. Para el tratamiento del segundo grupo de cinco pacientes, se requiere un período de espera entre los sujetos.

Después de los 6 meses de seguimiento intensivo, los sujetos serán evaluados al menos cada tres meses durante dos años con una historia clínica, examen físico y exámenes de sangre. Tras esta evaluación, los sujetos entrarán en un estudio de nuevo seguimiento anual por teléfono y cuestionario para un máximo de 13 años adicionales para evaluar para el diagnóstico de problemas de salud a largo plazo, como el desarrollo de nuevos tumores malignos.

Objetivos Primarios del Estudio

Esta prueba piloto se ha diseñado para probar la seguridad y la viabilidad de las células T autólogas transducidas con el CD19 TCRζ/4-lBB en pacientes sometidos a TACM de rescate

para MM tras recaída temprana después de la primera TACM.

Variables de seguridad y factibilidad primaria incluyen:

La ocurrencia de eventos adversos relacionados con el estudio, definidos como signos/síntomas NCJ CTC2: grado 3, toxicidades de laboratorio y eventos clínicos que están posiblemente, probablemente o definitivamente relacionados con el tratamiento de estudio en cualquier momento desde la infusión hasta la semana 24. Esto incluirá toxicidad por infusión y cualquier toxicidad relacionada posiblemente con las células CART-19 incluyendo, pero no limitado a:

a. Fiebres

b. Erupción

c. Neutropenia, trombocitopenia, anemia, aplasia medular

d. Disfunción hepática

e. Infiltrados pulmonares u otra toxicidad pulmonar

f. Síndromes tipo GVHD que afectan el tracto gastrointestinal o la piel.

La viabilidad para la fabricación de células CAR-19 a partir de productos de aféresis de pacientes. Se determinará el número de productos manufacturados que no cumplen los criterios de liberación para eficiencia de transducción de vectores, pureza de células T, viabilidad, esterilidad y contaminación tumoral.

La profundidad y la duración de la respuesta después de un trasplante de células autólogas madre con CART19 serán comparados con la profundidad y la duración de la respuesta que cada paciente inicialmente logra después de un trasplante estándar de células madre antólogas.

Selección y Retiro de Sujetos

Criterios de inclusión

Los sujetos deben haber sido objeto de una TACM previa para MM y haber progresado dentro de los 365 días de la infusión de células madre. Los sujetos que se han sometido a dos ASCTs anteriores como parte de un régimen en tándem de TACM de saneamiento previsto son elegibles. La progresión se define de acuerdo con criterios IMWG de enfermedad progresiva o, para los pacientes que obtuvieron CR o CRs después de ASCT inicial, según los criterios para la

recaída de CR (Durie *et al.* Leucemia 2006; 20 (9) :1467-1473). NB: No existe un requisito de que los pacientes deben inscribirse dentro de los 365 días de ASCT antes, y los pacientes pueden ser tratados con otros agentes, incluidos los agentes experimentales, a raíz de la recaída/progresión después de ASCT previa antes de la inscripción en este estudio.

Los sujetos deben haber firmado un consentimiento informado por escrito.

Los sujetos deben tener funciones vitales adecuada para recibir altas dosis de melfalán como se define por los siguientes criterios, medidos en las 12 semanas anteriores a la fecha de la infusión de melfalán:. a. Creatinina sérica $\leq 2,5$ o depuración estimada de creatinina ≥ 30 ml/min y no dependiente de diálisis. b. SGOT ≤ 3 veces el límite superior de bilirrubina normal y total $\leq 2,0$ mg/dl (excepto para pacientes en los que la hiperbilirrubinemia se atribuye al síndrome de Gilbert). c. Fracción de eyección ventricular izquierda (FEVI) $\geq 45\%$ o, si es LVEG $<45\%$, una evaluación formal por parte de un cardiólogo no identifica deterioro clínico significativo de la función cardiovascular. La evaluación LEVF debe haber sido realizada dentro de seis semanas de la inscripción. d. Función pulmonar adecuada con FEV1, FVC, TLC, DLCO (tras el ajuste apropiado para el volumen pulmonar y la concentración de hemoglobina) $\geq 40\%$ de los valores previstos. Las pruebas de función pulmonar deben haber sido realizadas dentro de seis semanas después de la inscripción.

Los sujetos deben tener una condición de desempeño ECOG de 0-2, a menos que un estado de mayor rendimiento se deba únicamente al dolor de huesos.

Criterios de Exclusión:

Los sujetos no deben:

Tener cualquier tipo de infección activa y no controlada.

Tener hepatitis B, hepatitis C, o infección por VIH activas.

Cualquier trastorno médico incontrolado que impida la participación como se indica.

Régimen de Tratamiento

Terapia para la recaída / mieloma múltiple progresivo:

Los pacientes pueden recibir, antes de la inscripción, terapia para mieloma múltiple en recaída/progresivo, de acuerdo a la preferencia de sus médicos tratantes. La terapia puede continuar luego de la inscripción.

Los pacientes deben dejar todo tratamiento durante dos semanas antes de la aféresis y durante dos semanas antes de alta dosis de melfalán. Si se espera que pasen más de dos semanas entre aféresis y dosis altas de melfalán, los pacientes pueden reanudar la terapia después de aféresis a criterio de sus médicos tratantes.

Dosis altas de melfalán (día -2)

Los pacientes serán ingresados en el hospital el día -3 o -2 y se someterán a examen por parte del médico encargado y se le realizarán pruebas de laboratorio de rutina, que incluyen parámetros de monitoreo para el síndrome de lisis tumoral, antes del inicio del protocolo de tratamiento. Se elaborará un análisis de a sangre para las pruebas de control de laboratorio (MM PEFE, inmunoglobulinas cuantitativas y análisis de cadenas ligeras libres en suero), antes de la iniciación de la terapia si dichas pruebas no se han elaborado dentro de los 7 días de la admisión.

La terapia de alta dosis consistirá de melfalán en una dosis de 200 mg/m^2 administrada por vía intravenosa durante 20 minutos aproximadamente en el día 2. La dosis de melfalán se reducirá a 140 mg/m^2 para los pacientes > 70 años de edad o para pacientes de cualquier edad quienes, a discreción del médico tratante, no pueden tolerar una dosis de 200 mg/m^2 Todos los pacientes recibirán profilaxis estándar anti-emética, la cual puede incluir dexametasona, y profilaxis antibiotica estándar.

Re-infusión de células tallo (día 0)

La infusión de células tallo se llevará a cabo en el día 0, por lo menos 18 horas después de la administración de una dosis alta de melfalán. Las células tallo serán infundidas por vía intravenosa durante aproximadamente 20-60 minutos después de premedicación de acuerdo con la práctica institucional estándar. Por lo menos 2 x 10^6 células madre CD34 +/ kg de peso corporal deben ser infundidas. Además, por lo menos 1 x 10^6 células madre CD34 + / kg de peso corporal debe estar disponible como un producto de las células madre de respaldo a infundir en el caso de retraso en el injerto o el fracaso del injerto tarde. El G-CSF debe administrarse subcutáneamente al comienzo del día 5+, dosificado según el estándar de la práctica institucional. Otras medidas de cuidados médicos de apoyo, tales como el soporte transfusional se tomaran de conformidad con las directrices institucionales estándar.

Infusión celular CART19 (día 12 -14)

Una sola dosis de CART-19 células T transducidas se dará compuesta de hasta 5 x 107

células CART-19. La dosis mínima aceptable para la infusión de las células transducidas con el vector TCRζ4-1BB de CD19 en este protocolo de paciente individual es $1x10^7$. Las células CART-19 se administraran en una única dosis por infusión intravenosa rápida el día 12-14 después de la infusión de células del tallo. Si el paciente no cumple ninguno de los criterios de inclusión descritos en la presente en la ventana de 2 a 14 días, la infusión de CART-19 puede retardarse más allá del día +12-14 hasta que los criterio se satisfacen.

Lenalidomida de Mantenimiento

Paras los sujetos que recibieron lenalidomida y toleraron su mantenimiento después de su primera TACM se volverá a iniciar el tratamiento de mantenimiento con lenalidomida en aproximadamente 100 +días, asumiendo que no hay contraindicaciones en el juicio del médico tratante. La dosis inicial será 10 mg al día a menos que la experiencia previa dicte una dosis inicial alternativa para un paciente en particular. La terapia de mantenimiento continuará hasta la progresión de la enfermedad o intolerancia.

Preparación y Administración del Fármaco del Estudio

Las células CART-19 T se preparan en el CVPF y no se liberan de la CVPF hasta que la FDA ha aprobado los criterios de liberación para las células infundidas (por ejemplo, dosis de células, la pureza de células, la esterilidad, el número medio de copias de los vectores / celular, etc) son cumplido. Una vez se libera, las células se llevan al lado de la cama para su administración.

Descongelación de células. Las células congeladas se transportan en hielo seco al lado de la cama del sujeto. Las células se descongelan en la proximidad del paciente usando un baño de agua mantenido de 36° C a 38° C. La bolsa se masajea suavemente hasta que las células se descongelen. No debe haber grumos congelados en el recipiente. Si el producto de células CART-19 parece tener daños o la bolsa filtraciones, o de otra manera parece estar comprometido, no debería ser infundido y debe ser devuelto a la CVPF como se especifica a continuación.

Premedicación. Los efectos secundarios siguientes a las infusiones de células T incluyen fiebre transitoria, escalofríos, y/o náuseas, véase Cruz para su revisión (Cytotherapy 2010; 12 (6) :743-749). Se recomienda que el sujeto sea pre-medicado con acetaminofén y clorhidrato de difenhidramina antes de la infusión de células CART-19. Estos medicamentos se pueden repetir

cada seis horas, según sea necesario. Un curso de la medicación anti-inflamatoria no esteroidea puede ser recetado si el paciente sigue teniendo fiebre y no se alivia con acetaminofeno. Se recomienda que los pacientes que no reciban corticosteroides sistémicos tales como la hidrocortisona, prednisona, metilprednisolona o dexametasona en ningún momento, excepto en el caso de una emergencia de vida o muerte, ya que esto puede tener un efecto adverso sobre las células T.

Reacción febril. En el improbable caso de que el sujeto desarrolle sepsis o bacteriemia sistémica después de infusión de células T CAR, los cultivos apropiados y el tratamiento médico deben ser iniciados. Si se sospecha que un producto de células T CART-19 está contaminado, el producto puede ser analizado de nuevo para esterilidad utilizando muestras archivadas que se almacenan en el CVPF.

Administración. La infusión se llevará a cabo en una habitación aislada en Rhoads, utilizando precauciones en los pacientes inmunodeprimidos. Las células T transducidas se pueden administrar por infusión intravenosa rápida a una tasa de flujo de aproximadamente 10 ml a 20 ml por minuto a través de un cáteter de calibre 18 sin látex de tipo Y con una llave de paso de 3 vías. La duración de la infusión se basa en el volumen total a ser infundido y la tasa de infusión recomendada. Cada bolsa de infusión tendrá fijada una etiqueta que contiene lo siguiente: "SÓLO PARA USO AUTÓLOGO." Además, la etiqueta tendrá al menos dos identificadores únicos, como las iniciales del sujeto, fecha de nacimiento y número del estudio. Antes de la infusión, dos individuos verificarán independientemente toda esta información en la presencia del sujeto y así confirmarán que la información está correctamente en correspondencia con el participante.

Los equipos médicos de emergencia (es decir, CAR de emergencia) estará disponible durante la infusión en caso de que el sujeto tenga una respuesta alérgica o una crisis hipotensora severa, o cualquier otra reacción a la infusión. Los signos vitales (temperatura, frecuencia respiratoria, pulso y presión arterial) se tomarán antes y después de la infusión, y después cada 15 minutos durante al menos una hora y hasta que estos signos sean satisfactorios y estables. Se le pedirá al sujeto que no se vaya hasta que el médico considere que es seguro que él o ella lo haga.

Embalaje

La infusión se compone de una sola dosis de 1-5 x 10^7 células CART 19 transducidas, con una dosis mínima aceptable de 1 x 10^7 células CART-19 para la infusión. Cada bolsa contiene una alícuota (volumen dependiente de dosis) de medio de criopreservación que contiene los siguientes reactivos de grado infusible (% v/v): 31,25% Plasmalyte-A, 31,25% dextrosa (5%), NaCl al 0.45%, hasta DMSO al 7,5%, dextrano 40 al 1%, albúmina sérica humana al 5%.

Aféresis

Un procedimiento de aféresis de gran volumen (12-15 litros o 4-6 volúmenes de sangre) se lleva a cabo en el centro de aféresis. PBMCs se obtienen para CAR-19 durante este procedimiento. Desde una única leucaféresis, la intención es recoger un mínimo de 5 x 10^9 células blancas de la sangre para fabricar células CART-19 T. También se obtienen los leucocitos de sangre de referencia para requisitos "look-back" de la FDA y para la investigación y criopreservados. Se espera que el producto celular esté listo para la liberación de aproximadamente 2-4 semanas después. Citometría de flujo de linfocitos con la subsecuente cuantificación, incluyendo la determinación de células B CD19 y CD20. Se realizó una evaluación de base para anticuerpo anti-VSV-G humano y anti-murino (HAMA). Si un sujeto ha tenido anteriormente una colección de aferesis adecuada depositada de acuerdo a las Buenas Prácticas de Fabricación en las Instalaciones Clínicas de Producción de Células y Vacunas, estas células pueden ser utilizadas como fuente de células para la fabricación de CART-19. Usando un producto de aféresis depositado se podría evitar el costo, tiempo y riesgo para el paciente de tener que colectar un producto adicional de aféresis

Quimioterapia Citoreductiva

La quimioterapia de linfodepleción será con altas dosis de melfalán como se describe en la presente.

Infusión de CART-19

La infusión se iniciará el día 12-14 después de reinfusión de células del tallo.

El día +12-14 antes de la primera infusión, los pacientes tendrán un CBC con diferencial, y evaluación de recuentos de CD3, CD4 y CD8 ya que la quimioterapia se da en parte para inducir linfopenia.

La primera dosis se administra usando una dosis única. Las células se descongelaron en

la próximadad del paciente. Las células descongeladas se administran a una tasa de infusión tan rápida como sea tolerada de tal manera que la duración de la infusión será de aproximadamente l 0-15 minutos. Con el fin de facilitar el mezclado, las células pueden administrarse simultáneamente usando un adaptador en Y. Los sujetos son infundidos y premedicados como se describe en la presente. Los signos vitales de los sujetos se evaluan y se realiza una pulsioximetría antes de la dosificación, al final de la infusión, y cada 15 minutos después de 1 hora y hasta que estos sean estables y satisfactorios. Una muestra de sangre para la determinación del nivel de CAR-19 de base se obtiene en cualquier momento antes de la primera infusión y 20 minutos a 4 horas después de cada infusión (y se envia a TCSL).

Los pacientes con efectos tóxicos relacionados con altas dosis de melfalán tendrán su programa de infusión retrasado hasta que estas toxicidades se hayan resuelto. Las toxicidades específicas que justifiquen la demora de las infusiones de células T incluyen: 1) Pulmonar: necesidad de oxígeno suplementario para mantener la saturación de más de un 95% o presencia de anormalidades radiográficas en la radiografía de tórax que son progresivas; 2) cardiaca: Nueva arritmia cardiaca no controlada con tratamiento médico 3) La hipotensión que requiera soporte vasopresor. 4) Infección activa: Hemocultivos positivos para bacterias, hongos o virus en las 48 horas de infusión de células T.

Manejo de Toxicidad

Proliferación incontrolada de células T. La toxicidad asociada con las infusiones de células T alogénicas o autólogas se ha manejado con un curso de la inmunosupresión farmacológica. La toxicidad asociada al cuerpo T ha sido reportada por responder a corticosteroides sistémicos. Si ocurre una proliferación no controlada de células T (toxicidad grado 3 o 4 relacionada con células CAR-19), los sujetos pueden ser tratados con corticosteroides. Los sujetos serán tratados con un pulso de metilprednisolona (2 mg/kg iv divididos en cada 8 h x 2 días), seguida de una reducción rápida.

Además, con base en las observaciones de los sujetos tratados en otro protocolo, existe cierta preocupación por el síndrome de activación de macrófagos (MAS), aunque se espera que la carga tumoral CD 19+ sea mucho menor en pacientes con mieloma que en los pacientes con CLL. El tratamiento y tiempo de tratamiento de esta toxicidad será a discreción del médico del paciente y el investigador del estudio. El manejo sugerido puede incluir: si el sujeto tiene una fiebre de más de 101º F que dura más de 2 días consecutivos y no hay evidencia de infección

(hemocultivos negativos, CXR u otra fuente), puede considerarse el tocilizumab 4 mg/kg. La adición de corticosteroides y terapia anti-TNF puede considerarse a discreción del médico.

Agotamiento de células B. Es posible que el agotamiento de células B e hipogammaglobulinemia se producirán. Esto es común con terapias dirigidas a anti-CD20. En caso de hipogammaglobulinemia clínicamente significativa (es decir, infecciones sistémicas), a los sujetos se les administra inmunoglobulina intravenosa (IVIG) por las directrices de dosificación clínicas establecidas para restaurar los niveles normales de los niveles de inmunoglobulinas séricas, como se ha hecho con Rituximab.

Falla primaria del injerto. La falla primaria del injerto (es decir, no injerto) puede ser más común después del segundo ASCT en comparación con el primer ASCT. Los criterios de elegibilidad estipulan que suficientes células tallo deben estar disponibles para reinfusión de rescate a discreción del médico tratante en caso de un fallo primario de injerto.

Resultados

Pacientes con myeloma multiple avanzado, refractorio a tres tratamientos ya han sido tratados con CTL019 en este ensayo en curso. Los resultados para dos de estos pacientes muestran que ambos han tenido efectos antitumorales sustanciales a partir de la terapia CTL019 con base en la evaluación de eficacia primaria en el punto de tiempo de tres meses. El tercer paciente todavía no ha alcanzado el punto de tiempo de tres meses. Los resultados para los dos pacientes se describen con más detalle a continuación.

El primer paciente con mieloma ha completado su evaluación de respuesta de +100 días y tuvo una muy buena respuesta a la terapia CART19. Las siguientes pruebas se realizaron con los siguientes resultados:

-SPEP/Inmunofijación: negativa

-inmunofijación de orina: banda debíl, inmedible de la cadena ligera kappa en su inmunofijación (también presente en el día 38, por lo que no es nuevo)

De lo contrario, el paciente cumple los criterios de remisión completa estricta que incluyen:

- relación de cadena ligera libre en suero: normal

- biopsia de médula osea: negativa

-Inmunofenotipado de IgA: IgA está por debajo del límite de detección

Aparte del débil e inmensurable resultado de la cadena kappa ligera en la inmunofijación de orina, el paciente cumplió con todos los criterios para "remisión completa estricta". El resumen del inmunofenotipado de células plasmáticas en 3 puntos de tiempo (día -2, día +38, día +103) se muestra en la Figura 8, y demuestra que la IgA del paciente está por debajo del límite de detección. El resumen muestra la carga de mieloma pesado el día -2 y ninguna detectable el día +38 y +103, lo cual clasifica el paciente como "MRD negativo" por el análisis de flujo. El día +103, el resumen muestra recuperación de células B y células plasmáticas CD19+ normales, policlonales. El paciente no tuvo síntomas de enfermedad o terapia y su desempeño es el de una persona normal.

El segundo paciente tratado aún no ha alcanzado el punto de tiempo del día +100. Sin embargo, en este punto de tiempo, le está yendo bien, pero es demasiado pronto para determinar el efecto de la infusión de CTL019.

Ejemplo 2: Terapia de células T CAR19 para el linfoma de Hodgkin

La terapia de células T CAR19 también se puede utilizar para tratar el linfoma de Hodgkin (HL). El linfoma de Hodgkin se caracteriza por la presencia de células malignas de Hodgkin Reed-Sternberg (HRS) que se derivan de células B de centro germinal clonal. Existen varios factores que indican la eficacia terapéutica de la terapia de células T CAR19 para HL. La tinción de CD19 de tumores HL muestra células que expresan CD19 ($CD19^{+}$) dentro del tumor y microambiente tumoral (Fig. 2). Un estudio ha demostrado que una población de células B clonales ($CD20^{+}CD27^{+}ALDH^{+}$) que expresa CD19 es responsable por la generación y mantenimiento de líneas celulares de linfoma de Hodgkin, y también circula en la sangre de la mayoría de pacientes con HL (Jones, Blood, 2009, 113 (23): 5.920-5926). Esta población de células B clonales también se ha sugerido para dar lugar a o contribuir a la generación de células HRS malignas. Así, la terapia CART19 agotaría esta población de células B que contribuye a la tumorigénesis o mantenimiento de las células tumorales. Otro estudio mostró que la depleción de células B retarda el crecimiento de tumores sólidos en múltiples modelos murinos (Kim, J inmunoterapia, 2008, 31 (5): 446-57). En apoyo a la idea de que la depleción de células B en el microambiente tumoral HL, resulta en algún efecto anti-tumoral, las terapias actuales, tales como Rituxan, están siendo probadas clínicamente para re-dirección y depleción de células B tumorales en HL (Younes, Blood, 2012, 119 (18): 4123-8). La carcinogénesis de nuevo

relacionada a la inflamación crónica también ha demostrado ser dependiente de células B (de Visser, Cancer Cell, 2005, 7 (5): 411-23). Los resultados de estos estudios indican que dirigir la población de células B, en particular en el microambiente tumoral HL, sería útil para el tratamiento de HL, reduciendo o inhibiendo la progresión de la enfermedad o el crecimiento tumoral.

Además, las células B normales que expresan CD19 también se infiltran en el microambiente tumoral en HL. Estudios anteriores con la terapia de CART19 en CLL y ALL (por ejemplo, descritos en los Ejemplos 4 y 5) muestran que la exposición de CART19 a dianas CD19+ conduce a la producción de citoquinas y producción de macrófagos. Por lo tanto, la modulación del microentorno tumoral de HL a partir de un microambiente pro-tumoral a un microambiente anti-tumoral se puede lograr mediante la infusión de CART19 para interactuar con las células B CD19+ normales presentes en la HL. Por ejemplo, la exposición de CART19 a dianas que expresan CD19 causa la producción de citoquinas, por ejemplo, citoquinas inflamatorias, que promueven la actividad anti-tumoral a través de la expansión de células T citotóxicas, la activación de macrófagos, y el reclutamiento de otras células efectoras inmunes con diversas funciones que inhiben el crecimiento tumoral, tales como leucocitos, macrófagos y células que presentan antígenos. Debido a que las células B CD19+ diana pueden no ser malignas (por ejemplo, células B que circulan normalmente), un efecto transitorio de CART19 en lugar de uno prolongado puede ser preferible para la modulación del microentorno tumoral.

Un estudio para examinar la eficacia terapéutica de terapia CART19 en pacientes HL se puede realizar como se describe a continuación (FIG. 3). El estudio también evalua la seguridad y tolerabilidad de CART19 en sujetos con HL, y determina el efecto de células CART19 en el microambiente tumoral de HL.

Se tratan en este estudio 8 pacientes con HL clásica. Los pacientes son de todas las edades, aunque se pueden establecer protocolos separados para la administración de fármacos para pacientes pediátricos y adultos. Los pacientes en este estudio no tienen opciones de tratamientos potencialmente curativas disponibles (tales como trasplante de células tallo autólogas (ASCT) o alogénicas), o no son adecuadas para este tipo de tratamientos curativos. Por ejemplo, los pacientes pueden ser cualquiera de los siguientes: PET+ después de la quimioterapia agresiva, PET+ después del tratamiento con brentuximab, o PET+ después de ASCT con o sin exposición previa a brentuximab. Los pacientes tendrán un pronóstico limitado

(supervivencia esperada de varios meses a menos o igual a 2 años) con las terapias actualmente disponibles. Y, por último, los pacientes no recibirán terapia de anticuerpos anti-CD20. Los pacientes son excluidos por falta de viabilidad, ej., si el paciente tiene un número insuficiente de células T para 6 infusiones de CART19.

Un CAR19 de ARNm se produce mediante transcripción in vitro. El ARNm de CAR19 es electroporado a células T del donor, y las células resultantes se expandieron y estimularon mediante incubación con esferas CD3/CD28. Las dosis que contienen $1x10^8$ - $5x10^8$ células T CAR19 electroporadas por ARN se administran al paciente tres veces a la semana durante dos semanas (ej.,, en el día 0, 2, 4, 7, 9 y 11). La tasa de respuesta global será evaluada mediante escaneo clínico, CT y PET a 1 mes después del tratamiento. La respuesta y supervivencia serán monitoreadas mensualmente durante los primeros 6 meses, y luego cada 3 meses hasta 2 años después de la primera infusión de CART19 (día 0). Técnicas de monitoreo incluyen biopsia del tumor o ganglio linfático (ej., para el análisis inmunohistoquímico y/o ARN para perfiles de expresión de genes) y barrido PET antes y después del tratamiento CART19. Por ejemplo, el efecto de las células CART19 en el microambiente tumoral HL se analizó mediante la comparación de los resultados de perfiles de expresión génica realizados en biopsias de ganglios linfáticos accesible desde pacientes seleccionados antes de tratamiento y aproximadamente una semana después del tratamiento (o el tiempo adecuado después del tratamiento para permitir la alteración del fenotipo celular). Para evaluar la seguridad y tolerabilidad del tratamiento CART19, se reporta la frecuencia y gravedad de los eventos adversos, incluyendo la frecuencia del síndrome de liberación de citoquinas (CRS) y el síndrome de activación de macrófagos (MAS).

La quimioterapia puede administrarse simultáneamente con el tratamiento CART19. La primera dosis de CART19 puede estar precedida por quimioterapia de linfodepleción, por ejemplo, Citoxan.

Ejemplo 3: Subgrupo no respondedor de pacientes con CLL exhibieron expresión aumentada de moléculas inhibidoras de punto de comprobación inmune

En este estudio, las células CART19 a partir de la fabricación clínica de 34 pacientes con CLL se evaluaron para la expresión de moléculas de inhibidor de punto de control inmune, tales

como PD-1, LAG3, y TIM3. La respuesta de esta cohorte a CART19 fue conocida y por lo tanto una correlación entre respuesta y patrones de expresión de biomarcadores podría ser evaluada.

Células CART19 fabricadas a partir de pacientes con CLL con diferentes respuestas a la terapia CART se analizaron mediante citometría de flujo para determinar la expresión de CAR y las moléculas de inhibidor de punto de comprobación PD-1, LAG3, y TIM3. Las células CART19 eran de: donantes sanos (HD) (n = 2); pacientes con CLL que respondieron a terapia CART (CR) (n = 5); pacientes con CLL que parcialmente respondieron a terapia CART (PR) (n = 8); Pacientes con CLL que no respondieron a terapia CART (NR) (n = 21). Las células se tiñeron con anticuerpos marcados fluorescentemente que reconocen específicamente CD3, CD4, CD8, CD27, CD45RO, la molécula de CAR19, y las moléculas de punto de comprobación inmune PD-1, LAG3, y TIM3, de acuerdo con métodos estándar para el análisis de citometría de flujo conocido en la técnica. La expresión de cada marcador, por ejemplo, CD4+, CD8+, etc., se determinó por software de análisis de citometría de flujo, y las subpoblaciones (ej., células T CD4+, células T CD8+, o células T que expresan CAR19) se analizaron adicionalmente para la expresión de moléculas de punto de comprobación inmune PD-1, LAG3 y TIM3.

Un ejemplo del análisis de perfiles de citometría de flujo utilizado para determinar la expresión de marcadores de superficie se muestra en la Figura 4A y 4B. Las células T que expresan CD4 se determinaron usando citometría de flujo, y se analizaron adicionalmente para expresión de CAR19 y PD-1, de tal manera que el eje x de los perfiles indican expresión de CAR19 (los cuadrantes superior izquierdo (Q5) e inferor izquierda (Q8) muestran la células CD4+ CAR19-negativas, mientras que los cuadrantes superior derecho (Q6) e inferior derecho (Q7) muestran las células CD4+ que expresan CAR19) y el eje y muestra la expresión de PD-1 (cuadrantes inferior izquierdo (Q8) y derecho (Q7) muestran la células CD4+ PD-1 negativas y los cuadrantes superior izquierdo (Q5) y derecho (Q6) muestran las células CD4+ que expresan PD-1). En la población CD4+ a partir de un respondedor CART, 44.7% de las células CD4+ expresaron en general PD-1, y aproximadamente 22,3% de las células que expresan CAR19 fueron PD-1 positivas, mientras que 27,2% de las células que expresan CAR19 fueron PD-1 negativas (FIG. 4A). En contraste, en la población CD4+ a partir de un no respondedor, hubo una disminución significativa en células que expresan CAR19 en general (alrededor de 15.3% en comparación con el 49,5% en CR), con 14.7% de las células que expresan CAR19 siendo PD-1 positivas mientras que sólo el 0,64% fueron PD-1 negativas (FIG. 4B). La comparación

entre los perfiles en la FIG. 4A y FIG. 4B muestra que un porcentaje mucho mayor de células CD4+ de un no respondedor expresan PD-1 (aproximadamente 92.9%) en comparación con el respondedor CART (aproximadamente 44.7%).

Utilizando los métodos y análisis descrito anteriormente, el porcentaje de células que expresan PD-1 (PD-1+) de la población CD4+ y la población CD8+ se determinó para cada paciente en cada grupo de respuesta. Los no respondedores se mostraron que tuvieron un mayor porcentaje de células PD-1+ en ambas poblaciones CD4+ (FIG 4C.) y CD8+ (FIG 4D) en comparación con aquellos que respondieron a la terapia CAR (CR); el aumento del porcentaje de PD-1 promedio fue estadísticamente significativo para ambas poblaciones CD4+ y CD8+. Los respondedores parciales (PR) mostraron mayores porcentajes de células PD-1+ que los respondedores (CR) en ambas poblaciones CD4+ (FIG. FIG. 4C) y CD8+ (FIG. 4D).

A continuación, el porcentaje de células que expresan PD-1 (PD-1+) de la población CD4+ que expresa CAR19 y la población CD8+ que expresa CAR19 se determinó para cada paciente en cada grupo de respuesta. Un análisis similar se realizó como antes, con el paso adicional de analizar las células CD4+ y CD8 para expresión de CAR19, y después de la identificación de las células que expresan CAR19, determinando el porcentaje de células con expresión de PD-1 a partir de las poblaciones de células que expresan CAR19. Se observó una tendencia similar a la observada en las poblaciones globales de CD4+ y CD8+ para poblaciones de CD4+ y CD8+ que expresan CAR19: no se mostraron respondedores con porcentaje mayor de células PD-1+ en ambas poblaciones CD4+ (FIG. 5A) y CD8+ (FIG. 5B) en comparación a los que respondieron a la terapia CAR (CR); el aumento del porcentaje de PD-1 promedio fue estadísticamente significativo para ambas poblaciones CD4+ y CD8+. Los respondedores parciales (PR) mostraron mayores porcentajes de células PD-1+ que los respondedores (CR) en ambas poblaciones CD4+ (FIG. 5A) y CD8+ (FIG. 5B).

Se llevó a cabo análisis adicional para determinar la distribución de células que expresan PD-1, LAG3, y TIM3 de pacientes con diferentes respuestas a la terapia CAR. Análisis de perfil de células representativas para expresión de PD-1, LAG3, y TIM3 en la población CD4+ se muestra en la FIG. 6. Las poblaciones de células se analizaron primero para expresión de CD4+ y CD8+. A continuación, se analizó la población CD4+ (o población CD8+, no mostrada) para expresión de PD-1 y CAR19 (FIG. 6, perfiles a la izquierda). Como se describió anteriormente, los no respondedores (NR) tuvieron un aumento significativo del porcentaje de células que

fueron PD-1+ en general en comparación con los respondedores CART (CR) (aproximadamente 92,9% de PD-1 positivo para NR en comparación con el 44.7% de PD-1 positivo para CR). Por otra parte, en los no respondedores, las células que expresan CAR19 fueron en su mayoría PD-1 positivas (14,7% PD-1 positivas y CAR+ en comparación con 0.64% de PD-1 negativo y CAR+). A continuación se analizaron las poblaciones para co-expresión de PD-1 y LAG3 (Fig. 6, perfiles medios). Las células que expresan tanto PD-1 y LAG3 se muestran en el cuadrante derecho superior (Q2). Los no respondedores tuvieron un aumento significativo del porcentaje de células que expresaron ambos inhibidores de punto de comprobación inmune, PD-1 y LAG3, en comparación con los respondedores CART (67,3% frente a 7,31%). La expresión de PD-1 también se analizó con la expresión de TIM3. En la FIG. 6, los perfiles adecuados, el cuadro indica las células que expresan tanto PD-1 como TIM3. Similar a los resultados obtenidos con PD-1 Y LAG-3, los no respondedores tuvieron un porcentaje significativamente mayor de células que expresaron ambos inhibidores de punto de comprobación inmune, PD-1 y LAG3, en comparación con los respondedores CART (83.3% frente a 28.5%). El porcentaje de células que expresan PD-1 (PD1+), células que expresan LAG3 (PD1+LAG3+), y células que expresan PD-1 y TIM3 (PD1+TIM3+) se determinó para cada paciente en cada grupo de respuesta utilizando el análisis de citometría de flujo como se describe anteriormente. Los no respondedores fueron mostrardos por tener un porcentaje aumentado de células PD1+LAG3+ (Fig. 7A) y células PD1+TIM3+ (Fig. 7B) en comparación con los respondedores CART que fueron estadísticamente significativos para ambas poblaciones de células. Respondedores parciales también mostraron un aumento del porcentaje de las dos poblaciones de células en comparación con los respondedores CART, con los promedios reducidos en comparación con los no respondedores.

Estos resultados indican que los pacientes que no responden a la terapia CAR exhiben expresión aumentada de inhibidores de punto de control inmune (ej., PD-1, LAG3, y TIM3) en comparación con los pacientes que responden o responden parcialmente a la terapia CAR. Por lo tanto, estos resultados muestran que los agentes que inhiben o disminuyen la expresión de inhibidores de punto de comprobación inmune, por ejemplo, PD-1, LAG3, o TIM3, pueden ser útiles para la administración a pacientes que reciben terapia CAR para evitar la supresión inmune a través de vías de punto de comprobación inmune (por ejemplo, mediadas por PD-1, LAG3, o TIM3), aumentando así la eficacia de las células que expresan CAR.

Ejemplo 4: Efectos de la inhibición de mTOR en Inmunosenescencia en los Ancianos

La eficacia de la inhibición de mTOR en inmunosenescencia se describe, por ejemplo, en el Ejemplo 1 de la Solicitud Internacional WO/2015/073644, y la totalidad de la solicitud se incorpora aquí como referencia.

Ejemplo 5: Mejora de la Respuesta Inmune a vacuna en personas de edad avanzada

La eficacia de la inhibición de mTOR en la mejora de una respuesta inmune se describe, por ejemplo, en el Ejemplo 2 de la Solicitud Internacional WO/2015/073644, y la totalidad de la solicitud se incorpora aquí como referencia.

Ejemplo 6: La inhibición de mTOR de baja dosis aumenta la energía y el ejercicio;

El efecto de la inhibición de mTOR sobre la energía y el ejercicio se describe, por ejemplo, en el Ejemplo 3 de la Solicitud Internacional WO/2015/073644, y la totalidad de la solicitud se incorpora en la presente como referencia.

Ejemplo 7: Inhibición de la quinasa S6 P70 con RAD001

El efecto de la inhibición de mTOR sobre la inhibición de la P70 S6 quinasa se describe, por ejemplo, en el Ejemplo 4 de la Solicitud Internacional WO/2015/073644, y la totalidad de la solicitud se incorpora en la presente como referencia.

Ejemplo 8: IL-7 exógena mejora la función de las células T CAR

Después de la transferencia adoptiva de células T CAR, algunos pacientes experimentan persistencia limitada de las células T CAR, lo cual puede resultar en niveles subóptimos de actividad anti-tumoral. En este ejemplo, los efectos de la administración de IL-7 humana exógena se evalúa en modelos de xenoinjerto de ratón donde se observa una respuesta subóptima inicial a células T CAR.

La expresión del receptor de IL-7 CD127 se evaluó primero en diferentes líneas celulares de cáncer y en células que expresan CAR. Dos líneas celulares de linfoma de células del manto (RL y Jeko-1) y una línea celular B-ALL (Nalm-6) se analizaron mediante citometría

de flujo para la expresión de CD127. Como se muestra en la Figura 9A, de las tres líneas celulares de cáncer probadas, se mostró que RL tenia la mayor expresión de CD127, seguido por Jeko-1 y Nalm-6. Las células CART19 fueron infunidas en ratones NSG y la expresión de CD127 se evaluó en células CART19 circulantes mediante citometría de flujo. Como se muestra en la Figura 9B, CD127 se expresa uniformemente en todas las células circulantes CART19.

A continuación, el efecto de tratamiento de IL-7 exógena sobre la actividad anti-tumoral de células CART19 se evaluó en un modelo animal de linfoma. Ratones GSN fueron injertados con una línea de células del manto que expresan luciferasa (RL luc) el día 0 (D0), seguido por el tratamiento de células CART19 el Día 6. Los ratones NSG se dividieron en grupos, donde un grupo no recibió células CART19, un segundo grupo recibió $0.5x10^6$ células CART19, un tercer grupo recibió $1x10^6$ células CART19, y un cuarto grupo recibió $2x10^6$ células CART19. El tamaño del tumor se monitoreó mediante la medición de la bioluminiscencia media de los tumores injertados durante más de 80 días. Solamente los ratones que recibieron $2x10^6$ células CART19 demostraron rechazo del tumor e inhibición del crecimiento tumoral (Figura 10A). Los ratones de los dos grupos que recibieron $0.5 x10^6$ células CART19 o $1x10^6$ células CART19 se mostraron por tener una respuesta anti-tumoral subóptima. Ratones de estos dos grupos fueron luego aleatorizados, donde tres ratones (ratón #3827 y #3829 que recibieron $0.5x10^6$ células CART19, y el ratón #3815 que recibió $1x10^6$ células CART19) recibieron IL-7 humana recombinante exógena a una dosis de 200 ng/ratón por vía intraperitoneal tres veces a la semana a partir del día 85, y dos ratones no lo hicieron. La carga tumoral de los ratones que recibieron IL-7 exógena desde el Día 85-125, detectada mediante bioluminiscencia media, se muestra en la Figura 10B. Todos los ratones que recibieron IL-7 mostraron una respuesta dramática de la reducción logarítmica 1-3 en la carga tumoral. Los ratones que originalmente recibieron una dosis más alta de células CART19 (ratón #3815 que recibió $1x10^6$ células CART19) mostraron una respuesta más profunda. Al comparar la carga tumoral de ratones que recibieron tratamiento con IL-7 con el control, antes y después de tratamiento con IL-7, la reducción tumoral en la carga tumoral sólo se observó en los ratones que habían recibido tratamiento con IL-7 (FIG. 10C).

También se examinó la dinámica de células T después de tratamiento con IL-7 en el modelo animal de linfoma. Las células CART19 humanas no fueron detectables en la sangre

antes del tratamiento con IL-7. Tras el tratamiento de IL-7, hubo un aumento rápido pero variable en los números de células T en los ratones tratados (Figura 11A). La extensión de la expansión de células T observada en los ratones que recibieron la IL-7 también se correlacionó con la respuesta tumoral. El ratón con el mayor número de células T detectadas en la sangre en la expansión máxima durante tratamiento con IL-7 (ratón #3815) tuvo la reducción más robusta en la carga tumoral (véase la Figura 10B). Además, el tiempo de la expansión máxima se correlacionó con la dosis de células T inyectada como línea de base. También se midió el número/nivel de células que expresan CD3 en la sangre antes y después de tratamiento con IL-7 . En los ratones de control, se detectaron muy pocas células que expresan CD3, mientras que los ratones tratados con IL-7 mostraron un aumento significativo en las células CD3+ después de tratamiento con IL-7 (Figura 11B).

Juntos, los resultados de este ejemplo demuestran que el tratamiento con IL-7 exógena aumenta la proliferación de células T y la actividad anti-tumoral *in vivo,* lo que indica que el uso de IL-7 en pacientes con resultados subóptimos después de terapia CAR puede mejorar la respuesta anti-tumoral en estos pacientes .

Ejemplo 9: Evaluación de CD22 CAR

Ensayo celular Jurkat-NFAT-Luciferasa (JNL) automatizado

Se realizó un ensayo automatizado para determinar la reactividad de los clones CD22 CART específicos. $3x10^4$ células de la línea celular Jurkat transducidas lentiviralmente que expresan de forma estable luciferasa de un promotor NFAT (células JNL) se sembraron en una placa de 96 pozos con líneas celulares diana que expresan CD22 (Daudi, Raji) y una línea celular que no expresa CD22 (K562) como control negativo. El día siguiente, se añadió sustrato de luciferina a cada pozo de la placa de 96 pozos y se determinó la luminiscencia relativa del reportero de luciferasa. En este ensayo, los constructos CAR CD22 se compararon con un constructo CAR CD19 y un constructo CAR CD22 (derivado de m971) (M971-HL), que sirvieron como controles positivos. Un constructo CAR m971-LH, que contiene las cadenas VH y VL de m971-HL pero en orientación inversa (L-H en lugar de H-L), contenía un CAR, pero no pudo unirse a su blanco debido a la falta de especificidad y sirvió como un control negativo. Las células T no transducidas que no contienen ningún CAR (Neg cnt) también sirvieron como

control negativo. La actividad de luciferasa a partir de la activación de células T Jurkat se representó gráficamente. Los resultados mostrados en la presente demuestran que varios de los clones JNL transducidos con CD-22 mostraron reactividad específica hacia las líneas celulares que expresan CD22 que aumentó de una manera dependiente de la dosis (Figs. 18A-18C).

Expresión de CD22 CAR en las células T humanas primarias

[001] Las células T humanas primarias se activaron con perlas estimulantes anti-CD3/antiCD28 el día 0, seguido por transducción lentiviral de constructos CAR especificados el día 1. Las células se expandieron *in vitro* hasta el día 10, momento en el que se analizaron por citometría de flujo para la expresión en superficie del CAR. Se utilizaron dos enfoques diferentes para determinar la expresión en superficie del CAR: La proteína-L-biotina seguida por estreptavidina-PE, y CD22-Fc recombinante humano seguido de anti-Fc-alexafluor 488. Los resultados se muestran en la FIG. 19. Los resultados mostrados en la presente demuestran que CD22 CAR clón 2 (hCD22-2), el clón 5 (hCD22-5), el clón 7 (hCD22-7), el clón 8 (hCD22-8), el clón 10 (hCD22-10), el clón 12 (hCD22-12), el clón 30 (hCD22-30), y el clón 31 (hCD22-31) mostraron una expresión en superficie positiva. CD22 CAR m971 sirvió como control positivo para la unión tanto de la proteína-L como de hrCD22-Fc, y el isotipo CAR sin especificidad (anti-gH) sirvió como control positivo para la Proteína-L. Se utilizaron células T que no expresan ningún CAR como control negativo.

Ensayo de muerte y detección de tumor por células T primarias

Las células T primarias activadas y transducidas como se describe anteriormente se mezclaron con las líneas celulares objetivoque expresan de forma estable la luciferasa en las proporciones indicadas (FIG. 20A-20F). Las líneas de células objetivo Raji, SEM, K562-hCD22, Daudi, y NALM6 todas expresaron la diana CD22, mientras que la línea celular K562 no expresó CD22 y sirvió como control negativo (Fig. 20A-20F). Los resultados presentados en la presente demuestran que varios clones CAR CD22 (por ejemplo, clones CAR CD22 2, 5, 7, 8, 10, 12, 30, y 31) y el control positivo CD22 m971-HL CAR exhibieron eliminación de células objetivo dependiente de la dosis, con la extensión de la eliminación variando dependiendo del tipo de célula objetivo. Las células T no transducidas (UTD) carecíeron de la capacidad de eliminar líneas celulares diana.

Arreglo de esfera de citoquinas de células T primarias

Se investigó la capacidad de las líneas celulares que expresan CD22 para inducir la liberación de citoquinas proinflamatorias a partir de células CART que expresan CD22. La concentración de citoquinas proinflamatorias ee detemrinó usando un kit de arreglo de esfera de citoquinas en muestras tomadas del ensayo de muerte de células T primarias. El interferón-g (IFN-g), factor de necrosis tumoral alfa (TNFa), y la interleucina 2 (IL-2) fueron medidos en muestras de entre 2.5:1 y 10:1 de proporciones E:T. Los resultados se muestran en la FIG. 21A-21F. Los resultados mostrados en la presente demuestran que varios clones CD22 CAR indujeron significativamente más IFN-g, TNFa e IL-2 que las células T m971-LH CAR (control negativo) o no transducidas (UTD), con los niveles de inducción de citoquinas que varían según el tipo de célula diana .

Ejemplo 10: Estudio de escalamiento de dosis de tratamiento con CART CD22

Un ensayo clínico de fase 1 se realiza para determinar la dosis óptima de CART CD22 con o sin CART CD19 en pacientes con ALL que han y no han recibido previamente terapia CART. El propósito de este estudio es determinar la factiilidad de producir Células T CAR -anti CD22 modificadas que satisfagan los criterios de liberación establecidos y para evaluar la seguridad de la administración de dosis crecientes de células T CAR -anti CD22 modificadas autólogas en niños y adultos jóvenes con tumors malignos de células B seguido de un régimen de linfodepleción de ciclofosfamida/fludarabina.

Los sujetos son entre 1 y 30 años de edad y con un peso mínimo de 15 kg con ALL CD22+. La actividad de la enfermedad se puede medir mediante el análisis de médula ósea o FDG-PET. Se permiten sujetos con mínima actividad residual de la enfermedad. Se permiten sujetos con un estado del sistema nervioso central (CNS) de 1 o 2. Los sujetos deben tener una adecuada función de organos y un recuento de CD3 adecuado.

Se realizó un estudio de escalamiento de dosis de fase 1 con una cohorte de expansión. Los sujetos se estratificaron en función de si han o no recibido previamente terapia CART. A los sujetos se se administra uno de los cuatro niveles de dosis de cuatro dosis de células T CAR anti-CD22 autólogas modificadas: $3x10^5$ células/kg de peso corporal, $1x10^6$ células/kg de peso corporal, $3x10^6$ células/kg de peso corporal y $1x10^7$ células/kg de peso corporal. Un subconjunto de los sujetos que recibieron la dosis de $3x10^6$ células/kg de peso corporal también

se les proporciona células T CAR anti-CD19 modificadas. Los 2 primeros pacientes en cada nivel de dosis tienen 16 años de edad o más.

Después de determinar la elegibilidad, se realiza la aféresis para aislar las células T. Luego los sujetos se someten a quimioterapia preparativa. Los sujetos son tratados con 25 mg/m^2 de fludarabina al día durante tres días y se les dio una dosis única de 900 mg/m^2 de ciclofosfamida. Luego las células T CAR anti-CD22 modificadas se administran y 28 días después se evalua la respuesta y la toxicidad.

Ejemplo 11: Utilización de receptores quiméricos de antígeno que se dirigen a CD-20 (CARS) para el tratamiento de tumores malignos de células B

Se realizó un ensayo celular Jurkat-NFAT-luciferasa (JNL) para determinar la reactividad de los clones específicos de CART CD20. Las células Jurkat que expresan de forma estable luciferasa a partir de un promotor de NFAT (células JNL) se transdujeron lentiviralemente con constructos CAR mostrados en la figura. 15A-15C. Las células JNL que expresan CAR (3E4) se mezclaron con líneas celulares diana Daudi que expresan CD20 (FIG. 15A) y la Raji (FIG. 15B), y un control negativo que no expresa CD20 K562 (Fig. 15C) en proporciones de célula efectora: célula diana (E:T) de 0.5: 1, 1:1, 2:1, y 4:1. Las células JNL transducidas lentiviralmente se sembraron en una placa de 96 pozos con líneas celulares diana que expresan CD20 (Daudi, Raji) y una línea celular que no expresa CD20 (K562) como control negativo. El día siguiente, se añadió sustrato de luciferina a cada pozo de la placa de 96 pozos y se determinó la luminiscencia relativa del reportero de luciferasa (a partir de la activación de células T Jurkat). En este ensayo, los constructos CAR CD20 se compararon con un constructo CAR CD19 y un constructo CAR CD22 (derivado de m971) descrito en Haso, Blood 14 Feb 2013, Vol. 121, No. 7 que sirvieron como controles positivos. El isotipo del CAR, que contiene un Car pero no es capaz de unirse al blanco debido a la falta de especificidad, y células T no transducidas que no contienen un CAR (Neg cnt) sirvieron como controles negativos. Los resultados se muestran en la FIG. 15A-15C. Varios de los clones JNL CD20 transducidos mostraron reactividad específica hacia las líneas celulares que expresan CD20 que aumentaron de una manera dependiente de la dosis.

Ejemplo 12: Identificación de Factores que Predicen la Recaida del Sujeto a la Terapia CD19CART en Leucemia Linfocítica Aguda de Células B (B-ALL)

El presente Ejemplo describe, entre otras cosas, la identificación de marcas genéticas novedosas transcripcionales que predicen la recaída del paciente frente a una terapia de CARTCD19 (por ejemplo, terapia CTL019) en leucemia linfocítica aguda de células B (B-ALL), para uso de acuerdo con la presente invención.

Entre otras cosas, el presente Ejemplo describe nuevas marcas genéticas basadas en los niveles de expresión de ARNm de los genes seleccionados en el paciente antes del tratamiento con CD19CART (ej., CTL019) (aféresis o médula ósea) o en muestras de producto CD19CART fabricados (por ejemplo, CTL019) antes de la re-infusión. En una modalidad, el presente ejemplo describe nuevas marcas genéticas que discriminan los sujetos con racaída a terapia de CTL019 en B-ALL de pacientes sin recaida a terapia CTL019 en B-ALL.

El presente Ejemplo describe métodos de selección de características no sesgadas para descubrir nuevas marcas genéticas que predicen la recaída de sujetos a terapia de CD19CART (ej., CTL019) en B-ALL, para uso de acuerdo con la presente invención.

El presente ejemplo también describe métodos de Análisis de Conjuntos de Genes para descubrir nuevas marmas genéticas, para uso de acuerdo con la presente invención.

Se identificaron marcas genéticas novedosas basadas en los niveles de expresión de ARNm en muestras de productos fabricados CD19CART antes de la reinfusión que predicen la recaída del paciente frente a la terapia de CD19CART en leucemia linfocítica aguda de células B (B-ALL). Las marcas identificadas se descubrieron en un studio RNAseq del genoma completo de las muestras del producto elaboradas que incluyen muestras de 7 sujetos con B-ALL. Las muestras de sujetos que padecen B-ALL (7 en total) fueron estratificados de la siguiente manera: Las muestras biológicas se tomaron de 4 sujetos quienes no recayeron (“no-reincidentes”) seguido de terapia CTL019, y 3 sujetos que recayeron("reincidentes") después de la terapia CTL019. Algunas marcas genéticas novedosas que diferencian a los respondedores de los no respondedores, y a los que recaen de aquellos que no recaen, en muestras de productos manufacturados fueron descubiertas y se describen con más detalle a continuación.

Luego se descubrieron nuevas marcas genéticas novedosas usando diferentes enfoques analíticos de datos: 1) selección no sesgada de características; 2) análisis de conjuntos de genes;

y 3) análisis de expresión diferencial de genes seleccionados de interés.

Se descubrieron nuevas marcas genéticas derivadas de la selección no sesgada de características al determinar cuales genes se expresaron diferencialmente entre los dos grupos de comparación de los reincidentes y de los no reincidentes que comparaban 3 reincidentes frente a 4 no reincidentes. Los genes se definieron como diferencialmente expresados si su expresión diferencial fue estadísticamente significativa en los 2 grupos de comparación con un valor de corte p de FDR de 0.25. La lista de genes para la comparación de reincidentes y no reincidentes (N = 17) se tabula en la **Tabla 29.** Se aplicaron modelos estadísticos de 2 grupos para determinar si el meta-gen fue estadísticamente diferente entre los grupos y un esquema de ejmplo que ilustra el enfoque se ilustra en la FIG. 32. FIG. 32 representa un mapa térmico ejemplar de los genes estimulados en TEFF activado frente a células TEFF en reposo para los respondedores completos (CR), respondedores parciales (PR) y no respondedores (NR) con CLL.

Sin desear estar limitado por una teoría particular, estos datos indican que el estado de diferenciación de las células T en producto CD19CART (por ejemplo, CTL019) se correlaciona con la respuesta del sujeto (es decir, CR, PR, o NR) y predicen la recaída del sujeto a la terapia CD19CART (ej., la terapia CTL019) en B-ALL. Las marcas genéticas de los respondedores son más parecidas a las de las células TREG y TEFF en reposo. Entre otras cosas, las marcas genéticas para los reincidentes (por ejemplo, un respondedor completo que recae a la terapia con CTL019) contienen genes estimulados en células TREG frente a TEFF en reposo. Sin desear estar ligado por una teoría particular, estos datos indican que sujetos quienes recaen a la terapia de CART (por ejemplo, CTL019) en B-ALL tienen niveles más altos de T_{REG} en comparación con los no reincidentes a la terapia de CART (por ejemplo, CTL019). La FIG. 17 representa resultados de ejemplo que ilustran que las células T_{REG} se enriquecen de manera diferencial en reincidentes (R) frente a no reincidentes , por ejemplo, los reincidentes expresan altos niveles de genes T_{REG} en comparación con respondedores completos (CR) (por ejemplo, no reincidentes).

Tabla 29: Genes de Ejemplo que Predicen la Recaída del Paciente a la Terapia de CTL019

Gen	miRBasa	Unigen	No. de Acceso	FDR
MIR199A1	MI0000242		NR_029586.1	2.11E-05
PPIAL4D		Hs.730589	NM_001164261.1	3.94E-05
MIR1203	MI0006335		NR_031607.1	4.63E-03
uc021ovp				6.73E-03

Gen	miRBasa	Unigen	No. de Acceso	FDR
ITM2C		Hs.111577	NM_001012514.2 NM_001012516.2 NM_001287240.1 NM_001287241.1 NM_030926.5	1.17E-01
HLA-DQB1		Hs.409934 Hs.534322	NM_001243961.1 NM_001243962.1 NM_002123.4	1.17E-01
TTTY10		Hs.461175	NR_001542.1	1.25E-01
TXLNG2P		Hs.522863	NR_045128.1 NR_045129.1	2.27E-01
MIR4650-1	MI0017277		NR_039793.1	2.27E-01
KDM5D		Hs.80358	NM_001146705.1 NM_001146706.1 NM_004653.4	2.27E-01
USP9Y		Hs.598540	NM_004654.3	2.27E-01
PRKY		Hs.584730	NR_028062.1	2.27E-01
RPS4Y2		Hs.367761	NM_001039567.2	2.27E-01
RPS4Y1		Hs.282376	NM_001008.3	2.27E-01
NCRNA00185		Hs.138453 Hs.729534 Hs.734681	NR_001543.3 NR_125733.1 NR_125734.1 NR_125735.1 NR_125736.1 NR_125737.1	2.28E-01
SULT1E1		Hs.479898	NM_005420.2	2.33E-01
EIF1AY		Hs.461178	NM_001278612.1 NM_004681.3	2.38E-01

Los siguientes genes mostraron aumento de los niveles en reincidentes y disminución de los niveles en pacientes no reincidentes: MIR199A1, MIR1203, uc021ovp, ITM2C, y HLA-DQB1. Los siguientes genes mostraron disminución de los niveles en pacientes con recaída y aumento de los niveles en pacientes sin recaída: PPIAL4D, TTTY10, TXLNG2P, MIR4650-1, KDM5D, USP9Y, PRKY, RPS4Y2, RPS4Y1, NCRNA00185, SULT1E1 y EIF1AY.

El análisis del conjunto de genes obtuvo un número de marcas genéticas que predicen la recaída del sujeto a la terapia CTL019 en B-ALL.

Entre otras cosas, el presente ejemplo describe las marcas genéticas novedosas basado en un análisis del conjunto de genes, que predicen la recaída del paciente a la terapia CD19CART (ej., CTL019) en B-ALL. El análisis del conjunto de genes se realizó en tres conjuntos de genes, es decir, los conjuntos de genes se obtuvieron a partir de (1) los experimentos adicionales se

basaron en experimentos no publicados por Szabo *et al,* (descrito a continuación).; (2) conjuntos de genes publicados por Abbas *et al* en Genome Research 2005; y (3) conjuntos de genes publicados por Gattinoni *et al.* en la revista Nature Medicine 2011. Los conjuntos de genes definidos por Szabo, Abbs, y Gattinoni y considerados en este análisis descrito en el Ejemplo 1 de la Solicitud de Patente Provisional de Estados Unidos 62/061553.

El conjunto de genes del núcleo Szabo incluye los siguientes genes que son aumentados en las células Teff (16h v 0 h): AIM2, ALAS1, B4GALT5, BATF, C3orf26, C4orf43, CCL3, CCl4, CCT3, CCT7, CD40LG, CHAC2, CSF2, CTNNA1, EBNA1BP2, EDARADD, EEF1E1, EIF2B3, EIF2S1, FABP5, FAM40B, FKBP4, FOSL1, GFOD1, GLRX2, HSPD1, HSPE1, IFNG, IL15RA, IL21, IL2RA, IL3, KCNK5, KIAA0020, LARP4, LRP8, LTA, manf, MIR1182, MIR155, MIR155HG, MTCH2, MYOF, NDUFAF1, NLN, NME1, NME1-NMe2, OTUD7B, PAM, PDIA6, PEA15, los animales Pfkm, PGAM1, PGAM4, PPIL1, PRDX4, PRSS23, PSMD1, PSMD11, PSMD14, PTRH2, PUS7, rbbp8, RPF2, Rpp25, SFXN1, SLC27A2, SLC39A14, SLC43A3, SORD, SPR, SRXN1, STIP1, STT3A, TBX21, TMCC2, TMEM165, TNFRSF9, TXN, TXNDC5, UCK2, VDR, WDR12, YWHAG, y ZDHHC16. El conjunto de genes del núcleo Szabo también incluye los siguientes genes que están aumentadas en las células Treg (16h v 0 h): AIM2, ALAS1, BATF, C5orf32, CCL17, CD40LG, CHAC2, CSF1, CTSL1, EBNA1BP2, EDARADD, EMP1, EPAS1, FABP5, FAM40B, FKBP4, FOSL1, GCLM, GK, GPR56, HMOX1, HSPD1, HSPE1, IKBIP, IL10, IL13, IL15RA, IL-1RN, IL2RA, IL3, IL4, IL-5, IL9, KCNK5, LTA, manf, MIR1182, MIR155, MIR155HG, MYOF, NDUFAF1, NLN, NME1, NME1-NMe2, PANX2, PDIA6, PGAM4, PPIL1, PPPDE2, PRDX4, PRKAR1B, PSMD1, PSMD11, PUS7, rbbp8, SLC27A2, SLC39A14, SLC43A3, SRXN1, STIP1, STT3A, TBX21, TNFRSF11A, TNFRSF1B, TNFRSF8, TNFRSF9, TXN, UCK2, VDR, VTRNA1-3, WDR12, YWHAG, ZDHHC16, y ZNF282.

Cada conjunto de genes (por ejemplo, conjuntos de genes Szabo, conjuntos de genes Abbas, y conjuntos de genes Gattinoni) se evaluó para determinar su asociación con la respuesta del sujeto (es decir, reincidente o no reincidente) de la siguiente manera: un meta-gen se calculó para cada sujeto, en donde el puntaje del meta-gen para el sujeto *j* como

$$m_j = \sum_{i=G}^{1} {x_{ij} - \mu(x_{.j})}\Big/{\sigma(x_{.j})}$$

donde x_{ij} es el valor de la expresión del gen *i* en el sujeto *j* para un grupo de genes

determinado $n=1,..,G$; $\mu(x_{.j})$ es la media de los genes $1,...,G$ en el sujeto j; y $\sigma(x_{.j})$ es la desviación estándar de los genes $1,...,G$ en el sujeto j.

Un modelo estadístico de 2 grupos se aplicó a cada conjunto de genes para determinar si el meta-gen fue estadísticamente diferente entre el producto CTL019 fabricado de reincidentes y no reincidentes. Un esquema que ilustra este enfoque se da en la FIG. 16. De los conjuntos de genes Szabo, Abbas, y Gattinoni, hubo un conjunto de genes que se enriquecen significativamente de manera diferente entre reincidentes y no reincidentes. Este conjunto de genes era de la colección Szabo y contiene genes aumentados en células T_{REG} frente a células T_{FEP} en reposo, y se correlacionó con la recaída del paciente a la terapia CTL019. En concreto, se encontró que este conjunto de genes es enriquecido en reincidentes, lo que indica que los reincidentes tienen niveles más altos de T_{REGS} en comparación con los no reincidentes. Por ejemplo, se encuentra que la puntuación de meta-gen para el conjunto de genes compuesto de genes estimulados en T_{REG} en comparación con las células T_{EFF} que se correlaciona con la recaída del paciente en muestras de productos (Véase la FIG. 17). La FIG. 17 representa resultados de ejemplo ($p = 0,000215$) que ilustran que los genes T_{REG} tienen altos niveles de expresión en pacientes con recaída (R) en comparación con respondedores completos no reincidentes (CR). El eje x es muestras por grupo de respuesta, donde CR = respondedor completo y R = reincidente. El eje y es puntajes normalizados de expresión de meta-genes.

Sin desear estar vinculado por una teoría particular, estos datos indican que la disminución de la marca T_{REG} en el paciente antes de la aféresis o durante la fabricación del producto CART reduce significativamente el riesgo de recaída del paciente.

Ejemplo 13: Las mutaciones de inserción son un mecanismo de resistencia a la terapia CTL019 en leucemia linfoide aguda de células B (B-ALL)

Varios mecanismos de resistencia han sido descubiertos mediante la comparación de los datos de secuenciación de ARNm a partir de muestras de los pacientes B-ALL tomadas al inicio del estudio y después de la recaída. Ciertos mecanismos de resistencia se conocen como "recaída de CD19", es decir, las células tumorales de los pacientes se caracterizan como CD19-, ya que no se unen al epítopo FMC63 utilizado en CTL019 como se mide por citometría de flujo. Varios mecanismos de resistencia se han descubierto y se describen en detalle en este Ejemplo.

La secuenciación del ARNm (ARNseq) se realizó para comparar los perfiles de transcripción de pacientes con B-ALL antes del tratamiento con CTL019 y después de la recaída. Tres pacientes fueron considerados: un paciente (Paciente #29), que era CD19- en el momento de la recaída, y dos pacientes (Pacientes #104 y #105), que eran CD19+ en el momento de la recaída. Véase la **Tabla 30** a continuación para una lista de pacientes, su clasificación, y el porcentaje de la leucemia en ambos puntos de tiempo.

Tabla 30.

Muestra	Tipo de recaída	% de Leucemia en MO, inicio del estudio	% de Leucemia en MO, recaída
Paciente #29	CD19-	N/A	N/A
Paciente #104	CD19+	33%	98.5%
Paciente #105	CD19+	46% pre-CART	65%

El análisis de los datos de ARNseq para el gen CD19 reveló varias observaciones dignas de mención.

Se encontraron tres inserciones en el exón 2 de CD19. Las inserciones sólo se encontraron en la muestra de recaída para el paciente # 29. No se observó ninguna lectura que apoya cualquiera de las tres inserciones, o cualquier otra inserción en el exón 2 de CD19 en los otros dos pacientes y al inicio del estudio para el paciente # 29. Las locaciones genómicas y las inserciones reales se tabulan en la **Tabla 31** a continuación.

Tabla 31.

Insertion	Location	Wild Type	Inserted Sequence
1	28943706	C	C --> CA
2	28943707	A	A --> AT
3	28943811	T	T --> TTTGG

Las longitudes de las tres inserciones son de 1, 1, y 4 bases de longitud, respectivamente, y probablemente todas son inserciones de desplazamiento de marco. Todas las tres inserciones resultan en codones de parada prematuros en el exón 2 (para las inserciones 1 y 2 se prooduce un nuevo codón de parada en ch16:28943752 y para la inserción 3 en ch16:28943887). La **Tabla**

32 a continuación muestra el número de lecturas que apoyan la inserción y el tipo silvestre, así como los porcentajes asociados. La inserción más frecuente es "inserción 3", que es una inserción de 4 bases y ocurre ~30%. Mas aún, de las 15 lecturas apareadas que mostraban más de una inserción, ninguna de las lecturas apareadas contenía más de una inserción, lo que sugiere que las inserciones son mutuamente excluyentes.

Tabla 32.

Muestra	Ins1 (Ins, en peso)	Ins1 (Ins, en peso)	Ins3 (Ins, en peso)
29B	0 62	0 62	0 50
29R	21 308	4 327	67 151
104B	0 69	0 69	0 79
104R	0 392	0 398	0 413
105B	0 42	0 42	0 63
105R	0 184	0 185	0 212

En la Tabla, "Muestra" indica el número del paciente, seguido de "B" para la muestra de referencia o "R" para una muestra tomada tras la recaída. La columna denominada Ins1 indica el número de lecturas que muestran ins1 (número de la izquierda) en comparación con la secuencia de tipo salvaje en esa posición (número de la derecha); la columna etiquetada Ins2 indica el número de lecturas que muestra Ins2 (número de la izquierda) en comparación con la secuencia de tipo salvaje en esa posición (número de la derecha); y la columna etiquetada Ins3 indica el número de lecturas que muestran Ins3 (número de la izquierda) en comparación con la secuencia de tipo salvaje en esa posición (número de la derecha). La tabla indica que sólo el paciente 29 mostró estas tres inserciones, y las inserciones solamente se observaron tras la recaída. Estos resultados sugieren que las inserciones en el exón 2 de CD19 conducen a resistencia en algunos pacientes.

Este trabajo identificó los mecanismos de resistencia a la terapia CTL019 en B-ALL, es decir, inserciones en el exón 2 de CD19 por el que las células tumorales se vuelven CD19- y resistentes a la terapia CTL019. Esta observación proporciona apoyo a una estrategia de combinación de CTL019 con CARs contra dianas distintas a CD19, por ejemplo, CD20, CD22, y ROR1.

Ejemplo 14: Expresión de antígenos de células B en pacientes reincidentes de cáncer de ALL

La expresión de varios antígenos de células B se determinó en pacientes con cáncer de leucemia linfoblástica aguda (ALL) reincidentes que habían sido previamente tratados con una terapia contra el cáncer distinta a una terapia CAR, es decir, que no habían sido tratados con cualquier terapia CAR.

Métodos

Las muestras fueron obtenidas no-identificadas como muestras de ALL humana primaria en médula ósea (BM) y sangre periférica (PB). Los anticuerpos anti-humanos se adquirieron en Abcam, Biolegend, Invitrogen, eBioscience, o Becton Dickinson. Las células mononúcleares se aislaron mediante separación de Ficoll, se lavaron una vez en PBS suplementado con suero bovino fetal al 2%, y se tiñeron durante 15 minutos a temperatura ambiente. Para la cuantificación del número de células, se utilizaron esferas Countbright (Invitrogen) de acuerdo con las instrucciones del fabricante. En todos los análisis, la población de interés fue aislada en base a las características secundarias de la dispersión seguida por la diferenciación por singulete, donde las células vivas fueron diferenciadas usando Live Dead Aqua (Invitrogen). El tiempo de exclusión se incluyó para el control de calidad. Para estudios animales se añadió el anticuerpo anti-CD45 murino (Biolegend) para excluir los leucocitos murinos. La expresión en superficie de CD22 se detectó por tinción con anticuerpo monoclonal anti-CD22 del clón HIB22 (Biolegend). La expresión en superficie de CD123 se detectó por tinción con anticuerpo monoclonal anti-CD123 a partir del clon 6H6 (eBioscience). La expresión en superficie de FLT3 se detectó por tinción con anticuerpo monoclonal anti-FLT3 a partir del clon IM2234U (Beckman Coulter). La expresión en superficie de ROR1 se detectó por tinción con anticuerpo monoclonal anti-ROR1 a partir del clon 2H6 (Abcam). La expresión en superficie de CD79b se detectó por tinción con anticuerpo monoclonal anti-CD79b a partir del clon CB3-1 (Biolegend). La expresión en superficie de CD79a se detectó por tinción con anticuerpo monoclonal anti-CD79a a partir del clon HM47 (R&D Systems). La expresión en superficie de CD10 se detectó por tinción con anticuerpo monoclonal anti-CD10 a partir del clon eBioCV – CALLA (eBioscience). La expresión en superficie de CD34 se detectó por tinción con anticuerpo monoclonal anti-CD34 a partir del clon 561 (Biolegend). La expresión en superficie de CD20 se

detectó por tinción con anticuerpo monoclonal anti-CD20 a partir del clon L27 (BD Biosciences). La cuantificación de la expresión del antígeno celular en unidades Capacidad de Unión de Anticuerpo (ABC) se realizó utilizando QuantumTM Simply Cellular® (Bangs Lab., Inc) de acuerdo con el procedimiento estándar (http://static.abdserotec.com/uploads/ifu/fcsc815b.pdf). La citometría de flujo se realizó en un citómetro Fortessa-LSR de cuatro láseres (Becton-Dickinson) y se analizó con FlowJo X 10.0.7r2 (Tree Star).

Resultados

En pacientes con ALL reincidentes, se expresaron varios antígenos de células B, incluyendo CD19, CD22, CD123, FLT-3, CD10, y CD34. Véase la Figura 22.

Con el fin de identificar las dianas de leucemia linfoblástica aguda de células B (B-ALL) potenciales adicionales, las muestras de 16 pacientes r/r fueron seleccionadas por citometría de flujo multiparamétrico para los siguientes marcadores: CD19 (16 pts), CD22 (16 pts), CD123 (16 pts), FLT-3 (9 pts), ROR-1 (3 pts), CD79b (15 pts), CD179b (8 pts), CD79a (16 pts), CD10 (16 pts), CD34 (16 pts) y CD20 (16 pts). CD22 y CD123 fueron altamente (>60%) y homogeneamente expresadas en los blastocitos de pacientes de ALL de r/r (la barra indica el porcentaje de expresión media, respectivamente, 99.50%, 98.80%, 95.70%, 72.00%, 47.00%, 15.00%, 13.45% , 4.200%, 98.00%, 87.65% y 7.00%). (Figura 22).

Ejemplo 15: Expresión de antígenos de células B en pacientes con cáncer CD19-negativo reincidente

La expresión de varios antígenos de células B se determinó en los pacientes que habían sido tratados previamente con un CAR CD19 y que han recaído con tumores CD19-negativos. La citometría de flujo se utilizó según los métodos del Ejemplo 14 para determinar la expresión de los antígenos, con una estrategia de exclusión representada en la FIG. 23.

La expresión de CD22 y CD123 se analizó en muestras de BM y PB de 6 pacientes con recaída de leucemia CD19-negativa, tanto antes del tratamiento CART19 (inicio del estudio) como después (recaída CD19-negativa). En todos los análisis, la población de interés fue aislada en base a las características secundarias de la dispersión seguida por la diferenciación por singulete, donde las células vivas fueron diferenciadas usando Live Dead Aqua (Invitrogen). El

tiempo de exclusión se incluyó para el control de calidad. La estrategia de exclusión incluía: tiempo de aislamiento de singuletes bajos de SSC en CD45dim CD10+ vivos.

Resultados

Casi todos los pacientes que se volvieron CD19-negativos permanecieron tanto CD22-positivos como CD-123-positivos. Véase la figura. 24 y la fig. 25. Los resultados se resumen en la figura 26, y demuestran que mientras el tratamiento CD19 CART resulta en una pérdida de la expresión de CD19 (según se mide por citometria de flujo), la expresión de CD22 y CD123 permanece alta.

Ejemplo 16: Tratamiento de acceso expandido con células CART autólogas redirigidas a CD22 en neoplasias malignas de células B refractarias

La leucemia linfoblástica aguda (ALL) recidivante/refractaria (r/r) de células B se asocia con un mal pronóstico en pacientes tanto pediátricos como adultos. Terapias novedosas que se dirigen a CD19 en blastocitos leucémicos, tales como células T de Receptores Quiméricos de Antígeno anti-CD19 (CART19, CTL019) o anticuerpos bi-específicos anti-CD19/CD3 (blinatumomab) inducen respuestas significativas en esta población. Sin embargo, las recaídas CD19-negativas han sido reportadas en 5-10% de los pacientes después de terapias con CART19 o blinatumomab.

Métodos

Líneas celulares y muestras primarias.

Las células de la línea celular ALL, NALM-6, se mantuvieron en cultivo con medio RPMI suplementado con suero bovino fetal al 10%, penicilina, y estreptomicina. Para algunos experimentos, las células NALM-6 fueron transducidas con luciferasa/GFP+ y luego ordenadas para obtener una población >99% positiva. Las líneas celulares de leucemia mieloide aguda MOLM-14 o K562 y la línea celular de T-ALL JURKAT se utilizaron como controles CD22-negativos.

Se obtuvieron los especímenes no identificados como ALL humana primaria en médula ósea (BM) y sangre periférica (PB) y las muestras de BM y PB de dos pacientes reincidentes después de la terapia de CART-19. Los blastocitos de ALL de pacientes tratados con CART-19

y que recayeron con leucemia CD19-negativa se recogieron al inicio del estudio (IR82, antes de la terapia de CART19) y recaída (IR243). Los blastocitos primarios de estos 2 puntos de tiempo se expandieron in vivo en ratones NSG y se transdujeron con luciferasa/GFP después de varios pasajes (Barrett, D (2011) Blood 118(15):e112-117). Para todos los estudios funcionales, las células de ALL se descongelaron al menos 12 horas antes del análisis y se dejaron reposar a 37° C.

Generación de constructos CAR y células CAR T.

Un receptor quimérico de antígeno (CAR) contra CD22 se generó utilizando las secuencias de cadena ligera (L) y pesada (H) de fragmento variable de cadena sencilla anti-CD22 descrita en la Solicitud de Patente de Estados Unidos No. 2011/0020344 A1, que describe la generación de un anticuerpo monoclonal completamente humano anti-CD22 M971 m971 (Xiao, X. (2009) MAbs. 1(3):297-303). Las secuencias fueron codon- optimizadas y dos constructos CAR diferentes se generaron utilizando dos orientaciones de cadena variable diferentes (H a L y L a H). Estos dos scFvs anti-CD22 luego se clonaron en una estructura CAR19 murina (CD8 bisagra CD8, dominio coestimulador 41BB y dominio de señalización CD3 zeta) y posteriormente en el vector lentiviral pTRPE. CAR19 murino se generó como se describió previamente (Milone, M. (2009) Terapia molecular: el diario de la Sociedad Americana de Terapia Genética 17 (8): 1453-64).

La producción de células T CAR-positivas se realizó como se describión previamente (Gill, S (2014) Blood 123 (15): 2343-2354). Las células T donantes normales CD4-positivas y CD8 positivas se sembraron a la concentración de $1x10^6$/ml, con una relación CD4: CD8 de 1: 1 y se expandieron en medio X-vivo 15 (Lonza, 04-418Q), suero humano AB 5% (Gemini, 100-512), penicilina/estreptomicina (Gibco, 15070063) y Glutamax (Gibco, 35050061) usando anti-CD3/CD28 Dynabeads (Life Technologies, 11161D) añadida el día 1 del cultivo y se retiraron el día 6. Las células T fueron transducidas con lentivirus que lleva ya sea CAR22, CAR19 o transfectadas falsamente el día 2. Las células T se expandieron en cultivo durante 10-15 días y se recolectaron cuando el volumen celular medio fue inferior a 300 fl. Las células T fueron luego criopreservadas en FBS con DMSO al 10% para futuros experimentos. Antes de todos los experimentos, las células T se descongelaron y se dejaron reposar durante la noche a 37° C.

Análisis de Citometría de flujo multiparamétrica.

Los anticuerpos anti-humanos se adquirieron en Biolegend, eBioscience, o Becton Dickinson. Las células se aislaron del cultivo in vitro o de animales, se lavaron una vez en PBS suplementado con suero fetal de ternera al 2%, y se tiñeron durante 15 minutos a temperatura ambiente. Para la cuantificación del número de células, se utilizaron esferas Countbright de acuerdo con las instrucciones del fabricante (Invitrogen). En todos los análisis, la población de interés fue aislada en base a las características secundarias de la dispersión seguida por la diferenciación por singulete, donde las células vivas fueron diferenciadas usando Live Dead Aqua (Invitrogen). El tiempo de exclusión se incluyó para el control de calidad. Para estudios animales se añadió el anticuerpo anti-CD45 murino (Biolegend) para excluir los leucocitos murinos. La expresión en superficie de CAR anti-CD22 se detectó por tinción con la proteína CD22-His (11958-H08H-50) y anticuerpo monoclonal anti-His-APC (IC050A). CAR19 se detectó como se describió previamente (Kalos, M. (2011) Science Translational Medicine 3(95):95ra73). La cuantificación de CD19 y la expresión del antígeno celular CD22 en las unidades de Capacidad de Unión a Anticuerpo (ABC) se realizó en NALM-6 y controles usando QuantumTM Simply Cellular® (Bangs Lab., Inc) de acuerdo con el procedimiento estándar (http://static.abdserotec.com /uploads/ifu/fcsc815b.pdf). La citometría de flujo se realizó en un citómetro Fortessa-LSR de cuatro láseres (Becton-Dickinson) y se analizó con FlowJo X 10.0.7r2 (Tree Star).

Ensayo de desgranulación

Los ensayos de desgranulación se realizaron como se describió anteriormente. Las células T se incubaron con células diana en una proporción 1: 5 en medio de células T. Anticuerpos anti-CD107a-PECY7 (Biolengend), anti-CD28 (BD Biosciences), anti-CD49d (BD Biosciences) y monensina (BD Biosciences) se agregaron al co-cultivo 30 minutos después de la hora de partida. Después de 4 horas, las células se cosecharon y se tiñeron para la expresión de CAR, CD3, CD8 y la tinción Live Dead Aqcua (Invitrogen). Las células se fijaron y se permeabilizaron (buffers Fix/Perm de Invitrogen) y luego la tinción intracelular se realizó para detectar múltiples citocinas (IFN, TNFa, IL-2, GM-CSF, MIP1b).

Ensayo de proliferación

Las células T se lavaron y se resuspendieron a $1x10^7$/ml en 100 ul de PBS y se tiñeron con 100 µl de CFSE 2,5 µM (Invitrogen) durante 5 minutos a 37° C. Luego la reacción se inactivó con medio frío, y las células se lavaron tres veces . Las dianas se irradiaron a una dosis

de 100 Gy. Las células T se incubaron a una relación 1:1 con las células diana irradiadas durante 120 horas, agregando medios a las 24 horas. Luego las células se recolectaron, se tiñeron para CD3, CAR y Live Dead aqua, y se agregaron esferas Countbright (Invitrogen) antes del análisis citométrico de flujo para cuantificación absoluta.

Ensayos de citotoxicidad:

Se utilizaron células NALM-6 de luciferasa/GFP+ o muestras de ALL primarias para ensayo de citotoxicidad como se describió anteriormente. 4 dianas fueron incubadas a las proporciones indicadas con las células T efectoras durante 4 ó 16 horas. La eliminación se calculó ya sea por un registro en imágen de bioluminiscencia en una cámara Xenogen IVIS-200 Spectrum o por citometría de flujo. En este último caso, las células se cosecharon, y se añadieron perlas Countbright y 7-AAD (Invitrogen) antes del análisis. Las células diana vivas residuales fueron CFSE-positivas 7-AAD-negativas.

Mediciones de Citocinas:

Las células efectoras y diana se co-incubaron a una relación 1: 1 en los medios de células T durante 24 horas. El sobrenadante se recogió y se analizó mediante el arreglo 30-plex Luminex (Luminex Corp, FLEXMAP 3D) de acuerdo con el protocolo del fabricante (Invitrogen) (Kalos, M. (2011)).

Experimentos in vivo

Se obtuvieron ratones NOD-SCID-γ cadena-/- (NSG). Todos los experimentos se realizaron en protocolos aprobados por el Comité de Cuidado y Uso Institucional de Animales (IACUC) de la Universidad de Pennsylvania. Los esquemas de los modelos de xenoinjerto utilizados se discuten en detalle en la sección de resultados. Las células (células NALM-6 o T) se inyectaron en 200 ul de PBS a la concentración indicada en las venas de la cola de los ratones. El registro de imágenes bioluminiscentes se realizó usando una cámara Xenogen IVIS-200 Spectrum y se analizó con el software LivingImage v. 4.3.1 (Caliper LifeSciencies). Los animales fueron sacrificados al final del experimento o cuando fue necesario de acuerdo con las políticas del IACUC.

Inmunohistoquímica

Se realizaron microarreglos tisulares (TMA) de 28 tejidos normales humanos (adiposo, adrenal, apéndice, cerebelo, cuello del útero, colon, endometrio, esófago, grasa, corazón, riñón,

hígado, ganglios linfáticos, pulmón, músculo, ovario, páncreas, paratiroides, placenta, próstata, salival, médula, bazo, estómago, testículo, timo, tiroides, amígdalas) con el fin de evaluar la expresión no tumoral de CD22 (triplicados). La tinción inmuno-histoquímica (IHC) de tejidos embebidos en parafina fijados en formalina se llevó a cabo sobre el instrumento Leica Bond-III usando el sistema de detección se unión de polímero Refine. Los anticuerpos contra CD22 (clon FPC1; Leica PA0249) fueron utilizados sin diluir. La recuperación de epítopos inducida por calor se llevó a cabo durante 20 minutos con solución ER2 (Leica Microsystems AR9640). Las imágenes fueron adquiridas por medios digitales utilizando el Aperio ScanScopeTM.

Perfiles de expresión génica.

La base de datos públicamente accesible de expresión de ARN (GeneAtlas U133A, gc) se analizó utilizando la página web BioGPS.org para la expresión de CD22. La expresión media del ARN de CD22 se reportó para 75 tipos diferentes de células humanas normales y 7 líneas de células tumorales (ver Figura 39).

Ensayo de liberación de cromo-51

Con el fin de evaluar la posible toxicidad extra tumoral de CART22, se realizó un ensayo de liberación de cromo, utilizando como tejidos humanos normales objetivo (CD34 +, neuronas humanas, progenitores neuronales humanos, queratinocitos) y K562 o NALM-6 como controles. Las células diana se incubaron con células 51Cr 50 μCi/0.5e6 durante 1-2 horas a 37° C. Las células se lavaron y se sembraron por triplicado con células efectoras a diferentes relaciones E:T. Después de 4 horas de incubación, una alícuota de cada pozo se colocó en una placa de lector y se secó durante la noche. El día siguiente la liberación de cromo se cuantificó usando el Contador de Centelleo Líquido 1450 Microbeta Plus.

Resultados

Tabla 33: Resumen de los donantes y los respectivos experimentos realizados para Evaluación de CART22.

Donantes	Expansión	Degranulación Citoquinas +i.c.	Proliferación. + Luminex	Eliminación	In vivo	Tox Screen
1	✓	✓ X2	✓ X2	✓ X2	✓	
2	✓	✓				

3	✓		✓	✓
4	✓			
5	✓		✓	

Con el fin de identificar posibles dianas B-ALL, las muestras de 16 pacientes r/r y 4 pacientes que recaen con enfermedad CD19-negativa después del tratamiento con la terapia CART19 fueron seleccionadas mediante citometria de flujo multiparamétrico para el marcador de células B, CD22. CD22 fue altamente (> 60%) y homogeneamente expresado en los blastocitos de pacientes con ALL 11/15 r/r (Figura 27A). CD22 también fue positive en 4/4 pacientes reincidentes con leukemia CD19 negativa, ambos antes del tratamiento con CART19 (basal) y después (recaída negativa CD19) (2 ptos mostrados). (Estrategia de aislamiento: SSC bajo→singuletes→vivo→CD45dim).

El esquema de los constructos CAR22 que se generaron usando diferentes orientaciones de cadena (H a L y L a H) se muestra en la Figura 28A. El scFv(m971) anti CD22 fue optimizado en sus codones y clonado en el vector murino CAR19 que contiene una bisagra CD8 y dominios 41-BB coestimulante y CD3 de señalización de zeta. La expresión de CD19, CD22 y el control de isotipo en la línea celular ALL NALM6 se muestra como la intensidad media de fluorescencia (MFI) (Fig. 28B) y la capacidad de unión del anticuerpo (ABC) (Fig 28C). Los resultados presentados en este documento demuestran que en células NALM-6, la expresión de CD19 es mayor que CD22. Sin embargo, en la mayoría de muestras de ALL primaria, las expresiones de CD19 y CD22 son similares (véase la fig. 28A).

Se realizaron expansiones de células T donantes normales para generar CART22 y CART19 (junto con células no transducidas (UTD)). Se midieron los tiempos de duplicación de la población y el volumen de las células con respecto a los días de cultivo. Al final de la expansión (día 11 en el cultivo) las células T CART22 y de control alcanzaron alrededor de 4.5 duplicaciones de la población (PD), sin diferencias significativas en comparación con las células CART19 o UTD (Figura 29A). El día 6 en el cultivo el volumen máximo fue de alrededor de 450 fl, mientras que en los siguientes días el volumen se redujo a 300 fl cuando las células se cosecharon y se congelan (Figura 29B). No se observó una diferencia significativa en comparación con CART19 o UTD. Se observó la expresión de CAR sobre las células T CD4-positivas y CD8-positivas en el día 11 de expansión mediante citometría de flujo (Figura 29C).

La compuerta para la expresión de CAR se basa en UTD. (Estrategia de aislamiento: Linfocitos FSS vs SSC→singuletes→vivo→CD3+).

Se realizó un ensayo de desgranulación CD107a con la producción de citoquinas intra-citoplasmáticas. CART19, CART22 HtoL y LtoH fueron co-cultivadas con diferentes objetivos (solos, PMA/ionomicina, MOLM-14 y NALM-6). CART19 y CART22 HtoL mostraron altos niveles de desgranulación de CD107a, producción de IL-2, IFNg y TNFa cuando se co-cultivaron con la línea celular ALL (NALM-6), pero no cuando se co-cultivaron con los controles negativos (Figura 30). UTD y CART22 LtoH no muestran desgranulación ni producciones de citoquinas (Figura 30). (Estrategia de aislamiento: Linfocitos FSS vs SSC→singuletes→vivo→CD3+).

En un ensayo de eliminación basado en luciferasa, CART22 y CART19 HtoL, pero no UTD fueron capaces de lisar células NALM-6 cuando se co-cultivaron durante 24 horas (Figura 31). Se observó una correlación directa entre la actividad citotóxica y las proporciones E:T, con un mejor efecto anti-leucemia a una proporción 2:1 (eliminación del 78% y 75% para CART19 y CART22).

En un ensayo de proliferación basado en CFSE, el co-cultivo durante 5 días de CART22 y CART19 con la línea celular de ALL NALM-6 dio lugar a la proliferación significativa de células T (94% y 92,9% respectivamente). También se muestran los controles (TCM = medio solo, PI = PMA/ ionomicina, MOLM-14) (Figura 32A). Los histogramas que muestran la dinámica de la dilución de CFSE en CART19 y CART22 demuestran que la mayoría de las células T experimentan múltiples ciclos de proliferación (Figura 32B). (Estrategia de exclusión: Linfocitos FSS vs SSC→singuletes→vivo→CD3+).

Las células CART22, CART19 y UTD se incubaron durante 24 horas con diferentes blancos irradiados (solos, PMA/ionomicina, MOLM-14 y NALM-6). Cuando se co-cultivaron con la línea celular de ALL NALM-6, solamente CART22 y CART19 HtoL fueron capaces de liberar múltiples citocinas (aquí se muestra IFNg, IL-2, GM-CSF, TNFa y MIP1b) (Figura 33).

Las células CART22, CART19 y UTD se co-incubaron durante 4 horas con blastocitos derivados a partir de un paciente con ALL (CHP-959-101) al inicio del estudio y después del tratamiento con CART19 cuando el paciente recae con una enfermedad CD19-negativa. Se midió la desgranulación. Tanto el CART19 y el CART22 fueron capaces de desgranular en el

estado basal (cuando los blastocitos son CD19+ y CD22+) pero en la recaída solo el CART22 desgranuló (cuando la enfermedad es CD-19 negativa) (Figura 34A). La desgranulación de CD107a se midió en CART19 CD8-positiva y CD8 negativa y el efector CART22 después de la incubación con la muestra de CHP101 en la recaída. Sólo CART22 mostró desgranulación en células T tanto CD8 como CD4 (Figura 34b). (Estrategia de aislamiento : Linfocitos FSS vs SSC→singuletes→vivo→CD3+).

La eficacia in vivo de CART22 contra NALM-6 se evaluó de la siguiente manera: 1 millón de células de NALM-6 luciferasa+/ratón se inyectaron iv. en ratones NSG. Después de 6 días el injerto tumoral fue evaluado por bioluminiscencia. Luego los ratones fueron aleatorizados para recibir las células T no transducidas o diferentes dosis de CART22 (de 1.25 a 5 millones de células totales/ratón, con un 75% de expresión de CAR). Luego los ratones se monitorearon para la carga tumoral, expansión de células T PB, y supervivencia (Figura 35A). La carga tumoral por bioluminiscencia (BLI) se midió y se observó respuesta anti leucemia relacionada con la dosis. Los ratones que recibieron células 5E6 CART22 mostraron un mejor control del tumor (Figura 35B). Los ratones tratados con CART22 mostraron una mejor supervivencia global (SG) estadísticamente significativa en comparación con los ratones tratados con UTD. También para superviviencia global hubo una correlación significativa entre la dosis más alta de CART22 y mejor SG (Figura 35C). La expansión in vivo de células-T se monitoreó semanalmente por sangrados retro-orbital. Una semana después de la infusión de células T, los ratones que recibieron la dosis más alta de CART22 mostraron la mejor expansión de CART (media de 12 células T/µl) (Figura 35D).

La comparación in vivo entre CART22 y CART19 contra NALM-6 se evaluó de la siguiente manera: 1 millón de células de NALM-6 luciferasa+/ratón se inyectaron iv. en ratones NSG. Después de 6 días el injerto tumoral fue evaluado por bioluminiscencia. Luego los ratones fueron aleatorizados para recibir células T no transducidas, CART19 o CART22 (5 millones de células totales, con expresión de CAR del 75%). Luego, los ratones fueron monitoreados para carga tumoral, expansión de células T PB, y supervivencia (Figura 36A). La carga tumoral por bioluminiscencia (BLI) se midió y se observó respuesta anti leucemia en ratones tratados tanto con CART22 como CART19, mientras que los ratones tratados con UTD progresaron rápidamente (Figura 36B). Los ratones tratados con CART19 mostraron una mejor

supervivencia global (SG) en comparación con CART22, posiblemente debido a la diferente expresión objetivo en NALM-6 (CD19 >> CD22) (Figura 36C).

CART22 y CART19 se compararon in vivo en un modelo de ALL primaria. Los blastocitos de un paciente con ALL primaria (JH331) fueron subcultivados in vivo y transducidos con luciferasa para seguir la carga tumoral. 1 millón de células JH331 luciferasa+/ratón se inyectaron iv. en ratones NSG. Después de 14 días el injerto tumoral fue evaluado por bioluminiscencia. Luego los ratones fueron aleatorizados para recibir células T no transducidas, CART19 o CART22 (5 millones de células totales, con expresión de CAR del 75%). Luego, los ratones fueron monitoreados para carga tumoral, expansión de células T PB, y supervivencia (Figura 37A). La carga tumoral por bioluminiscencia (BLI) se midió y se observó una respuesta anti leucemia en los dos ratones tratados con CART22 y CART19, mientras los ratones tratados con células UTD rápidamente progresaron (Figura 37B).

Se realizaron microarreglos tisulares para la expresión de CD22 en 28 tejidos normales humanos por tinción de inmunohistoquímica. Los órganos linfoides resultaron positivos para la expresión de CD22 (amígdalas, ganglios linfáticos, bazo y timo) (Figura 38A). Todos los órganos no linfoides no mostraron expresión de CD22 (Figura 38B). Se observaron células B residentes CD22-positivas en múltiples tejidos (Figura 38C).

La expresión de ARN de CD22 se observó a alto nivel en células B, amígdalas, ganglios linfáticos, como se muestra en los datos de expresión de GeneAtlas U133A. Las líneas de B-linfoblastos y leucemia/linfoma también fueron altamente positivas (Figura 39).

Tanto las células CART22 y CART19 pero no UTD activaron la lisis de la línea celular ALL NALM-6 en un ensayo de liberación de cromo-51 para la toxicidad CART22 (Figura 40). No se observó ningún efecto citotóxico de CART22 en ningún tejido normal (CD34 +, progenitores neuronales humanos o neuronas y queratinocitos) o control (línea celular K562).

Ejemplo 17: Combinación de células CAR T anti-CD123 y anti-CD19 para el tratamiento y prevención de recaída por pérdida de antígeno

Leukemia linfoblástica aguda de células B (B-ALL) quimio refractaria o reincidente (r/r) se asocia con un mal pronóstico, pero, como se ha demostrado recientemente, sigue siendo exquisitamente sensible al sistema inmunológico. En particular, las células T de receptores

quiméricos de antígeno anti-CD19 (CART19, CTL019) y anticuerpos biespecíficos anti-CD19/CD3 (blinatumomab) generan tasas de respuesta completas sin precedentes de 45 a 90% en esta población de pacientes. Ambos enfoques re-dirigen células T autólogas para reconocer las células que expresan CD19. Blinatumomab utiliza una infusión continua a largo plazo de un constructo biespecífico que combina un fragmento variable de cadena sencilla anti-CD19 (scFv) con un scFv anti-CD3; en el caso de células T CART19 se modifican genéticamente para expresar un scFv anti-CD19 fusionado con el receptor de células T de señalización con dominios co-estimulatorios incorporados. Un estudio reciente mostró que el 90% de los pacientes con r/r B-ALL tratados con CTL019 alcanzan remisión completa (CR) con una supervivencia general (SO) de 78% a los 6 meses. También se obtuvieron resultados alentadores con CART19 en pacientes con otras neoplasias de células B, tal como leucemia linfocítica crónica y linfoma no Hodgkin.

Sin embargo, un subgrupo de pacientes tratados con CART19 o blinatumomab desarrolla recaída y una porción significativa de estas recaídas se caracterizan por la pérdida de CD19. En B-ALL, las recaídas CD19-negativas han sido reportadas en 10-20% de los pacientes después de terapias con CART19 o blinatumomab y no se ha descrito en el contexto de otros tratamientos; en general alrededor de 30% de las recaídas después blinatumomab y hasta el 50% después de CART19 son CD19-negativas. CD19 es un prototipo de marcador de células B que se expresa a partir de las primeras etapas de desarrollo de células B a células B maduras. CD19 juega un papel importante en la biología de las células B puesto que las células B deficientes de CD19 exhiben la desventaja de crecimiento selectivo. Así, la ausencia de CD19 es un hallazgo muy inusual en B-ALL y se ha reportado raras veces en pacientes antes de la era de inmunoterapias potentes dirigidas a CD19. El posible mecanismo de la pérdida de antígeno es actualmente objeto de investigación y muy probablemente es causado por la presión selectiva sobre sub-clones de leucemia de estos potentes agentes anti-CD19. Debido a la reciente aprobación por la FDA de blinatumomab y el estado de emergencia otorgado a CTL019, es probable que un número creciente de pacientes con r/r B-ALL serán tratados con estos agentes. Por lo tanto, se necesitan estrategias eficaces novedosas con el fin de poder de tratar a los pacientes que reincidirán con erupciones negativas CD19 después de CART19 o blinatumomab. Lo ideal sería un nuevo enfoque que no trate sólo a los pacientes con recaída por pérdida antígeno activa pero si se emplea de adelantado podría potencialmente prevenir su ocurrencia.

El receptor de interleucina-3 alfa (o CD123) está implicado en la hematopoyesis y se ha demostrado que se expresa en varias neoplasias hematológicas, incluyendo leucemia mieloide aguda (AML), leucemia linfoide aguda (ALL), neoplasia de células dendríticas plasmacitoides, leucemia de células pilosas, y linfoma de Hodgkin. A diferencia de los antígenos de superficie asociados a linaje tales como CD33 (mieloide) o CD19 (B-linfoide), CD123 se expresa jerárquicamente en células progenitoras hematopoyéticas y en AML, CD123 se expresa en las células madre leucémicas que están implicadas en la resistencia a la quimioterapia y recaída después del tratamiento inicial . Debido a estas características, CD123 ha generado un gran interés para terapia dirigida, y varios agentes se están desarrollando, como la proteína de fusión de Toxina de difteria –IL3 (SL-401, DT388IL3), anticuerpos monoclonales desnudos anti-CD123 (CSL-360, CSL- 362), conjugados de fármaco con anticuerpo , anticuerpos bi específicos o constructos de fusión CD3Fv-IL3, y más recientemente, células T con receptor quimérico de antígeno anti-CD123. Algunos de estos enfoques están siendo validados en ensayos clínicos y muchos más se probarán en clínica en los próximos años. El marcaje de CD123 con células T con receptor de antígeno quimérico (CART123) puede conducir a respuestas profundas y de largo plazo en xenoinjertos de AML primarios humanos y puede establecer una memoria de células T anti-leucemia. Aquí, CD123 se expresa en recaidas de B-ALL CD-19-negativas que se producen después de terapias dirigida a CD19 y que las células T CAR-123 combinadas con CART19 (CTL019) es una terapia eficaz para el tratamiento y para la prevención de recaídas de pérdida de antígeno en B xenoinjertos de B-ALL.

MATERIALES Y MÉTODOS

Líneas celulares y muestras primarias. Las líneas celulares se obtuvieron originalmente de ATCC (Manassas, VA) (K-562) o DSMZ (Braunschweig, Alemania) (MOLM-14 y NALM-6). Todas las líneas celulares se probaron para la presencia de contaminación por micoplasma (Kit de Detección de Micoplasmas MycoAlert™ , LT07-318, Lonza, Basilea, Suiza). Para algunos experimentos, las líneas celulares fueron transducidas con luciferasa de luciérnaga/eGFP y luego ordenadas para obtener una población >99% positiva. La línea celular K-562 positiva de luciferasa también se transdujo con CD19 truncado o CD123 truncado para obtener líneas celulares que no expresan ninguno de éstos, sólo CD19 o sólo CD123. MOLM-14 y K562 se utilizaron como controles, como se indica en las figuras pertinentes. Las líneas celulares se mantuvieron en cultivo con medio RPMI 1640 (Gibco, 11875-085, Life Technologies, Grand

Island, NY) suplementado con suero bovino fetal al 10% (FBS, Gemini, 100-106, West Sacramento, CA), y 50 UI/ml de penicilina/estreptomicina (Gibco, Life Technologies, 15.070-063). Se obtuvieron especímenes de médula ósea (BM) de ALL humana primaria de-identificada y sangre periférica (PB) de las prácticas clínicas de la Universidad de Pennsylvania/Hospital de Niños de Filadelfia bajo el protocolo de la Junta de Revisión Institucional (IRB), comprados de las Células Madre y Núcleo de Xenoinjertos de la Universidad de Pennsylvania o de muestras de investigación de los ensayos clínicos actuales CTL019 (Traducción y Laboratorio de Estudio Correlativo, de la Universidad de Pennsylvania). Para todos los estudios funcionales, las células primarias se descongelaron al menos 12 horas antes del experimento y se dejaron en reposó a 37° C.

Expansión in vivo de erupciones primarias de B-ALL. Métodos descritos en D.M. Barrett, AE Seif, C. Carpenito, DT Teachey, JD Fish, CH June, S.A. Grupp, GS Reid, Imágenes bioluminiscentes no-invasivas de un paciente con leukemia linfoblástica aguda primaria: una estrategia para el modelado preclínico. *Blood*118, e112-117 (2011).

Fluorescencia en hibridación in situ (FISH) e Inmunohistoquímica. El análisis FISH y la inmunohistoquímica se realizaron de acuerdo con el método estándar y como se describe. (MA-Belaud Rotureau, M. Parrens, P. Dubus, JC Garroste, A. de Mascarel, JP Merlio, Un análisis comparativo de FISH, RT-PCR, PCR e inmunohistoquímica para el diagnóstico de linfomas de células del manto. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* 15, 517-525 (2002)). El análisis FISH se realizó de acuerdo con el método estándar. En resumen, las células ALL recolectadas se suspendieron en fijador (ácido acético y metanol), se depositaron en placas y se dejaron secar. La sonda de color dual de fusión de genes BCR/ABL (Abbott Molecular), se aplicó en la solución de buffer de hibridación. Las láminas fueron cubiertas, selladas y dejadas en la cámara HYBrite a 37ºC durante 6 horas. Después de la eliminación del sellador y el cubreobjetos, los portaobjetos se lavaron dos veces, transferidos, secados, y con una contratinción con DAPI. Los portaobjetos se examinaron bajo el microscopio fluorescente, con un mínimo de 200 núcleos evaluados en cada espécimen.

Generación de constructos CAR y células CAR T. El receptor murino de antígeno quimérico anti-CD19 (bisagra CD8, dominio coestimulatorio 4-1BB y dominio de señalización zeta CD3) se generó como se describió anteriormente. (Milone, et al., *Molecular therapy : the journal of*

the American Society of Gene Therapy 17, 1453-1464 (2009) y Imai, *Leukemia* 18, 676-684 (2004)). Este es el mismo constructo utilizado actualmente en los ensayos clínicos CTL019 de la Universidad de Pennsylvania. Para CAR123 scFv anti-CD123 (constructo 1172 (SEQ ID NO: 707, y como se describe en PCT/US2014/017328) se utilizó y la misma estructura del constructo de CAR19. La producción de células T que expresan CAR se realizó como se ha descrito previamente. (Gill, et al., *Blood* **123,** 2343-2354 (2014)). Células T CD4 y CD8 de donante normal o células mononucleares PB (PBMC) se obtuvieron del Núcleo de Inmunología Humana de la Universidad de Pennsylvania. Las células T se sembraron en placas a $1x10^6$/ml con una relación CD4: CD8 de 1:1 y se expandieron en 15 medios X-vivo (Lonza, 04-418Q), suplementado con suero AB humano al 5% (Gemini, 100-512), penicilina/estreptomicina (Gibco, 15070063) y Glutamax (Gibco, 35050061) usando Dynabeads anti-CD3/CD28 (Life Technologies, 11161D) añadidas el día 1 del cultivo y retiradas el día 6. Las células T fueron transducidas con lentivirus el día 2. Las células T se expandieron en cultivo durante 8-15 días y se recolectaron cuando el volumen celular medio fue inferior a 300 fl. Las células T fueron luego criopreservadas en FBS con DMSO al 10% para futuros experimentos. Antes de todos los experimentos, las células T se descongelaron y se dejaron reposar durante la noche a 37° C.

Citometría de flujo multiparamétrica. La citometría de flujo se realizó como se describió previamente (Kenderian, *Leukemia,* (2015)). Los anticuerpos anti-humanos se adquirieron en Biolegend, eBioscience, o Becton Dickinson. Las células se aislaron del cultivo in vitro o de animales, se lavaron una vez en PBS suplementado con suero fetal de ternera al 2%, y se tiñeron durante 15 minutos a temperatura ambiente. Para la cuantificación del número de células, se utilizaron esferas Countbright de acuerdo con las instrucciones del fabricante (Invitrogen). En todos los análisis, la población de interés fue aislada en base a las características secundarias de la dispersión seguida por la diferenciación por singulete, donde las células vivas fueron diferenciadas usando Live Dead Fixable Aqua (Invitrogen). El tiempo de exclusión se incluyó para el control de calidad. Se detectó expresión en superficie de CAR19 como se describió anteriormente, utilizando un anticuerpo anti-idiotipo. La detección de CAR123 se realizó usando un anticuerpo anti-ratón de cabra (Jackson Laboratories) o CD123-Fc/His (Sino Biologicals) y anti-His-APC (R&D) o PE (AbCam). La citometría de flujo se realizó en un citómetro Fortessa-LSR II de cuatro láser (Becton-Dickinson) y se analizó con FlowJo X 10.0.7r2 (Tree Star).

Ensayos de la función efectora de células T in vitro. Los ensayos de desgranulación, proliferación CFSE, citotoxicidad y mediciones de citoquinas se realizaron como se describió previamente. (Gill, *Blood* **123,** 2343-2354 (2014) y Kalos, Science translational medicine **3,** 95ra73 (2011)).

Ensayo de desgranulación. Brevemente, las células T se incubaron con células diana en una proporción 1: 5 en medio de células T. Anticuerpos Anti-CD107a-PECY7 (Biolegend), anti-CD28 (BD Biosciences), anti-CD49d (BD Biosciences) y monensina (BD Biosciences) se añadieron al co-cultivo. Después de 4 horas, se recogieron las células y se tiñeron para la expresión de CAR, CD3, CD8 y tinción Live Dead aqua (Invitrogen). Las células se fijaron y se permeabilizaron (buffers Fix/Perm de Invitrogen) y luego la tinción intracelular se realizó para detectar múltiples citocinas (IFN, TNFα, IL-2, GM-CSF, MIP1β).

Ensayo de proliferación. Las células T se lavaron y se resuspendieron a $1x10^7$/ml en 100 ul de PBS y se tiñeron con 100 ul de CFSE 2,5 uM (Invitrogen) durante 5 minutos a 37° C. Luego la reacción se inactivó con medio frío, y las células se lavaron tres veces . Las dianas se irradiaron a una dosis de 100 Gy. Las células T se incubaron a una proporción de 1:1 con células diana irradiadas durante 120 horas, agregando medio a 24 horas. Luego las células se recolectaron, se tiñeron para CD3, CAR y Live Dead aqua, y las esferas Countbright se agregaron (Invitrogen) antes del análisis citométrico de flujo para cuantificacion absoluta.

Ensayos de Citotoxicidad. Se utilizaron líneas celulares de luciferasa/eGFP+ para el ensayo de citotoxicidad como se describió anteriormente. En resumen, los blancos se incubaron a las proporciones indicadas con células T efectoras durante 24 horas. La muerte fue calculada por imágenes de bioluminiscencia en una cámara Xenogen IVIS-200 Spectrum.

Mediciones de citocinas: Las células efectoras y diana se co-incubaron a una relación 1: 1 en medio de células T durante 24 horas. El sobrenadante se recogió y se analizó mediante el arreglo 30-plex Luminex (Luminex Corp, FLEXMAP 3D) de acuerdo con el protocolo del fabricante (Invitrogen).

Experimentos con animales. Se realizaron experimentos in vivo como se describió previamente. (Kenderian, *Leukemia*, (2015)). Los esquemas de los modelos de xenoinjerto utilizados se discuten en detalle en las figuras pertinentes y la sección de resultados. Cadena

NOD-SCID-γ -/-(NSG) originalmente obtenida de Laboratorios Jackson fueron adquiridos del centro de células madre Xenoinjerto de la Universidad de Pennsylvania. Todos los experimentos se realizaron según un protocolo (# 803230), aprobado por el Comité Institucional de Cuidado y Uso de Animales (IACUC) que se adhiere a la Guía del NIH para el Cuidado y Uso de Animales de Laboratorio. Las células (líneas celulares de leucemia o células T) se inyectaron en 200 ul de PBS a la concentración indicada en las venas de la cola de los ratones. El registro de imágenes bioluminiscentes se realizó usando una cámara Xenogen IVIS-200 Spectrum y se analizó con software LivingImage v. 4.3.1 (Caliper LifeSciencies). A los animales se les practicó la eutanasia al final del experimento o cuando se encontraron en puntos finales pre-especificados de acuerdo con los protocolos del IACUC.

Microscopía multifotónica. Los ratones se anestesiaron y se mantuvieron a temperatura de núcleo de 37° C. La médula ósea fue fotografiada después de quitar el cuero cabelludo e inmovilizar el cráneo. El registro se realizó utilizando un sistema de microscopio Leica SP5 de 2-fotones (Leica Microsystems) equipado con un láser de picosegundos (coherente). Cada adquisición de imágenes duró 20 minutos, seguido de una evaluación de la sedación de ratón. CellTrace, Violeta, GFP, y CellTrace Naranja (o TRITC) se excitaron usando una luz láser de 850 nm. Las imágenes se obtuvieron usando un lente 20x de inmersión en agua. Las imágenes resultantes se analizaron con el software Volocity (PerkinElmer).

Análisis Estadístico. Todas las estadísticas se llevaron a cabo como se indicó utilizando GraphPad Prism 6 para Windows, versión 6.04 (La Jolla, CA). Se utilizó la prueba t de Student para comparar dos grupos; en el análisis donde se compararon múltiples grupos, se realizó un análisis unidireccional de la varianza (ANOVA) con la corrección Holm-Sida para múltiples comparaciones. Cuando se compararon múltiples grupos en múltiples puntos de tiempo/relaciones, se utilizó la prueba t de Student o ANOVA para cada punto de tiempo/relación. Las curvas de supervivencia se compararon mediante la prueba de rangos logarítmicos. En las figuras los asteriscos se utilizan para representar los valores p (* = <0.05, ** = <0.01, *** = <0.001, **** = <0.0001) y "ns" significa "no significativo" (p> 0,.05). Más detalles de las estadísticas para cada experimento se muestran en las leyendas de las figuras.

RESULTADOS

CD123 se expresa en B-ALL, en las células madre de la leucemia y en las recaídas CD19-negativas

Con el fin de evaluar la expresión de CD123 en leucemia linfoblástica aguda de células B, 42 muestras de pacientes adultos y pediátricos con ALL se analizaron, incluyendo 14 sujetos inscritos en nuestros ensayos clínicos CTL019 actuales. Como se muestra en la Figura 49A, 49B y 49A, CD123 se expresa altamente y homogéneamente sobre la superficie de la mayoría de erupciones de ALL, lo que representa un candidato ideal para la terapia dirigida. Por otra parte, CD123 también se encontró expresado en las células madre putativas de leucemia (LSC), identificadas como CD34+ CD38- (Figura 49C). Los pequeños subconjuntos de erupciones CD19 negativas se pueden identificar en algunos pacientes con B-ALL y estas células podrían contribuir a recaídas por pérdida de antígeno, si contenían células con un fenotipo maligno. Con el fin de evaluar la presencia de enfermedad en subconjuntos CD19 -negativos, las células CD19 CD123+ de una población robusta de B-ALL positive para el cromosoma filadelfia fue clasificada (CD45dim, estrategia de exclusión mostrada en la Figura 56B). Se encontró que estas células fueron clonales para la translocación BCR-ABL, aunque a una frecuencia inferior que las erupciones CD19+ (Figura 49D). Este hallazgo indica que el marcaje CD19 solo, en algunos casos, podría conducir a una recaída subclonal derivada de las células CD19-CD123+. Además, este hallazgo sugiere que el marcaje de CD123 podría conducir a respuestas más profundas a través de la eliminación de la LSC y posiblemente clones de leucemia CD19-negativos.

Por último, la expresión de CD123 también fue evaluada en las muestras de pacientes de B-ALL que recaen después de CTL019 con pérdida de CD19. De manera importante, en contraste con la pérdida completa de CD19, la mayoría de pacientes mantuvieron la expresión de CD123 en la recaída (Figuras 49E, 49F y 56C). Estos hallazgos indican que CD123 representa un marcador ideal para marcar erupciones de ALL CD19-negativas que ocurren después de CART19 o blinatumomab.

Células T de receptores quiméricos de antígeno anti-CD123 son activos contra B-ALL humana in vitro e in vivo

Se generaron células T de receptores quiméricos de antígeno anti-CD123 (CART123) que fueron transducidas y expandidas de manera lentiviral con esferas magnéticas anti-CD3/CD28. La actividad in vitro e in vivo de CART123 contra la leucemia linfoblástica aguda B fue evaluada como se describe en el presente documento.

La línea celular de B-ALL NALM-6 que es CD19 ++ y CD123 + (Figuras 50A y 57A) y muestras primarias de B-ALL se utilizaron. Una comparación vitro cabeza a cabeza entre CART123 y CART19 reveló tasas similares de degranulación de CD107a cuando las células T fueron co-cultivadas con NALM-6 o ALL primaria (Figura 50B). CART123 también fueron capaces de eliminar células NALM-6 con una eficacia similar a la CART19 en una manera dependiente de dosis (Figura 50C). En más experimentos a largo plazo, CART123 proliferó (Figuras 50D y 50E) y produjo múltiples citocinas (Figura 50F) cuando se co-cultivaron con NALM-6 o ALL primaria durante 3-5 días. Estos resultados indican que CART123 exhiben potencia equivalente a CART-19 contra múltiples blancos de B-ALL.

Con el fin de confirmar estos datos en un modelo in vivo, se utilizó un modelo primario de ALL. En este modelo, los blastocitos primarios obtenidos de pacientes con B-ALL se pasaron en ratones silenciados (GSN) NOD-SCID cadena-γ y transducidas con un constructo reportero que contiene eGFP y luciferasa clic de escarabajo (GFP / Luc). Los ratones fueron inyectados con erupciones de ALL primaria GFP/ Luc+ por vía intravenosa. (JH331, CD19 +, CD123 +, añadir fenotipo) y después del injerto, los ratones fueron aleatorizados para recibir CART19, CART123 o controlar las células T no transducidas (UTD). Los ratones tratados con células T de control sucumbieron rápidamente a la enfermedad, mientras que los ratones tratados con bien sea CART19 o CART33 mostraron una erradicación tumoral y supervivencia a largo plazo (Figuras 51A, y 51B). Las células T CAR123 se expandieron significativamente en la sangre periférica (PB) de los ratones en comparación con las células T de control y expresaron altos niveles de CAR123 (Figura 51C). La actividad anti-leucemia de CART123 fue específica y se basó en el reconocimiento de CD123 en la superficie de las erupciones como cuando se injertaron ratones con una leucemia CD123- CD19 + (AV576), solo CART19 mostró actividad anti-leucemia, mientras CART123 no tuvo efecto en comparación con los controles UTD (Figuras 57B y 57C).

Con el fin de detectar una posible correlación de dosis de CART123 y la actividad anti-tumoral, se desarrolló un modelo in vivo de ratones con alta carga de leucemia (usando la línea celular NALM-6). En este modelo las dosis estándar de CART123 (2.000.000 de células CAR+) no puede eliminar el tumor. Estos ratones fueron inyectados con diferentes dosis de CART123 (1.25, 2 y 5 millones de células CAR+) y se observó una actividad anti-leucemia relacionada con la dosis (Figura 57D).

CART123 pero no CART19 son muy activos en un modelo preclínico novedoso de recaída por pérdida. de antígeno.

Con el fin de probar nuevas estrategias, para orientar las recaidas CD19-negativas, se desarrolló un nuevo modelo in vivo de recaída por pérdida de antígeno. Erupciones de células B obtenidas de un paciente (CHP101) inscrito en uno de nuestros ensayos clínicos CTL019 se recogieron al comienzo del estudio (antes de la terapia de CTL019), cuando la enfermedad fue CD19 ++ y CD123+, y en la recaída después de CTL019 cuando el paciente desarrolló una enfermedad CD19-negativa (CD123 todavía expresado, Figura 58A). Luego las erupciones fueron ampliadas en los ratones NSG y transducidas con luciferasa click de escarabajo verde (CBG) para la enfermedad de base (CD19 +) o luciferasa clic de escarabajo rojo (CBR) para recaída (CD19-) (véase la sección de odos). Es importante destacar que, durante la expansión in vivo, las erupciones retuvieron marcadores de identidad de células B distintos de CD19 (datos no mostrados). En un primer experimento Ratones NSG fueron injertados, ya sea con la enfermedad de base CD19 + (CBG, verde) o leucemia CD19-neg (CBR, rojo). Ambos grupos fueron aleatorizados para recibir CART19 o células T de control (UTD) (Figura 52A). Como se muestra en la Figura 52B, en ambos grupos los ratones tratados con UTD mostraron rápida progresión tanto del estado basal y de la recaída de enfermedad, de forma independiente por la expresión de CD19. Por el contrario, en el grupo de ratones tratados con CART19, sólo los ratones injertados con la enfermedad de base (CD19-positivo) respondieron al tratamiento con CART19 mientras que los ratones injertados con una mezcla 1: 1 del estado basal y de la recaída de enfermedad (CD19-negativa) mostraron refractariedad como se esperaba. Esto también fue reproducido in vitro en un ensayo de desgranulación de CD107a (Figura 58B). Para simular la presencia in vivo de diferentes clones que expresan CD19 o que carecen de ésta, los ratones GSN fueron injertados con una mezcla 1: 1 del estado basal y de la recaída de enfermedad; el día 8 ratones fueron aleatorizados para recibir células T CART19 o de control. La carga tumoral se controló con imágenes de bioluminiscencia que podrían discriminar entre leucemia CD19+ (CBG, verde)/CD19- (CBR, rojo) con relación al crecimiento in vivo. Como se muestra en la Figura 52C, en ratones que recibieron UTD tanto CD19 + (verde) y CD19- (rojo) presente en la leucemia el día 6 se incrementó de manera similar en el día 11, mientras que en los ratones tratados con CART19 la enfermedad de base (verde) fue completamente curada mientras que la recaída de la enfermedad (rojo) mostró progresión.

Se utilizó este modelo de xenoinjerto único de B-ALL primaria CD19 negativa y de falla de CART19 para evaluar el papel de CART123 en el tratamiento de las recaídas de pérdida de antígeno. Las erupciones CD19 negativa primarias (CBR positivo) fueron inyectadas en ratones NSG (Figura 52D) y los ratones fueron aleatorizados para recibir CART19, CART123 o células T de control. Las células T CART19 y de control mostraron completa falta de actividad anti-tumoral, mientras que CART123 llevó a la completa erradicación de la enfermedad y la supervivencia a largo plazo en estos ratones (Figuras 52E y 52F). De hecho, en un modelo preclínico de B-ALL primaria refractario a CART19, el CART123 novedoso es capaz de erradicar la enfermedad y conferir supervivencia a largo plazo.

Con el fin de entender el comportamiento diferencial de CART19 y CART123 en este modelo in vivo a un único nivel celular, una serie de experimentos se realizó mediante la inyección de una mezcla de CART19 diferencialmente marcado (CellTrace violeta, azul) y CART123 (CellTracker Naranja o TRITC, rojo) a ratones con erupciones primarias CD19-positivas (GFP) o erupciones de recaída-CD19 negativo (GFP) y siguieron en su comportamiento usando microscopía 2-fotón intravital de médula calvarial aproximadamente 24 horas después de la inyección (esquema de experimento, Figura 53A). Estos estudios demostraron que CART19 y CART123 llevados a los espacios de médula en donde la leucemia y que el reconocimiento de células CAR del antígeno cognado se correlacionan con la detención de la motilidad. En concreto, en ratones injertados con leucemia CD19+ CD123+ al inicio del estudio, 62,9% +/- 3,8 de CART19 y 81,1% +/- 1.2 de CART123 fueron encontrados como estancado con una morfología redondeada adyacente a las erupciones, mientras que en ratones injertados con la recaída de leucemia CD19-CD123 +, sólo las células CART123 las detuvieron junto a las células tumorales (CART123 80,9% + / - 5,1 vs CART19 12,4% + / - 2.2) (Figuras 53B y 53C). Estos resultados indican que en ALL reincidente CD19-negativa solamente CART123 pudo establecer sinapsis productivas con las células de la leucemia (GFP) y por lo tanto reducir su movilidad, mientras que las células CART19 continuaron muestreo y se mueven en el medio ambiente, sin reconocer las erupciones de leucemia.

La combinación de CART123 y CART19 es capaz de prevenir las recaídas CD19-negativas

CART123 demostró ser eficaz en el tratamiento de las recaídas CD19 -negativas que se producen después de terapias dirigidas a CD19 en un modelo preclínico de resistencia a CART19. Sin embargo, un enfoque combinatorio podría tratar la enfermedad de CD19-positivo

activa mientras evita al mismo tiempo las recaídas por pérdida de antígeno. Con el fin de probar esta hipótesis el problema clínico emergente de ALL- B con un potencial para el escape-CD19 negativo fue modelado por inyección tanto de primaria de CD19- y la enfermedad CD19 + en ratones NSG. Los ratones fueron aleatorizados para recibir células T de control (UTD), CART19 o la combinación de CART19 y CART123, con la misma dosis total de células T (Figura 54A). Como se muestra en la Figura 54B, los ratones tratados con las células T de control tuvieron progresión de ambos clones de leucemia y CART19 mostró una rápida progresión en su mayoría de la enfermedad CD19-negativa (rojo). Por el contrario los ratones tratados con la combinación de CART123 y CART19 mostraron una eliminación de la enfermedad y supervivencia general mejorada, como se muestra en la Figura 54C. El análisis de los ratones sacrificados al final del experimento no mostró evidencia de leucemia residual en el grupo de células T CAR agrupadas. En contraste, los ratones con enfermedad progresiva después de monoterapia con CART19 retuvieron el fenotipo negativo CD19 esperado (Figura 36D).

Por último, las células T fueron transducidas con 2 lentivirus, uno que lleva CAR19 y el otro CAR123 con el fin de desarrollar un CART capaz de ser activado por ambos CD19 y/o CD123. Como se muestra en la Figura 55A, se detectaron cuatro subgrupos de células T transducidas de manera diferente: Células T CAR19 y CAR123 dobles negativas, CAR19 sencillas positivas, CAR123 sencillas positivas y CAR19/CAR123 dobles positivas . Estos cuatro subconjuntos fueron ordenados y su funcionalidad y especificidad se probó contra K562-WT, K562 CD19+ o K562 CD123+. La Figura 55B muestra los resultados de un ensayo de desgranulación CD107a donde los subconjuntos sencillas positivas responden a su blanco específico, mientras que sólo la población doble positiva es capaz de desgranulación en presencia tanto de CD19 como CD123 que expresa K562. Además, las células CART estimuladas de manera dual exhiben citotoxicidad más potente contra un blanco doble positivo en comparación con un número equivalente de células CART estimuladas sencillas, lo que sugiere un incremento potencial en la eficacia mediante el uso de un CAR que se activa por dos antígenos diferentes (Figura 55C).

DISCUSIÓN

Las inmunoterapias dirigidas a CD19 están cambiando el paradigma del tratamiento de la recaída y la leucemia linfoblástica aguda refractaria. Los pacientes con un resultado previamente desalentador ahora tienen un potencial real para lograr una respuesta completa y remisión de la

enfermedad a largo plazo. Sin embargo, como se muestra bajo algunas circunstancias para leucemia tratada con otras formas de terapia dirigida potente, las células de leucemia son capaces de desarrollar mutaciones de pérdida de antígeno que llevan a la resistencia y reincidencia. En el caso de CART19, se han observado dos patrones principales de recaídas. Los pacientes con pérdida temprana de CART19 mediante falla de persistencia están en riesgo de recaída del clon original; de hecho, los análisis de la enfermedad mínima residual indican que entre 1-6 meses de actividad CART sostenida pueden ser necesarios para erradicar completamente la enfermedad. En contraste, alrededor del 50% de las recaídas se producen a pesar de la persistencia de CART19 y se caracterizan por la aparición de una leucemia CD19-negativa. Esta última observación implica una presión selectiva potente por CART19. En particular, las reincidencias CD19-negativas también se han producido después de la terapia de blinatumomab aunque éstas representan la minoría de las ocurrencias de reincidencia después de esta terapia que podria decirse es menos potente. Existen múltiples mecanismos potenciales para el desarrollo de la enfermedad CD19 negativa. Uno de estos es la selección y ventaja de la supervivencia relativa de los clones CD19 negativos que estuvieron presentes originalmente con una frecuencia muy baja, y esto fue inicialmente considerado el factor más probable que lleva a recaídas CD19-negativas. Más recientemente otros mecanismos, tales como la desregulación del splicing de CD19 también se han considerado importantes. En la presente se demuestra por primera vez que las erupciones CD19-ve raras en B-ALL pueden contener el contraste de las anormalidades citogenéticas encontradas en las erupciones de leucemia CD19-positiva más comunes, lo que confirma esto como un mecanismo potencial de reincidencia CD19-negativa. Se confirmó estos hallazgos, al demostrar que las erupciones CD123+CD19-ve pueden injertarse en ratones inmunodeficientes, lo que indica que CD123 puede ser un marcador de células madre leucémicas en B-ALL, como lo es en AML.

El objetivo de este estudio era definir nuevas estrategias para el tratamiento de pacientes que reinciden con la pérdida de antígenos después de las terapias dirigidas a CD19. CD123 se expresó altamente en la mayoría de B-ALL, y en particular CD123 permanece expresado en aquellos que reinciden con la enfermedad CD19-negativa. Se demostró que la presencia de células leucémicas clonales en la población CD19-CD123+ indica que se dirige a CD123 en combinación con CART19 puede aumentar la probabilidad de erradicar los sub-clones que podrían proliferar debido a una ventaja selectiva sobre la presión CART19. CD123 ha sido previamente validado como un marcador de la célula madre leucémica en AML. Aquí se

demostró que el CD123 a ser expresado en la célula madre leucémica definido inmunofenotípicamente (LSC) en ALL, que aumenta la posibilidad de dirigirse a CD123 en LSC podría promover la erradicación de ALL.

Para estudiar el rol de CART 123 en las reincidencias por pérdida de antígeno, se desarrolló un modelo de xenoinjerto novedoso de reincidencias CD19-negativas a partir de erupciones primarias derivadas de un paciente de B-ALL (CHP101) inscrito en uno de los ensayos CTL019 de la Universidad de Pennsylvania/Hospital de Infantes de Filadelfia. Este paciente, originalmente tenia un fenotipo CD19+CD123+ clásico pero luego reincidió después del tratamiento con CART19 con la enfermedad CD19-CD123+. El uso de este modelo demostró que CART123 podría erradicar la enfermedad de reincidencia, y en combinación con CART19 podría prevenir la reincidencia de pérdida de antígenos. Esta es la primera demostración de una combinación CART dual en un modelo derivado de paciente, clínicamente relevante. Además, a través del uso de imágenes intravitales, se demostró que las células CART entran a la médula en menos de 24 horas después de la inyección intravenosa, buscan sus blancos, y disminuyen con el objeto de interactuar con las células que portan los antígenos cognados. Además, se demostró que una señalización dual de CART123/19 fue más eficaz que bien sea CART solo o un grupo de ambos CAR, consistente con resultados publicados anteriormente.

Anteriormente, se mostró la eficacia pre-clínica del receptor quimérico de antígeno anti-CD123 para el tratamiento de leucemia mieloide aguda. CART123 causa toxicidad hematopoyética debido al reconocimiento de CD123 sobre células madre y progenitoras hematopoyéticas, un desafío potencialmente importante para la clínica es la profunda toxicidad de las células madre que podría conducir a una mieloablación permanente. Se planteó la hipótesis de que para minimizar la toxicidad hematopoyética, un nuevo constructo de células T activadas únicamente con la co-participación de CD19 y CD123 simultáneamente podría obviar esta toxicidad hematopoyética Aquí se encontró que las células CART que reciben una señal de activación del reconocimiento CD19 y una señal estimulatoria del reconocimiento de CD123 podrían eliminar las células B-ALL, así como evitar la toxicidad hematopoyética profunda que hemos descrito anteriormente. Aunque este concepto se publicó anteriormente utilizando un sistema artificial de reconocimiento CD19/PSMA, este constructo clínicamente relevante representa un avance importante en el campo con un camino relativamente claro hacia la traducción clínica. Notablemente, aunque tal diseño CAR dual probablemente será asociado con

toxicidad reducida, que puede dejar sin resolver el problema de la recaída por pérdida de antígeno al hacer el reconocimiento CAR más restrictivo, en vez de menos restrictivo. Sin embargo, si el marcaje de CD123 erradica exitosamente las células madre ALL, este enfoque podría ser tanto seguro como eficaz.

En resumen, en la presente se demuestra una estrategia novedosa y eficaz para el tratamiento de B-ALL mediante el marcaje de CD123. Este enfoque es particularmente atractivo ya que CD123 es expresado en células malignas CD19-negativas raras en algunos pacientes con B-ALL y es retenido en las reincidencias por pérdida de antígeno que ocurren después de las inmunoterapias dirigidas a CD19. Por otra parte, la combinación de CART19 con CART123 puede prevenir la aparición de reincidencias CD19-negativas.

Ejemplo 18: Dosis bajas de RAD001 estimula la proliferación de CART en un modelo de cultivo celular

El efecto de dosis bajas de RAD001 sobre la proliferación de células CART en vitro se midió al cultivar conjuntamente células que expresan CART con las células blanco en presencia de diferentes concentraciones de RAD001.

Materiales y Métodos

Generación de células T transducidas por CAR

Un vector de transferencia lentiviral anti-humano CD19 CAR (huCART19) humanizado se utilizó para producir el material genómico empaquetado en las partículas lentivirales VSVg pseudotipadas. La secuencia de aminoácidos y nucleótidos del CAR CD19 anti-humano humanizado (huCART19) es CAR 1, ID 104875 descrito en la publicación PCT, WO2014/153270, presentada el 15 de marzo 2014, y se designa SEC ID NO. 85 y 31 en la misma.

El ADN de transferencia del vector lentiviral se mezcla con los tres componentes de embalaje VSVg, gag/pol y rev en combinación con el reactivo de lipofectamina para transfectar las células Lenti-X 293T. El medio se cambió después de 24 horas y 30 h después, se recolectó el medio que contiene el virus, se filtró y se almacenó a -80°C. Los CARTs son generados mediante transducción de células T no manipuladas frescas o congeladas que se obtienen mediante selección magnética negativa de sangre de donantes saludables o de leukopak. Las

células T se activaron mediante la incubación con perlas anti-CD3/anti-CD28 durante 24h, después de lo cual el sobrenadante viral o virus concentrado (MOI = 2 o 10, respectivamente) se agregó a los cultivos. Las células T modificadas se dejaron expandirse durante 10 días aproximadamente. El porcentaje de células transducidas (que expresan los CARs en la superficie celular) y el nivel de expresión de CAR (intensidad de fluorescencia relativa, Geo Media) se determinaron mediante análisis de citometría de flujo entre los días 7 y 9. La combinación de la disminución del ritmo de crecimiento y el tamaño de las células T ~350 fL determina el estado de las células T para ser criopreservado para un análisis posterior

Evaluación de la proliferación de CARTs

Para evaluar la funcionalidad de CARTs, las células T se descongelan y se contaron, y la viabilidad se evaluó mediante Cellometer. El número de células CAR-positivas en cada cultivo se normalizó utilizando células T no transducidas (UTD). El impacto de RAD001 en CARTs se probó en titulaciones con RAD001, a partir de 50 nM. La línea celular diana utilizada en todos los experimentos de co-cultivo es NALM6 (Nalm-6), una línea celular de leucemia linfoblástica aguda de células pre-B humana (ALL) que expresa CD19 y que es transducida para expresar luciferasa.

Para medir la proliferación de los CARTs, se cultivan células T con células diana en una proporción de 1:1. EL ensayo se corre por 4 días, cuando las células se tiñen para determinar la expresión de CD3, CD4, CD8 y CAR. El número de células T se evaluó por citometría de flujo utilizando esferas de conteo como referencia.

Resultados

La capacidad proliferativa de células CART se probó en un ensayo de co-cultivo de 4 días. El número de células T CD3-positivas y CAR-positivas (barras oscuras) y las células T CD3 positivas totales (barras claras) se evaluaron después de cultivar las células T CAR-transducidas y no transducidas con NALM6 (Nalm-6) (Fig. 59). Las células huCART19 se expandieron cuando se cultivaron en presencia de menos de 0.016 nM de RAD001, y en menor medida en concentraciones más altas del compuesto. Es importante destacar que, tanto a 0,0032 y 0,016 nM de RAD001 la proliferación fue mayor que la observada sin la adición de RAD001. Las células T no transducidas (UTD) no mostraron expansión detectable.

Ejemplo 19: RAD001 a dosis bajas estimula la expansión de CART in vivo

En este ejemplo se evalúa la capacidad de las células huCAR19 para proliferar in vivo con diferentes concentraciones de RAD001.

Materiales y Métodos:

Células NALM6-luc: La línea celular de leucemia linfoblástica aguda humana NALM6 (ALL) se desarrollo a partir de la sangre periférica de un paciente con ALL reincidente. Las células fueron luego etiquetadas con luciferasa de luciérnaga. Estas células en suspensión crecen en medio RPMI suplementado con suero bovino fetal inactivado por calor al 10%.

Ratones: Se recibieron ratones NSG (NOD.Cg-PrkdcscidIl2rgtm1Wjl/SzJ) de 6 semanas de edad del Laboratorio Jackson (número de stock 005557).

La implantación del tumor: Las células NALM6-luc se cultivaron y se expandieron in vitro en RPMI suplementado con suero bovino fetal inactivado por calor al 10%. Luego las células se transfirieron a un tubo cónico de 15 ml y se lavaron dos veces con PBS estéril frío. Las células NALM6-luc luego se contaron y se resuspendieron a una concentración de $15x10^6$ células por mililitro de PBS. Las células se colocaron en hielo e inmediatamente (dentro de una hora) se implantaron en los ratones. Las células NALM6-luc se inyectaron por vía intravenosa a través de la vena de la cola en un volumen de 100 µll, para un total de $1.5x10^6$ células por ratón.

Dosificación celular de CAR T: A los ratones se les administró $5x10^6$ células T CAR 7 días después de la implantación del tumor. Las células se descongelaron parcialmente en un baño de agua a 37 °C y luego se descongelaron completamente por la adición de 1ml de PBS estéril frío al tubo que contiene las células. Las células descongeladas se transfirieron a un tubo Falcon de 15 ml y se ajustó a un volumen final de 10 ml con PBS. Las células se lavaron dos veces a 1000 rpm durante 10 minutos cada vez y luego se contaron en un hemocitómetro. Las células T se resuspendieron luego a una concentración de $50x10^6$ células CAR T por ml de PBS frío y se mantuvieron en hielo hasta que se dosificaron los ratones. Los ratones fueron inyectados por vía intravenosa a través de la vena de la cola con 100 µlde las células T CAR para una dosis de $5x10^6$ células T por ratón. Se tratraron ocho ratones por grupo ya sea con 100 µl de PBS solo (PBS), o células CAR T CD19 humanizadas.

Dosificación RAD001: Una micro-emulsión concentrada de 50 mg igual a 1 mg de RAD001 se formuló y luego se resuspendió en D5W (dextrosa al 5% en agua) en el momento de

la dosificación. Los ratones recibieron una dosis diaria por vía oral (mediante la alimentación oral forzada) con 200 µl de la dosis deseada de RAD001.

Análisis PK: Los ratones fueron dosificados a diario con RAD001 a partir de los 7 días después de la implantación del tumor. Los grupos de dosificación fueron los siguientes: 0.3 mg/kg, 1 mg/kg, 3 mg/kg, y 10 mg/kg. Los ratones se hicieron sangrar en los días 0 y 14 después de la primera y última dosis de RAD001, en los siguientes puntos de tiempo para el análisis PK: 15 minutos, 30 minutos, 1 hora, 2 horas, 4 horas, 8 horas, 12 horas y 24 horas.

Resultados

La expansión y farmacocinética de RAD001 fue probada en ratones NSG con tumores NALM6-luc. La dosis oral diaria de RAD001 sola no tuvo un impacto en el crecimiento de tumores NALM6-luc (Figura 60). El análisis farmacocinético de RAD001 muestra que es bastante estable en la sangre de ratones que portan tumor (Figura 61A y 61B). Tanto el día 0 y el día 14 los análisis PK mostraron que las concentraciones RAD001 en la sangre están por encima de 10 nm incluso 24 horas después de la administración a la dosis más baja ensayada (0,3 mg / kg).

Con base en estas dosis, las células CAR T huCAR19 se dosificaron con y sin RAD001 para determinar la capacidad proliferativa de estas células. La dosis más alta utilizada fue 3 mg/kg con base en los niveles de RAD001 en la sangre 24 horas después de la dosificación. Debido a que la concentración de RAD001 estaba por encima de 10 nM 24 horas después de la dosis final de RAD001, se utilizaron varias dosis más bajas de RAD001 en el estudio in vivo con células T CAR. Las células T CAR se dosificaron IV un día antes del comienzo de la dosificación oral diaria de RAD001. Los ratones se controlaron mediante FACS para la expansión de células T.

Las dosis más bajas de RAD001 mostraron una mayor proliferación de las células CAR T (Figuras 62A y 62B). Esta proliferación mejorada es más evidente y prolongada con las células CAR T CD4+ que las células CAR T CD8+. Sin embargo, con las células CAR T CD8+, la proliferación mejorada puede mostrarse de manera temprana después de la dosis de células CAR T.

Ejemplo 20: Ciertos pacientes con DLBCL primaria muestran células cancerosas positivas dobles CD3+/PD1+

Aunque ha habido avances convincentes en el espacio de la inmunoterapia del cáncer recientemente en forma de células T modificadas por el receptor quimérico de antígeno (CAR) y los inhibidores de punto de comprobación, herramientas avanzadas para explorar los mecanismos terapéuticos de su combinación no están ampliamente disponibles. Para hacer frente a esta creciente necesidad, una robusta plataforma de inmunohistoquímica cuantitativa fluorescente que utiliza tecnología multiplex AQUA (Análisis Cuantitativo Automatizado) fue desarrollada para evaluar la expresión del inhibidor de punto de comprobación, enumerar las células T CAR y determinar la interacción entre las células tumorales y las células inmunes a través de nuevos algoritmos de co-localización. La utilidad de este método se caracterizó tanto en sistemas de modelos preclinicos como clínicos. En un modelo de ratón inmunodeficiente de linfoma de células B, se evaluó La detección de células B malignas por las células T CAR en órganos linfoides primarios. Se determinó el fenotipo y la condición funcional de las células CAR T a través de análisis multiplex de la expresión de CD4, CD8, PD1 y FOXP3. Además, para permitir que las inmunoterapias de combinación en entorno de Linfoma de Células B Grandes Difusas (DLBCL), la prevalencia de los mecanismos de resistencia inmunes adaptivos en la forma de expresión de PD1 y PD-L1 en los compartimentos celulares tumorales e inmuno se examinó a través de puntos de referencia creados por manchas citoplásmicas y nucleares, tanto en biopsias primarias y secundarias de pacientes con DLBCL (n = 63). Para apoyar la selección de pacientes para los ensayos CAR T, la expresión y la prevalencia de los antígenos tumorales relevantes que no se pudieron calificar de forma reproducible por métodos tradicionales fueron cuantificadas para producir puntos de corte objetivos. Estos métodos IHC multiplexados cuantitativos para la selección óptima de los pacientes se pueden utilizar en los próximos nuevos ensayos de inmunoterapia de combinación.

La preparación de muestras, tratamiento de imágenes y análisis de imágenes para muestras de tejido DLBCL se realizó en pacientes humanos con DLBCL primaria (n = 49) y DLBCL secundaria (15).

Preparación de muestras. Las muestras de tejidos embebidos en parafina (FFPE) fueron desparafinadas. Luego las diapositivas fueron rehidratadas a través de una serie de lavados de xileno a alcohol antes de la incubación en agua destilada. A continuación, la recuperación de

antígeno inducida por calor se realizó utilizando condiciones de presión y temperatura elevadas, se dejó enfriar, y se transfirió a solución salina tamponada con Tris. Luego se realizó la tinción donde las siguientes etapas se llevaron a cabo. En primer lugar, la peroxidasa endógena fue bloqueada seguido de incubación con una solución de bloqueo de proteínas para reducir la tinción de anticuerpos no específica. A continuación, las láminas fueron teñidas con un anticuerpo primario anti-PD1 de ratón. Los portaobjetos luego fueron lavados antes de la incubación con un anticuerpo secundario HRP anti-ratón. Los portaobjetos se lavaron y después se detectó la tinción de PD-1 usando TSA + Cy® 5 (Perkin Elmer). Luego los reactivos de anticuerpos primarios y secundarios se eliminaron a través de microondas. Los portaobjetos se lavaron de nuevo antes de la tinción con un anticuerpo primario anti-CD3 de conejo. Los portaobjetos se lavaron y después se incubaron con un cóctel de anticuerpo secundario HRP anti-conejo más de 4', 6-diamidino-2-fenilindol (DAPI). Los portaobjetos se lavaron y después se detectó tinción CD3 usando TSA-Cy® 3 (Perkin Elmer). Las láminas fueron lavadas justo antes de cubiertas con un cubreobjetos con medio de montaje y se dejaron secar durante la noche a temperatura ambiente.

Imágenes y análisis de la muestra . Luego se adquirieron imágenes de fluorescencia utilizando el Sistema de Análisis Slide Intelligent Vectra 2 usando el software Vectra versión 2.0.8 (Perkin Elmer). Primero, se llevó a cabo el registro de imagen monocrómica de la lámina al aumento de 4X usando DAPI. Se utilizó un algoritmo automatizado (desarrollado utilizando Inform) para identificar áreas de la diapositiva que contienen el tejido.

Las áreas de la lamina identificadas por contener tejido se registraron en imagen con un aumento 4x para canales asociados con DAPI (azul), Cy®3 (verde), y Cy®5 (rojo) para crear imágenes RGB. Estas imágenes de magnificación 4x se procesaron mediante un algoritmo de enriquecimiento automatizado (desarrollado utilizando inForm) en el campo de selector de vista para identificar y clasificar los posibles campos de magnificación 20X de vista de acuerdo con la expresión más alta Cy® 3.

Las 40 mejores campos de visión se registraron en imágenes de magnificación 20x a través de las longitudes de onda DAPI Cy®3, y Cy® 5. Las imagines primarias fueron revisadas para su aceptabilidad, y las imágenes que estaban fuera de foco, carecían de cualquier célula tumoral, fueron muy necróticas, o contenían altos niveles de señal de fluorescencia no asociadas con la localización de anticuerpos esperada (es decir, la tinción de fondo) fueron

rechazadas antes del análisis. Las imágenes aceptadas fueron procesadas usando ACUAduct (Perkin Elmer), En donde cada fluoróforo fue separado espectralmente mediante un separador espectral en canales individuales y guardado como un archivo aparte.

Los archivos procesados se analizaron adicionalmente usando AQUAnalysis™ o a través de un proceso totalmente automatizado usando AQUAserve™. Cada imagen DAPI se procesó por enmascarador de células para identificar todos los núcleos celulares dentro de esa imagen, y luego se dilató por 2 píxeles para representar el tamaño aproximado de una célula entera. Esta máscara resultante representó todas las células dentro de esa imagen. Cada imagen Cy® 5 se procesó por enmascarador biomarcador para crear una máscara binaria de todas las células que son PD-1-positivas. Cada imagen Cy® 3 se procesó por enmascarador biomarcador para crear una máscara binaria de todas las células que son CD3-positivas. Se combinaron las máscaras binarias para todas las células PD-1-positivas y CD3-positivas para crear una máscara binaria de todas las células que son el doble positivas para PD-1 y CD3. El porcentaje de positividad de biomarcador (PBP) para todas las células CD3 que expresan PD-1 se derivó, utilizando la calculadora de positividad, dividiendo el área total, medida en píxeles y determinada por el evaluador de área, de la máscara de todas las células tumorales PD-1-positivas con el área total, medida en píxeles y determinada por el evaluador de área, de la máscara de todas las células CD3 positivas. Los valores representativos de PBP para todas las células CD3 positivas que expresan PD-1 en muestras humanas primarias y secundarias DLBCL se muestran en la **Figura 63.** El estado CD# y PD-1 mostró que las tasas de prevalencia de las células CD3+/PD-1 primarias es mayor que en el conjunto DLBCL secundario, proporcionando la oportunidad de escoger un paciente bien sea para el tratamiento único o en combinación.

Se llevo a cabo un experimento similar en el cual PD-L1 se detecto usando un anticuerpo primario de ratón anti-PDL1 y TSA+Cy5 (Perkin Elmer) sobre muetsras de tejido DLBCL de pacientes humanos con DLBCL primario. Se pudo detectar también PD1 y CD3 en la smismas muestras. El experimento mostró que el microentorno del tumor comprende células que expresan PD1, CD3 y PDL1. El experimento también identifico una subpoblación de células que son CD3+PD1+ (datos no mostrados). Estos resultados apoyan el modelo que el microentorno del tumor comprende células tumorales, células inmunes efectoras PD1+ y células Treg PDL1.

Ejemplo 21: Expresión mutuamente excluyente de CD19 y PD-L1 en muestras que comprenden células DLBCL

Preparación de muestras. Las muestras de tejidos embebidos en parafina (FFPE) fueron desparafinadas. Luego los portaobjetos fueron rehidratados a través de una serie de lavados de xileno a alcohol antes de la incubación en agua destilada. A continuación, la recuperación de antígeno inducida por calor se realizó utilizando condiciones de presión y temperatura elevadas, se dejó enfriar, y se transfirió a solución salina tamponada con Tris. Luego se realizó la tinción donde las siguientes etapas se llevaron a cabo. En primer lugar, la peroxidasa endógena fue bloqueada seguido de incubación con una solución de bloqueo de proteínas para reducir la tinción de anticuerpos no específica. A continuación, los portaobjetos se tiñeron con un anticuerpo primario anti-PDL1 de conejo. Los portaobjetos luego fueron lavados antes de la incubación con un anticuerpo secundario de HRP anti-conejo. Los portaobjetos se lavaron y después la tinción de PDL1 se detectó utilizando TSA+Cy®3 (Perkin Elmer). Luego los reactivos de anticuerpos primarios y secundarios se eliminaron a través de microondas. Los portaobjetos se lavaron de nuevo antes de la tinción con un anticuerpo primario anti-CD19 de ratón. Los portaobjetos se lavaron y después se incubaron con un cóctel de anticuerpo secundario HRP anti-ratón más 4',6-diamidino-2-fenilindol (DAPI). Los portaobjetos se lavaron y después se detectó la tinción de CD19 usando TSA-Cy® 5 (Perkin Elmer). Las láminas fueron lavadas justo antes de cubiertas con un cubreobjetos con medio de montaje y se dejaron secar durante la noche a temperatura ambiente.

Imágenes y análisis de la muestra . Luego se adquirieron imágenes de fluorescencia utilizando el Sistema de Análisis Slide Intelligent Vectra 2 usando el software Vectra versión 2.0.8 (Perkin Elmer). Primero, se llevó a cabo el registro de imagen monocrómica de la lámina al aumento de 4X usando DAPI. Se utilizó un algoritmo automatizado (desarrollado utilizando Inform) para identificar áreas de la diapositiva que contienen el tejido.

Las áreas de la lámina identificadas por contener tejido fueron fotografiadas en el aumento de 4X por canales asociados con DAPI (azul), Cy®3 (verde), y Cy®5 (rojo) para crear imágenes RGB. Estas imágenes de magnificación 4x se procesaron mediante un algoritmo de enriquecimiento automatizado (desarrollado utilizando inForm) en el campo de selector de vista para identificar y clasificar los posibles campos de magnificación 20X de vista de acuerdo con la expresión más alta Cy® 3.

Las 40 mejores campos de visión se registraron en imágenes de magnificación 20x a través de las longitudes de onda DAPI Cy®3, y Cy® 5. Las imágenes primarias fueron revisadas para su aceptabilidad, y las imágenes que estaban fuera de foco, carecían de cualquier célula tumoral, fueron muy necróticas, o contenían altos niveles de señal de fluorescencia no asociadas con la localización de anticuerpos esperada (es decir, la tinción de fondo) fueron rechazadas antes del análisis. Las imágenes aceptadas fueron procesadas usando ACUAduct (Perkin Elmer), en donde cada fluoróforo fue espectralmente no mezclado por un separador espectral en canales individuales y se guarda como un archivo separado.

Los archivos procesados se analizaron adicionalmente usando AQUAnalysis™ o a través de un proceso totalmente automatizado usando AQUAserve™ como se describe en el ejemplo anterior.

Valores representativos de PBP para todas las células CD19-positivas y PD-L1-positivas en muestras humanas primarias y secundarias DLBCL se muestran en la **Figura 64.** La expresión de CD19 y PDL1 varió en muestras de DLBCL. CD19 y la expresión de PDL1 tienden a ser mutuamente excluyentes, es decir, en general, una célula dada expresa CD19 o PD-L1 pero no ambos. Si bien no se desea estar limitado por la teoría, esto puede ser debido a que CD19 se expresa en las células tumorales DLBCL mientras que PD-L1 se expresa en células no tumorales, por ejemplo, células que soportan el microambiente tumoral. Esta observación sugiere que una terapia de combinación de un inhibidor de CD19 (por ejemplo, una célula que expresa CAR de CD19) y un inhibidor de la señalización de PD-L1 puede ser útil para la orientación de estas dos poblaciones de células.

Se realizó un experimento similar en el que se detectaron CD19, CD3, y el ácido nucleico de CART19 en muestras que comprenden líneas de células mixtas con células Jurkat CART19 + y células CD19 + REH. CD19 y CD3 se detectaron por el anticuerpo, y CART19 se detectó utilizando una sonda de ARN en contra de la 3 'UTR del ácido nucleico CAR. El experimento mostró que las muestras de línea celular comprenden células que expresan CD19, CD3 y el CART19 (datos no mostrados). El experimento también demostró que las muestras de línea celular comprenden una sub-población de células que es CD3 + / CART19 + (datos no presentados). Se realizó un análisis de proximidad, que mostró que las células CART19 eran físicamente proximales a las células CD19 + (datos no presentados). Estos experimentos apoyan el modelo de que las células CD3 + CART19 se infiltran en un microambiente del tumor que comprende células CD19 +.

Ejemplo 22: expresión bicistrónica de lo CAR

En este Ejemplo, se comparó la eficacia de dos tipos de poblaciones de células. En la primera población de células, se refiere como "agrupados", cada célula expresa un CAR. Una primera pluralidad de células CD19 fue transducida con CAR, una segunda pluralidad de células CD22 fue transducida con CAR o CAR CD123, y luego se combinaron las dos pluralidades de células. En el segundo tipo de población de células, una pluralidad de células se transdujeron con un vector bicistrónico que expresa CD19 CAR y un segundo CAR, por lo que la mayoría o todas las células expresaron ambos constructos. El segundo CAR fue CAR CD22 en algunos experimentos y CD123 CAR en otros. Estas poblaciones de células se ilustran en la figura. 65.

Dos nuevas construcciones, se esquematizan en la figura. 66, se generaron usando el sistema P2A con el fin de expresar dos CARs de larga duración en la misma célula T utilizando un vector lentiviral bicistrónico. Las células T se expandieron de acuerdo con un protocolo estándar y transducidas utilizando dos lentivirus que llevan respectivamente CAR19 y CAR123 (multiplicidad de infección, MOI = 3). Se realizó una transducción similar para CAR19 y CAR22. Fig. 67 muestra la coexpresión de CD19 y CD22 CARs. Cuatro poblaciones distintas en base a la expresión específica de CAR19 y/o CAR123 pueden ser reconocidos, incluyendo un doble CAR19 + / + CAR123 población (Fig. 68, panel superior).

Estas cuatro poblaciones fueron ordenadas y se realizó un experimento CD107a degranulación. CART19 / 123 dual mostraron desgranulación ya sea con la línea celular K562 CD19-positivo o CD123 + K562, mientras que los subconjuntos solo CAR + mantuvieron su respectiva especificidad.

Las células transducidas con el CAR CD19 bicistrónico y CAR CD123 se comparó con las células que expresan CD19 agrupados o CD123 CAR (Fig. 68, panel inferior). GSN ratones fueron arraigado con un B-ALL línea celular (NALM-6, CBG +). En el día 7 ratones fueron aleatorizados basados en la carga tumoral (BLI, bioluminiscencia) para recibir las células T de control (UTD), CART19, CART123, la combinación 1: 1 combinado de CART123 y CART19 o el doble CART19 / 123 (el mismo número total de CAR + Células). La carga tumoral 6 días después de la infusión de células T (día 13) se muestra en el gráfico: la respuesta más profunda a corto plazo contra la leucemia se observa en el grupo de CART dual. Más específicamente, CD19 CAR células que expresan solo (cuadrados) y CD123 CAR células que expresan solo (triángulos) ambos mostraron eficacia inicial en comparación con el control (círculos), seguido

por el aumento del nivel de células leucémicas. las células que expresan CD19 agrupados o CD123 (diamante) también mostraron la eficacia inicial seguida por el aumento del nivel de las células leucémicas. En contraste, las células transfectadas con el vector bicistrónico (triángulos invertidos, "CAR dual") mantuvieron una respuesta prolongada al menos 60 días después del tratamiento. Este experimento indica que los CARs de doble ejercen un efecto anti-leucemia potente que no sólo es superior a un solo tratamiento CAR pero es superior a las células TCAR agrupados.

Ejemplo 23: CART22 es eficaz contra CD19-neg B-ALL en un modelo animal.

Se ensayaron células CD19-negativas de B-ALL para la capacidad de respuesta a células que expresan CAR CD19 y las células que expresan CD22 CAR en un modelo animal. Un millón de células CD19-negativas B-ALL se infunden en los ratones en el día 0, y 2E6 células T CAR + fueron infundidas en el día 7 (después de la aleatorización). La carga tumoral se midió por bioluminiscencia. Como se muestra en la figura. 69, mientras que el cáncer avanzaba en los ratones de control negativo y los ratones tratados con CART19, CART22 es capaz de limpiar CD19-negativas ALL en xenoinjertos GSN.

Ejemplo 24: Los bajos niveles de moléculas inmunes de punto de control están asociados con mejores resultados

Se detectaron las moléculas de punto de control inmunitario (PD-L1, PD1, LAG3, y TIM3) en muestras de pacientes de linfoma por inmunohistoquímica. También se realizaron tejidos de control positivo y negativo y líneas celulares. El análisis de la expresión punto de control inmune se realizó mediante análisis de imagen cuantitativo en una región de interés que puede incluir células tumorales y células no tumorales tales como células inmunes. Se tomaron muestras de tejido, los nódulos linfáticos y la médula ósea.

Se comparó la expresión del punto de control y de proteínas inmunes en pacientes con respuesta completa (CR) y los pacientes que tienen enfermedad progresiva (PD). Como se muestra en la figura. 70, los pacientes CR tendían a tener niveles bajos de PD-L1, PD1, LAG3, y TIM3 antes y después del tratamiento, mientras que los pacientes con EP tienden a tener altos niveles de estas moléculas antes y después del tratamiento. Este ejemplo es compatible con la terapia de

combinación con una célula que expresa CAR y un inhibidor de puesto de control inmunológico, y es compatible con las pruebas para determinar los niveles de moléculas inmunes puesto de control en pacientes que reciben una terapia CAR.

Ejemplo 25: ensayos funcionales de las células que expresan CAR CD22-

Varios constructos CAR CD22 fueron validados funcionalmente en un ensayo de NFAT. Brevemente los experimentos se realizaron como sigue. Un vector lentiviral (pELPS) que lleva un ácido nucleico, que codifica una CAR CD22 con un dominio scFv de unión a CD22-se introdujo por electroporación en una línea de células Jurkat T modificado para expresar la luciferasa bajo el control de un elemento de respuesta NFAT (JNL). Las células se cultivaron y se dejaron expresar el constructo de CAR. Las células electroporadas se aplicaron a una placa recubierta con el antígeno diana (CD22). La detección de la señal de luciferasa en la placa revestida fue indicativo de la actividad de la CAR CD22 de unión a su antígeno, lo que lleva a la activación de las células T y la expresión de luciferasa.

La Fig. 71 es un gráfico que muestra la activación (en RLU) de varios constructos CAR CD22 en presencia y ausencia de un competidor M971 scFv. Estos resultados indican que CD22-53 y CD22-12, y un subconjunto de los otros scFv, se unen al antígeno aproximadamente, así como el control positivo M971. Los resultados también indican que las diferentes scFv compiten con M971 en diferentes grados.

Fueron probados dieciséis dominios de unión a CD22 humanos adicionales y se encontró que tienen actividad de unión débil (datos no mostrados), por lo que no se volvieron a tratar.

La Fig. 72 es un gráfico que muestra la activación (en RLU) de varias células JNL CAR que expresan CD22, incluyendo CD22-57, CD22-58, CD22-59, CD22-60, CD22-61, CD22-62, y CD22-63, la secuencias de scFv de los cuales se proporcionan en este documento. Tres diferentes proteínas diana (CD22-FL-Fc, CD22-D567-Fc, y CD22-D67) fueron utilizados para recubrir las placas de cultivo de tejidos; También se incluyó un control negativo (Fc). Un CAR de unión a la mesotelina (Meso-G07) se utilizó como control negativo. CD22-12 y CD22-53 se utilizaron como controles positivos. El experimento indicó que todos los CARs (CD22-57, CD22-58, CD22-59, CD22-60, CD22-61, CD22-62, y CD22-63) eran funcionales en este ensayo. Además, estos resultados indicaron que los CARs probados (incluyendo CD22-12 y -53) se unen a los dominios 6 y 7 de CD22. El mapeo de los dominios se realizó en dominios de unión a CD22. Se utilizaron tres formas diferentes de antígenos: CD22 de longitud completa con los 7 dominios externos,

Dominio 567 (en la que los dominios se eliminaron 1-4) y dominio 67 (en la que los dominios se eliminaron 1-5). Si bien no se desea estar ligado por la teoría, parece que la unión de varios clones de CD22 permite mapear los epítopos ilustrados en la figura. 75.

Contructos CAR CD22 también se ensayaron para la capacidad de promover la secreción de IFN-gamma y IL-2. Brevemente, las células T primarias transducidas de donantes sanos que expresan los diversos CARs CD22 se co-cultivaron con las células diana CD22-positivo Raji-Luc y Daudi-Luc, así como el control negativo K562-Luc. Las células T y las células diana se cultivaron en una relación efector al objetivo de células (E: T) de 10 a 1. Los sobrenadantes se recogieron después de 20 horas de co-cultivo. La Fig. 73 muestra tres gráficos de barras que indican la producción de IFN-gamma en pg / ml. Co-cultivo con Raji-Luc (panel superior) y Daudi-luc (panel central) líneas de células inducidas secreción de IFN-gamma por hCD22-12, las células T CAR hCD22-53, así como los dos controles positivos y CAR19 M971-HL. En particular, se observaron cantidades más altas cuando se ensayaron las células hCD22-53, y en menor medida, cuando se ensayaron las células hCD22-12. Se observaron resultados similares cuando se probaron NALM6-Luc, Pfeiffer-Luc, y K562-CD22-Luc, y SEM-Luc células (datos no presentados). Se observó la secreción de IFN-gamma Minimal cuando la línea celular de control negativo K562-Luc fue probado (panel inferior).

CD22-12 mostró una actividad comparable a M971 en ensayos de muerte celular y la secreción de citoquinas (Ejemplo 9). Dos scFv, nombrados CD22-64 y CD22-65, fueron producidos por la maduración de afinidad de hCD22-12. Los constructos de CAR en el que estos scFv se ensayaron para la actividad en un ensayo de NFAT como se describe anteriormente. Como se muestra en la figura. 74, tanto CD22-64 y CD22-65 CD22 se unen tan bien o mejor que CD22-12 y CD22-53, lo que lleva a la activación JNL. Las barras de la figura representan, de izquierda a derecha, CD22-Fc longitud completa; CD22-Fc D567; y un único control negativo Fc utilizado para el recubrimiento de las placas. La comprobación de cuatro variantes de CD22-12 sugirió que LCDR3 y HCDR3 contribuyeron a la unión en cierto grado (datos no mostrados), y que HCDR3 pueden tolerar más mutaciones que LCDR3.

EQUIVALENTES

Las divulgaciones de cada una y todas las patentes, solicitudes de patentes, y publicaciones citadas en el presente documento se incorporan en este documento como referencia en su totalidad. Si bien esta invención ha sido divulgada con referencia a aspectos específicos, es evidente que otros aspectos y variaciones de esta invención pueden ser elaborados por otros expertos en la materia sin apartarse del verdadero espíritu y alcance de la invención. Se pretende que las reivindicaciones adjuntas sean interpretadas para incluir todos los aspectos y variaciones equivalentes.

REIVINDICACIONES:

1. Una célula que expresa una molécula de CAR que se une a CD19, por ejemplo, un CAR CD19, para uso en el tratamiento de un sujeto que tiene una enfermedad asociada con la expresión de CD19, y en el que dicho sujeto ha recibido, está recibiendo o está a punto de recibir uno o más inhibidores de células B, en donde el inhibidor de células B comprende un inhibidor de una o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a.

2.Un método de tratamiento de un sujeto que tiene una enfermedad asociada con la expresión de CD19, que comprende administrar al sujeto una cantidad eficaz de una o más células que expresan una molécula de CAR que se une a CD19, por ejemplo, un CAR CD19, en combinación con uno o más inhibidores de células B, en donde el inhibidor de células B comprende un inhibidor de una o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a.

3. Uninhibidor de células B, por ejemplo, un inhibidor de una o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a, para su uso en el tratamiento de un sujeto que es, o se identifica como ser, un no-respondedor, respondedor parcial o reincidente a un inhibidor de CD19, por ejemplo, una terapia CAR CD19.

4. Un método de tratamiento de un paciente que es, o se identifica como ser, un no respondedor, respondedor parcial, o reincidente a un inhibidor de CD19, por ejemplo, una terapia CAR CD19, que comprende administrar al sujeto un inhibidor de células B, por ejemplo, un inhibidor de una o más de CD10, CD20, CD22, CD34, CD123, FLT-3, o ROR1, CD79b, CD179b, o CD79a.

5. La composiciónn para el uso o el método de cualquiera de las reivindicaciones anteriores, en el que el inhibidor de células B comprende un inhibidor de una o más de CD10, CD20, CD22, CD34, CD123, FLT-3, o ROR1.

6. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que el inhibidor de células B comprende un número efectivo de una o más células que expresan una molécula de CAR que se une una o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a.

7. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que la una o más células que expresan una molécula de CAR que se une CD19 se administran simultáneamente con, antes de, o después de los uno o más inhibidores de células B.

8. La composición para usarse o el método de cualquiera de las reivindicaciones precedentes, en donde el sujeto ha recaído o es identificado por recaer después del tratamiento con la una o más células que expresan una molécula de CAR que s eune a CD19, por ejemplo, un CAR CD19.

9. La composición para uso o el método de la reivindicación 11, en el que el sujeto ha recaído o se identifica por tener una recaída basado en uno o más de reaparición de blastos en la sangre, la médula ósea (> 5%), o cualquier sitio extramedular, después de una respuesta completa

en donde el que el sujeto ha recaído o se identifica por tener una recaída basado en la detección de blastos CD19- por encima de un umbral predeterminado, por ejemplo, más de 1%, 2%, 3%, 4%, 5%, o 10% .; o

en donde el que el sujeto ha recaído o se sepa que recayeron sobre la base de un aumento en los niveles de ARN de una o más de MIR199A1, MIR1203, uc021ovp, ITM2C, o HLA-DQB1; o

en donde el sujeto ha recaído o se sepa que recayeron sobre la base de una disminución en los niveles de ARN de una o más de PPIAL4D, TTTY10, TXLNG2P, MIR4650-1, KDM5D, USP9Y, PRKY, RPS4Y2, RPS4Y1, NCRNA00185, SULT1E1, y EIF1AY .

10. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, que comprende además la realización de lymphodepletion sobre ese tema, por ejemplo, antes de la administración de las una o más células que expresan una molécula de CAR que se une CD19 en

donde, la linfodepleción comprende opcionalmente la administración de uno o más de melfalán, Cytoxan, ciclofosfamida y fludarabina.

11. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que el inhibidor de células B comprende un número efectivo de una o más células que expresan: una molécula de CAR que se une CD10, por ejemplo, como se describe en el presente documento; una molécula de CAR que se une a CD20, por ejemplo, como se describe en el presente documento; una molécula de CAR que se une a CD22, por ejemplo, como se describe en el presente documento; una molécula de CAR que se une CD34, por ejemplo, como se describe en el presente documento; una molécula de CAR que se une CD123, por ejemplo, como se describe en el presente documento; una molécula de CAR que se une FLT-3, por ejemplo, como se describe en el presente documento; o una molécula de CAR que se une ROR1, por ejemplo, como se describe en el presente documento.

12. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que el CAR CD19 comprende un anticuerpo o fragmento de anticuerpo que incluye un dominio de CD19 de unión, un dominio transmembrana, y un dominio de señalización intracelular que comprende un dominio de estimulación, y en el que dicha unión CD19 dominio comprende uno o más de (por ejemplo, los tres) de la cadena ligera complementaria para determinar la región 1 (LC CDR1), la cadena ligera complementaria región determinante de 2 (LC CDR2), y la cadena ligera complementaria región determinante de 3 (LC CDR3) de cualquier scFv CD19 o la cadena ligera de secuencia de unión de aminoácidos del dominio enumerado en las Tablas 2 o 3, y uno o más de (por ejemplo, los tres) de la cadena pesada determinante de la complementariedad región 1 (HC CDR1), de la cadena pesada complementaria región determinante de 2 (HC CDR2), y cadena pesada de región complementaria determinar 3 (HC CDR3) de cualquier scFv CD19 o cadena pesada de secuencia de aminoácidos dominio de unión enumerados en las Tablas 2 o 3.

13. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que un CAR CD19 comprende una región variable de cadena ligera de un scFv enumerados en las Tablas 2 o 3 y cualquier región variable de la cadena pesada de un scFv que figuran las Tablas 2 o 3.

14. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que el CAR CD19 comprende un dominio de unión a CD19 que comprende una secuencia seleccionada de un grupo que consiste en SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3 , SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11 y SEQ ID NO: 12, o una secuencia con 95 a 99% de identidad de la misma, o un polipéptido de SEQ ID NO: 58.

15. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que el inhibidor de células B comprende un CAR CD20 que comprende un anticuerpo o fragmento de anticuerpo que incluye un dominio de CD20 de unión, un dominio transmembrana, y un dominio de señalización intracelular que comprende un dominio estimulante y en el que dicho dominio de unión a CD20 comprende una o más de la cadena ligera determinante de la complementariedad región 1 (LC CDR1), la cadena ligera complementaria región determinante de 2 (LC CDR2), y la cadena ligera complementaria región determinante de 3 (LC CDR3) de cualquier cadena ligera CD20 secuencia de aminoácidos del dominio de unión a la lista en la Tabla 13, y uno o más de la cadena pesada de determinante de la complementariedad región 1 (HC CDR1), de la cadena pesada complementaria región determinante de 2 (HC CDR2), y la cadena pesada complementaria región determinante de 3 (HC CDR3) de cualquier secuencia de aminoácidos dominio de unión a la cadena pesada de CD20 aparece en la Tabla 12A o 12B.

16. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que el inhibidor de células B comprende un CAR CD22 que comprende un anticuerpo o fragmento de anticuerpo que incluye un dominio de unión a CD22, un dominio transmembrana, y un dominio de señalización intracelular que comprende un estimulador dominio, y en donde dicho dominio de unión a CD22 comprende una o más de la cadena ligera determinante de la complementariedad región 1 (LC CDR1), la cadena ligera complementaria región determinante de 2 (LC CDR2), y la cadena ligera complementaria región determinante de 3 (LC CDR3) de cualquier luz CD22 secuencia de cadena dominio de unión de aminoácidos enumerados en la Tabla 8A o 8B y una o más de la cadena pesada de determinante de la complementariedad región

1 (HC CDR1), de la cadena pesada complementaria región determinante de 2 (HC CDR2), y la cadena pesada región determinante de complementariedad 3 (HC CDR3) de cualquier secuencia de aminoácidos dominio de unión a la cadena pesada de CD22 enumerados en la Tabla 7A, 7B o 7C.

17. La composición para uso o el método de la reivindicación 16, en el que el CAR CD22 comprende una región variable de cadena ligera que figuran en la Tabla 10A o 10B, cualquier región variable de cadena pesada que figuran en la Tabla 9A o 9B, o cualquier región variable de cadena ligera que figuran en la Tabla 10A o 10B y cualquier cadena pesada de la región variable que aparece 9.9A tabla o 9B.

18. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que el inhibidor de células B comprende un CAR CD123 que comprende un anticuerpo o fragmento de anticuerpo que incluye un dominio de unión a CD123, un dominio transmembrana, y un dominio de señalización intracelular que comprende un estimulador dominio, y en donde dicho dominio de unión a CD123 comprende uno o más de la cadena ligera determinante de la complementariedad región 1 (LC CDR1), la cadena ligera complementaria región determinante de 2 (LC CDR2), y la cadena ligera complementaria región determinante de 3 (LC CDR3) de cualquier luz CD123 secuencia de aminoácidos del dominio de unión de cadena enumeran en la Tabla 18, y uno o más de la cadena pesada de determinante de la complementariedad región 1 (HC CDR1), de la cadena pesada complementaria región determinante de 2 (HC CDR2), y la cadena pesada región determinante de complementariedad 3 (HC CDR3) de cualquier secuencia de aminoácidos dominio de unión a la cadena pesada de CD123 enumeran en la Tabla 17.

19. La composición para uso o el método de la reivindicación18, en el que el CAR CD123 comprende cualquier región variable de cadena ligera que figuran en la Tabla 16, cualquier región variable de cadena pesada que figuran en la Tabla 16, o cualquier región variable de cadena ligera que figuran en la Tabla 16 y cualquier región variable de cadena pesada Tabla 16.

20. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que el inhibidor de células B comprende un CAR CD123 que comprende un anticuerpo o fragmento de anticuerpo que incluye un dominio de unión a CD123, un dominio transmembrana, y un dominio de señalización intracelular que comprende un estimulador dominio, y en donde dicho dominio de unión a CD123 comprende uno o más de la cadena ligera determinante de la complementariedad región 1 (LC CDR1), la cadena ligera complementaria región determinante de 2 (LC CDR2), y la cadena ligera complementaria región determinante de 3 (LC CDR3) de cualquier luz CD123 secuencia de aminoácidos dominio de unión a la cadena de lista en la Tabla 27, y uno o más de región determinante de la complementariedad de la cadena pesada 3 determinante de la complementariedad región 1 (HC CDR1), de la cadena pesada complementaria región determinante de 2 (HC CDR2), y la cadena pesada (HC CDR3) de cualquier secuencia de aminoácidos dominio de unión a la cadena pesada de CD123 enumerados en la Tabla 26.

21. La composición para uso o el método de la reivindicación 20, en el que el CAR CD123 comprende cualquier región variable de cadena ligera que figuran en la Tabla 25, cualquier región variable de cadena pesada que figuran en la Tabla 25, o cualquier región variable de cadena ligera que figure en la tabla 25 y cualquier región variable de cadena pesada que figure en la Tabla 25.

22. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que el inhibidor de células B comprende un CAR que comprende un anticuerpo o fragmento de anticuerpo que incluye un dominio de unión a antígeno, un dominio transmembrana, y un dominio de señalización intracelular que comprende un dominio estimulante y en el que dicho antígeno de dominio de unión comprende uno o más de (por ejemplo, todos) de la región determinante de la complementariedad de la cadena ligera 1 (LC CDR1), la región determinante de la complementariedad de la cadena ligera 2 (LC CDR2), y la región determinante de la complementariedad de la cadena ligera 3 (LC CDR3), y uno o más de (por ejemplo, todos) la región determinante de la complementariedad de la cadena pesada 1 (HC CDR1), la región determinante de la complementariedad de la cadena pesada 2 (HC CDR2), y la región determinante de la complementariedad de la cadena pesada 3 (HC CDR3).

23. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que el inhibidor de células B comprende un CAR que comprende un scFv.

24. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que el inhibidor de células B comprende un CAR que comprende un dominio transmembrana que comprende un dominio de transmembrana de una proteína seleccionada del grupo que consiste en la cadena alfa, beta o zeta de el receptor de células T, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137 y CD154.

25. La composición para uso o el método de la reivindicación 22, en el que el dominio de unión a antígeno está conectado al dominio transmembrana por un region.40 bisagra. En donde opcionalmente, la región bisagra comprende la SEQ ID NO: 14, o una secuencia con 95 a 99% de identidad de la misma.

26. La composición para uso o el método de la reivindicación 22, en el que el dominio coestimuladora es un dominio de señalización funcional obtenido a partir de una proteína seleccionada del grupo que consiste de OX40, CD2, CD27, CD28, CDS, ICAM-1, LFA-1 (CD11a / CD18), ICOS (CD278), y el 4-1BB (CD137). en donde opcionalmente el dominio coestimulador comprende una secuencia de SEQ ID NO: 16 o SEQ ID NO: 51.

27. La composición para uso o el método de la reivindicación 22, en donde el dominio de señalización intracelular comprende un dominio de señalización funcional de el 4-1BB y / o un dominio de señalización funcional de CD3 zeta. ; o

en donde el dominio de señalización intracelular comprende la secuencia de SEQ ID NO: 16 y / o la secuencia de SEQ ID NO: 17 o SEQ ID NO: 43.

28. La composición para uso o el método de la reivindicación 36,22, en el que el CAR comprende además una secuencia líder. En el que, opcionalmente, la secuencia líder comprende la SEQ ID NO: 13.

29. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que las células comprenden células T o células NK.

30. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que la enfermedad asociada con la expresión de CD19 se selecciona de una enfermedad proliferativa, tal como un cáncer, tumor, o cáncer o una condición precancerosa tal como una mielodisplasia, un síndrome mielodisplásico o una pre-leucemia, o es una indicación no relacionados con el cáncer asociado con la expresión de CD 19, o en donde la enfermedad es uno o más de un cáncer hematológico, leucemia aguda, las células B leucemia linfoide aguda (BOLA), T-cell leucemia linfoide aguda (ALTO), leucemia linfocítica pequeña (SLL), leucemia linfoide aguda (LLA); leucemia crónica, leucemia mielógena crónica (CML), leucemia linfocítica crónica (CLL), linfoma no Hodgkin, o mieloma. ; o en donde la enfermedad es un cáncer de CD19-negativo, por ejemplo, un cáncer recidivante CD19-negativo.

31. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, que comprende además la administración de:

un agente que aumenta la eficacia de una célula que expresa una molécula de CAR., o

un agente que mejora uno o más efectos secundarios asociados con la administración de una célula que expresa una molécula de CAR., o

un agente que trata la enfermedad asociada con CD19; o

un inhibidor de punto de control.

32. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que el sujeto recibe un tratamiento previo de, tratamiento concurrente, o tratamiento de terapia de post-CAR con un agente, por ejemplo, un inhibidor de punto de control, antes de la iniciación

de un CAR terapia.

33. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que el paciente comprende una célula de cáncer CD19-negativa, y una célula de cáncer que es positiva para uno o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a.

34. La composición para uso o el método de la reivindicación 57, cualquiera de las reivindicaciones precedentes, que además comprende administrar al paciente un inhibidor de una o más de los CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a para el que la célula de cáncer es positivo.

35. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, que comprende además una etapa de determinar si el paciente comprende una célula de cáncer CD19-negativo o si el paciente comprende una célula de cáncer que es positiva para uno o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a.

36. Una composición que comprende, por separado o mezclados:

(I) una o más células que expresan una molécula de CAR que se une CD19, por ejemplo, una molécula de CAR que se une CD19 descrito en el presente documento, por ejemplo, un CAR de CD19, y

(Ii) uno o más inhibidores de células B seleccionado entre los inhibidores de una o más de CD10, CD20, CD22, CD34, CD123, FLT-3, o ROR1.

37. Una composición que comprende:

(I) un primer ácido nucleico que codifica una molécula de CAR que se une CD19, por ejemplo, una molécula de CAR que se une CD19 descrito en el presente documento, por ejemplo, un CAR de CD19, y

(Ii) un segundo ácido nucleico que codifica una molécula de CAR que se une a un antígeno de células B seleccionado de entre uno o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a, en el que la primera ácido nucleico y segundo ácido nucleico están en la misma o una molécula de ácido nucleico separada.

38. Una composición que comprende una o más células efectoras inmunes y:

(I) una primera codificación de ácido nucleico, o un polipéptido que comprende primera, una molécula de CAR que se une CD19, por ejemplo, una molécula de CAR que se une CD19 descrito en el presente documento, por ejemplo, un CAR de CD19, y

(Ii) una segunda codificación de ácido nucleico, o un segundo polipéptido que comprende, una molécula de CAR que se une a un antígeno de células B seleccionado de entre uno o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b o CD79a.

39. La composición de la reivindicación 38, en el que:

el primer ácido nucleico o polipéptido primero y el segundo ácido nucleico o segundo polipéptido están cada uno contenidos dentro de, por ejemplo, expresada por, una primera célula efectora inmune .;

la composición comprende una primera célula efectora inmune que contiene, por ejemplo, expresando el primer ácido nucleico o polipéptido primera y una segunda célula efectora inmune que contiene, por ejemplo, expresando el segundo ácido nucleico o segundo polipéptido .;

la composición no comprende una célula que contiene, por ejemplo, que expresan tanto de la primera de ácido nucleico o polipéptido primero y el segundo ácido nucleico o segundo polipéptido.

40. Una célula que comprende una composición de ácido nucleico de la reivindicación 37, en el que la célula es una célula T, opcionalmente humana una célula T CD8 +, o una célula NK.

41. Una célula de la reivindicación 40, expresando además una molécula inhibidora que

comprende un primer polipéptido que comprende al menos una porción de una molécula inhibidora, asociado con un segundo polipéptido que comprende una señal positiva a partir de un dominio de señalización intracelular, en el que opcionalmente la molécula inhibidora comprenden primero polipéptido que comprende al menos una parte de PD1 y un segundo polipéptido que comprende un dominio coestimulador y dominio primario de señalización.

42. Un método de fabricación de una célula, que comprende introducir una composición de ácido nucleico de la reivindicación 37 en una célula T o célula NK, por ejemplo, la transducción de una célula T o célula NK con un vector de cualquiera de las reivindicaciones 94-100., en el que el método de la reivindicación 108, comprende opcionalmente:

el ensayo de una firma genética que indica si un sujeto tratado con la célula es probable que la recaída, o ha recaído;

ensayo de la firma gen en la célula antes de la infusión en el tema .; o

disminuir la firma de T_{REG} de una población de células que comprend ela célula transducida, en donde la disminución d ela firma de T_{REG} comprende opcionalmente llevar a cabo una depleción de CD25 sobr el apoblación de células.

43. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, en el que el inhibidor de CD19 comprende un CAR CD19 y el inhibidor de células B comprende un CAR CD123, en donde, opcionalmente el CAR CD19 o CAR CD123 comprende un dominio de señalización intracelular de división de tal manera que la activación total de la célula, por ejemplo, la población de células efectoras inmunes, se produce cuando tanto el CD19 CAR y CD123 se unen CAR a una célula diana, por ejemplo, una célula CD19 + CD123 + de destino (por ejemplo, a-ALL de células B bLAST), en comparación con la activación cuando el CAR se unen CD19 CAR y CD123 a una célula diana que expresa una de CD19 o CD123 (por ejemplo, una de células madre hematopoyéticas).

44. La composición para uso o el método de cualquiera de las reivindicaciones anteriores, que comprende además el trasplante de una célula, por ejemplo, una célula madre hematopoyética, o una médula ósea, en el mamífero.

45. Un método de tratamiento de un sujeto que tiene DLBCL, por ejemplo DLBCL primaria, que comprende administrar al sujeto una cantidad eficaz de una o más células que expresan una molécula de CAR que se une a CD19, por ejemplo, un CAR de CD19, en combinación con un inhibidor de PD1, en el que opcionalmente el sujeto tiene, o se identifica por tener, al menos 5%, 6%, 7%, 8%, 9%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, o 90% de las células DLBCL que son CD3 + / PD1 +.

46. Un método de tratamiento de un sujeto que tiene DLBCL, por ejemplo DLBCL primaria, que comprende administrar al sujeto una cantidad eficaz de una o más células que expresan una molécula de CAR que se une a CD19, por ejemplo, un CAR CD19, en el que opcionalmente el sujeto tiene, o se identifica por tener, al menos 5%, 6% , 7%, 8%, 9%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, o 90% de las células DLBCL que son CD3 + / PD1+.

47. Un método de tratamiento de un sujeto que tiene DLBCL, que comprende administrar al sujeto una cantidad eficaz de una o más células que expresan una molécula de CAR que se une CD19, por ejemplo, un CAR de CD19, en combinación con un inhibidor de PD-L1, en el que opcionalmente el tema tiene, o se identifica como que tiene, a menos de 20%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, o 1% de las células en el cáncer, por ejemplo, el microambiente del cáncer, es doble positivo para CD19 y PD-L1.

48. Una molécula aislada de ácido nucleico que codifica un receptor quimérico de antígeno (CAR), en el que el CAR comprende un anticuerpo o fragmento de anticuerpo que incluye un dominio de unión a CD20, un dominio transmembrana, y un dominio de señalización intracelular y en donde el dominio de unión a dicha CD20 comprende una o más de la región 1 determinante de la complementariedad de la cadena ligera (LC CDR1), región 2 determinante de la complementariedad de la cadena ligera (LC CDR2), y región 3 determinante de la complementariedad de la cadena ligera (LC CDR3) de cualquier secuencia de aminoácidos del dominio de cadena ligera de CD20 que aparece en la Tabla 13, 15A, o 15B, y una o más de la región 1 determinante de la complementariedad de la cadena pesada (HC CDR1), región 2 determinante de la complementariedad de la cadena pesada (HC CDR2), y región 3 determinante

de la complementariedad de la cadena pesada (HC CDR3) de cualquier secuencia de aminoácidos del dominio de cadena ligera de CD20 que aparece en la Tabla 12A, 12B, 14A, o 14B.

49. Una molécula de CAR aislado que comprende un dominio de unión a CD20, un dominio transmembrana, y un dominio de señalización intracelular, en el que el dominio de unión a CD20 comprende una o más de una o más de la región 1 determinante de la complementariedad de la cadena ligera (LC CDR1), región 2 determinante de la complementariedad de la cadena ligera (LC CDR2), y región 3 determinante de la complementariedad de la cadena ligera (LC CDR3) de cualquier secuencia de aminoácidos del dominio de cadena ligera de CD20 que aparece en la Tabla 13, 15A, o 15B, y una o más de la región 1 determinante de la complementariedad de la cadena pesada (HC CDR1), región 2 determinante de la complementariedad de la cadena pesada (HC CDR2), y región 3 determinante de la complementariedad de la cadena pesada (HC CDR3) de cualquier secuencia de aminoácidos del dominio de cadena ligera de CD20 que aparece en la Tabla 12A, 12B, 14A, o 14B.

50. Un método de tratamiento de un mamífero que tiene una enfermedad asociada con la expresión de CD20, que comprende administrar al mamífero una cantidad efectiva de la célula que comprende una molécula de CAR de la reivindicación 49.

51. Una molécula aislada de ácido nucleico que codifica un receptor de antígeno quimérico (CAR), en el que el CAR comprende un anticuerpo o fragmento de anticuerpo que incluye un dominio de unión a CD22, un dominio transmembrana, y un dominio de señalización intracelular y el dominio en el que dicha unión a CD22 comprende una o más de la región 1 determinante de la complementariedad de la cadena ligera (LC CDR1), región 2 determinante de la complementariedad de la cadena ligera (LC CDR2), y región 3 determinante de la complementariedad de la cadena ligera (LC CDR3) de cualquier secuencia de aminoácidos del dominio de cadena ligera de CD20 que aparece en la Tabla 8A, 8B, 10A, o 10B, y una o más de la región 1 determinante de la complementariedad de la cadena pesada (HC CDR1), región 2 determinante de la complementariedad de la cadena pesada (HC CDR2), y región 3 determinante

de la complementariedad de la cadena pesada (HC CDR3) de cualquier secuencia de aminoácidos del dominio de cadena ligera de CD20 que aparece en la Tabla 7A, 7B, 7C, 9A o 9B.

52. Una molécula aislada de CAR que comprende un dominio de unión a CD22, un dominio transmembrana, y un dominio de señalización intracelular, en el que el dominio de unión a CD22 comprende una o más de región 1 determinante de la complementariedad de la cadena ligera (LC CDR1), región 2 determinante de la complementariedad de la cadena ligera (LC CDR2), y región 3 determinante de la complementariedad de la cadena ligera (LC CDR3) de cualquier secuencia de aminoácidos del dominio de cadena ligera de CD20 que aparece en la Tabla 8A, 8B, 10A, o 10B, y una o más de la región 1 determinante de la complementariedad de la cadena pesada (HC CDR1), región 2 determinante de la complementariedad de la cadena pesada (HC CDR2), y región 3 determinante de la complementariedad de la cadena pesada (HC CDR3) de cualquier secuencia de aminoácidos del dominio de cadena ligera de CD20 que aparece en la Tabla 7A, 7B, 7C, 9A o 9B.

53. Un método de tratamiento de un mamífero que tiene una enfermedad asociada con la expresión de CD22, que comprende administrar al mamífero una cantidad efectiva de la célula que comprende una molécula de CAR de la reivindicación 52.

RESUMEN

La invención proporciona composiciones y métodos para tratar enfermedades asociadas con la expresión de CD19, por ejemplo, mediante la administración de una célula T recombinante que comprende el CAR de CD19 tal como se describe en el presente documento, en combinación con uno o más inhibidores de células B, por ejemplo, inhibidores de una o más de CD10, CD20, CD22, CD34, CD123, FLT-3, ROR1, CD79b, CD179b, o CD79a. La invención también proporciona dominios de unión a antígeno novedosos y moléculas de CAR que se dirigen a CD20 y CD22 y usos, por ejemplo como monoterapia o en terapia de combinación.

La invención también proporciona kits y composiciones descritas en el presente documento.