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.
UTFD P3178WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2018/012558	5 January 2018 (05-01-2018)	5 January 2017 (05-01-2017)
Applicant		
THE BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS		

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.

[X] 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:
      [X] 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. [X] 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. [X] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] 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,**
   [X] 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. 9A,9B
      [ ] as suggested by the applicant
      [X] 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/US2018/012558

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

      [X] 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).

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/US2018/012558

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.:

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/US2018/012558

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/113 C12N15/864 C12N9/22
ADD.

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)
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, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/025469 A1 (UNIV TEXAS [US]) 18 February 2016 (2016-02-18)	152
A	page 49, paragraph 2 - page 55, last line; figures 13,17B,23,24	1-86, 96-151, 153-186

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[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
14 May 2018	24/05/2018

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	Wiame, Ilse

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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	WO 2014/197748 A2 (UNIV DUKE [US]) 11 December 2014 (2014-12-11)	1-3,5-8, 10-13, 15-18, 20-36, 39-54, 56-78, 80-86, 96-140
Y	paragraph [0182] - paragraph [0192]; figure 39 paragraph [0160] - paragraph [0167]; figure 16 figure 20; examples 4-13	141-186

X	NICLAS E. BENGTSSON ET AL: "Progress and prospects of gene therapy clinical trials for the muscular dystrophies", HUMAN MOLECULAR GENETICS, vol. 25, no. R1, 8 October 2015 (2015-10-08), pages R9-R17, XP055460661, gb ISSN: 0964-6906, DOI: 10.1093/hmg/ddv420	87,88, 90,91, 106, 109-113, 120,121, 123, 133-136, 138,140
Y	page R13, left-hand column, last paragraph - right-hand column, paragraph 1; figure 2	89, 141-186

X	YUDA WEI ET AL: "Prevention of Muscle Wasting by CRISPR/Cas9-mediated Disruption of Myostatin In Vivo", MOLECULAR THERAPY : THE JOURNAL OF THE AMERICAN SOCIETY OF GENE THERAPY, vol. 24, no. 11, 1 November 2016 (2016-11-01), pages 1889-1891, XP055460686, US ISSN: 1525-0016, DOI: 10.1038/mt.2016.192 page 1890, column 2, line 4 - line 17; figure 1a	87,88, 90,91, 96-102, 106, 109-113, 120,121, 123-129, 133-136, 138,140

X,P	LEONELA AMOASII ET AL: "Single-cut genome editing restores dystrophin expression in a new mouse model of muscular dystrophy", SCIENCE TRANSLATIONAL MEDICINE, vol. 9, no. 418, 29 November 2017 (2017-11-29), page eaan8081, XP055452628, US ISSN: 1946-6234, DOI: 10.1126/scitranslmed.aan8081 the whole document	1-186

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/174056 A1 (GENETHON [FR]; INSERM [FR]; UNIV D'EVRY VAL D'ESSONNE [FR]) 3 November 2016 (2016-11-03) page 21, paragraph 1; figure 1A page 24, line 14 - line 33 -----	87, 90-95, 106-113, 120,121, 123-129, 133-138, 140
Y	WO 2016/115543 A2 (UNIV WASHINGTON [US]) 21 July 2016 (2016-07-21) sequence 19 -----	89
X,P	WO 2017/095967 A2 (UNIV DUKE [US]; GERSBACH CHARLES A [US]; ROBINSON-HAMM JACQUELINE N [U) 8 June 2017 (2017-06-08) paragraphs [0189] - [0191]; claims 21-22 -----	87-91
X,P	US 2017/362635 A1 (CHAMBERLAIN JEFFREY S [US] ET AL) 21 December 2017 (2017-12-21) paragraph [0054] - paragraph [0068]; sequence 159 -----	87-91

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/012558

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016025469 A1	18-02-2016	CA 2959130 A1	18-02-2016
		CN 106714845 A	24-05-2017
		EP 3180034 A1	21-06-2017
		JP 2017525696 A	07-09-2017
		US 2016058889 A1	03-03-2016
		WO 2016025469 A1	18-02-2016
WO 2014197748 A2	11-12-2014	AU 2014274840 A1	21-01-2016
		CA 2914519 A1	11-12-2014
		CN 105658805 A	08-06-2016
		EP 3004370 A2	13-04-2016
		JP 2016521555 A	25-07-2016
		KR 20160023765 A	03-03-2016
		US 2016201089 A1	14-07-2016
		WO 2014197748 A2	11-12-2014
WO 2016174056 A1	03-11-2016	CA 2983364 A1	03-11-2016
		EP 3289081 A1	07-03-2018
		US 2018100144 A1	12-04-2018
		WO 2016174056 A1	03-11-2016
WO 2016115543 A2	21-07-2016	AU 2016206518 A1	10-08-2017
		CA 2972811 A1	21-07-2016
		CN 107250364 A	13-10-2017
		EP 3245291 A2	22-11-2017
		JP 2018503374 A	08-02-2018
		KR 20170107481 A	25-09-2017
		SG 11201705324U A	28-07-2017
		WO 2016115543 A2	21-07-2016
WO 2017095967 A2	08-06-2017	CA 3001623 A1	08-06-2017
		WO 2017095967 A2	08-06-2017
US 2017362635 A1	21-12-2017	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-86, 102, 141-186(completely); 96-101, 103-140(partially)

A nucleic acid comprising:
a sequence encoding a first DMD guide RNA targeting a first genomic target sequence,
a sequence encoding a second DMD guide RNA targeting a second genomic target sequence,
a sequence encoding a first promoter, wherein the first promoter drives expression of the sequence encoding the first DMD guide RNA, and
a sequence encoding a second promoter, wherein the second promoter drives expression of the sequence encoding the second DMD guide RNA,
wherein the first genomic target sequence and the second genomic target sequence each comprise a dystrophin splice acceptor site;
and related embodiments.

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2. claims: 87-95(completely); 96-101, 103-140(partially)

A nucleic acid comprising a sequence encoding a promoter and a sequence encoding a Cas9 protein or a nuclease domain thereof, wherein the sequence encoding the promoter comprises a sequence encoding a muscle-specific promoter;
and related embodiments.

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/US2018/012558	05.01.2018	05.01.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C12N15/113 C12N15/864 C12N9/22

Applicant
THE BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS

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 P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Wiame, Ilse Telephone No. +31 70 340-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2018/012558

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. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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.

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	1-86, 89, 103-105, 114-119, 122, 130-132, 139, 141-151, 153-186
	No:	Claims	87, 88, 90-102, 106-113, 120, 121, 123-129, 133-138, 140, 152
Inventive step (IS)	Yes:	Claims	4, 9, 14, 19, 37, 38, 55, 79
	No:	Claims	1-3, 5-8, 10-13, 15-18, 20-36, 39-54, 56-78, 80-186
Industrial applicability (IA)	Yes:	Claims	1-186
	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 2014/197748 A2 (UNIV DUKE [US]) 11 December 2014 (2014-12-11)

D2 WO 2016/025469 A1 (UNIV TEXAS [US]) 18 February 2016 (2016-02-18)

D3 NICLAS E. BENGTSSON ET AL: "Progress and prospects of gene therapy clinical trials for the muscular dystrophies",
HUMAN MOLECULAR GENETICS,
vol. 25, no. R1, 8 October 2015 (2015-10-08), pages R9-R17, XP055460661,
gb
ISSN: 0964-6906, DOI: 10.1093/hmg/ddv420

D4 YUDA WEI ET AL: "Prevention of Muscle Wasting by CRISPR/Cas9-mediated Disruption of Myostatin In Vivo",
MOLECULAR THERAPY : THE JOURNAL OF THE AMERICAN SOCIETY OF GENE THERAPY,
vol. 24, no. 11, 1 November 2016 (2016-11-01), pages 1889-1891, XP055460686,
US
ISSN: 1525-0016, DOI: 10.1038/mt.2016.192

D5 LEONELA AMOASII ET AL: "Single-cut genome editing restores dystrophin expression in a new mouse model of muscular dystrophy",
SCIENCE TRANSLATIONAL MEDICINE,
vol. 9, no. 418, 29 November 2017 (2017-11-29), page eaan8081, XP055452628,
US
ISSN: 1946-6234, DOI: 10.1126/scitranslmed.aan8081

D6 WO 2016/174056 A1 (GENETHON [FR]; INSERM [FR]; UNIV D'EVRY VAL D'ESSONNE [FR]) 3 November 2016 (2016-11-03)

D7 WO 2016/115543 A2 (UNIV WASHINGTON [US]) 21 July 2016 (2016-07-21)

D8 WO 2017/095967 A2 (UNIV DUKE [US]; GERSBACH CHARLES A [US]; ROBINSON-HAMM JACQUELINE N [U) 8 June 2017 (2017-06-08)

D9 US 2017/362635 A1 (CHAMBERLAIN JEFFREY S [US] ET AL) 21 December 2017 (2017-12-21)

Re Item IV

Lack of unity of invention

1 This Authority considers that there are two inventions covered by the claims indicated as follows:

1. claims: 1-86, 102, 141-186(completely); 96-101, 103-140(partially)

   A nucleic acid comprising:

   a sequence encoding a first DMD guide RNA targeting a first genomic target sequence,

   a sequence encoding a second DMD guide RNA targeting a second genomic target sequence,

   a sequence encoding a first promoter, wherein the first promoter drives expression of the sequence encoding the first DMD guide RNA, and

   a sequence encoding a second promoter, wherein the second promoter drives expression of the sequence encoding the second DMD guide RNA,

   wherein the first genomic target sequence and the second genomic target sequence each comprise a dystrophin splice acceptor site;

   and related embodiments.

2. claims: 87-95(completely); 96-101, 103-140(partially)

   A nucleic acid comprising a sequence encoding a promoter and a sequence encoding a Cas9 protein or a nuclease domain thereof, wherein the sequence encoding the promoter comprises a sequence encoding a muscle-specific promoter; and related embodiments.

2 The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

2.1 The prior art has been identified as documents D3 and D4:

Document D3 discloses (Fig. 2 and p. R13, par. spanning col. 1-2):

- a nucleic acid comprising a sequence encoding the muscle-specific promoter CK8 and a sequence encoding a Cas9 protein;

- a nucleic acid comprising a sequence encoding a first DMD guide RNA under the control of a first promoter and a sequence encoding a second DMD guide RNA under the control of a second promoter, wherein the first guide RNA and the second guide RNA target a genomic target sequence in a dystrophin gene; and

use thereof for correcting a dystrophin defect.

Document D4 discloses (Fig. 1a and p. 1890, col. 2, l. 4-17) a nucleic acid comprising a sequence encoding the muscle-specific promoter dMCK and a sequence encoding a Cas9 protein.

2.2 In view of the prior art above the problem to be solved by the present application can be considered as the (i) the provision of a further nucleic acid comprising a sequence encoding a first DMD guide RNA under the control of a first promoter and a sequence encoding a second DMD guide RNA under the control of a second promoter, wherein the first guide RNA and the second guide RNA target a genomic target sequence in a dystrophin gene, and (ii) the provision of a further nucleic acid comprising a sequence encoding the muscle-specific promoter and a sequence encoding a Cas9 protein.

2.3 The present application provides two different solutions to said problem, as listed above.

2.4 The common concept linking together the subject-matter of the claims is a nucleic acid encoding a component of a CRISPR gene editing tool useful for correcting a defect in a muscle cell.

This common concept is not novel, see documents D3 and D4 as described above.

2.5 Moreover, no technical feature could be identified which can be considered a special technical feature in the meaning of Rule 13.2 PCT.

2.6 Consequently, neither the objective problem underlying the subjects of the claimed inventions, nor their solutions defined by the special technical features allow for a relationship to be established between the said inventions, which involves a single general inventive concept.

2.7 In conclusion, the groups of claims are not linked by common or corresponding special technical features and define two different inventions not linked by a single general inventive concept. The application, hence does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

Re Item V

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

3 Claims 145 to 151 and 153 to 185 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Patentability, in particular novelty and inventive step, of claim 186 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the composition.

4 The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of claims 87, 88, 90-102, 106-113, 120, 121, 123-129, 133-138, 140 and 152 is not new.

4.1 Document D1 discloses (p. 52, l. 5 to p. 55, line 12) a cell produced by contacting a cell with a nucleic acid encoding a DMD guide RNA targeting a dystrophin splice acceptor site and a nucleic acid encoding Cas9 nuclease under the control of a promoter, wherein a DMD guide RNA-Cas 9 complex disrupts a dystrophin splice site and induces selective skipping of a DMD exon and/or reframing of a dystrophin reading frame, whereby a dystrophin defect is corrected.

Claim 152 is a product-by-process claim, which is directed to the product per se, irrespective of the method by which it is obtained. Since the cell of D1 cannot be distinguished from a cell obtained by the method of any of claim 145-151, the subject-matter of claim 152 is not new.

4.2 Document D3 discloses (Fig. 2A and p. R13, par. spanning col. 1-2) a recombinant AAV vector comprising a sequence encoding the muscle-specific promoter CK8 and a sequence encoding a Streptococcus pyogenes Cas9 protein and nuclear localization signals, wherein the vector is used for direct injection into mouse skeletal muscle.

The subject-matter of claims 87, 88, 90, 91, 106, 109-113, 120, 121, 123, 133-136, 138 and 140 is therefore not new.

4.3 Document D4 discloses (Fig. 1a and p. 1890, col. 2, l. 4-17 and col. 3, l. 21-30) a recombinant AAV8 vector comprising a sequence encoding the muscle-specific promoter dMCK and a sequence encoding a Streptococcus aureus Cas9 protein and and a poly A sequence and 5' and 3' inverted terminal repeats and a nuclear localization signal, wherein the vector is used for injection into mouse muscles.

The subject-matter of claims 87, 88, 90, 91, 94-102, 106, 109-113, 120, 121, 123-129, 133-136, 138 and 140 is therefore not new. It is to be noted that the term "derived from" in claims 90-91, 98-102 and 124-129 is broadly interpretable.

4.4 Document D6 discloses (p. 21, par. 1 and Fig. 1A and p. 24, l. 14-33) a recombinant AAV vector comprising a sequence encoding the muscle-specific promoter C5-12 and a sequence encoding a human codon-optimized Cas9 protein from N. meningitidis and and a poly A sequence and nuclear localization signals; and C2C12 muscle cells or human HeLa Cells transfected with said vector.

The subject-matter of claims 87, 90-95, 106-113, 120, 121, 123-129, 133-138 and 140 is therefore not new. It is to be noted that the term "derived from" in claims 90-91 and 124-129 is broadly interpretable.

5 The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of claims 1-3, 5-8, 10-13, 15-18, 20-36, 39-54, 56-78, 80-86, 89 and 96-186 does not involve an inventive step.

5.1 Document D2 is regarded as being the prior art closest to the subject-matter of claim 1, and discloses (fig. 39, "Single vector, multiplex CRISPR system" and par. [182]-[192]) a gRNA expression construct comprising a nucleic acid comprising a sequence encoding a first DMD gRNA under the control of a first

promoter and a sequence encoding a second DMD gRNA under the control of a second promoter, wherein the first gRNA and the second gRNA target a genomic target sequence in a dystrophin gene.

The subject-matter of claim 1 therefore differs from this known gRNA expression construct in that the first and second gRNA each target a genomic target sequence comprising a dystophin splice acceptor site; and is therefore new.

The problem to be solved by the present invention may therefore be regarded as to provide an alternative.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

Document D2 discloses that the gRNA target site may comprise a dystrophin splice acceptor site (par. [162] and [167]). Furthermore, if each gRNA targets a different dystrophin splice acceptor site, this results in a double cut in the genomic DNA, leading to excision of one or more exons, which is also suggested in document D2 (fig. 16). Moreover, the present invention is not directed to a double cut whereby a portion of the genomic DNA is excised, but to a single cut strategy (see also section 7.1 below).

5.2 The features of dependent claims 2, 3, 5-8, 10-13, 15-18, 20-36, 39-54, 56-78, 80-86 and 96-186 do not appear to contribute to inventive step.

5.3 The subject-matter of dependent claims 4, 9, 14, 19, 37, 38, 55 and 79 is neither known from, nor rendered obvious by, the available prior art. The reasons are as follows:

Document D1 is regarded as being the prior art closest to the subject-matter of claim 4, and discloses (p. 49, par. 2 to p. 55, last line and fig. 13, 17B, 23 and 24) a gRNA expression construct comprising a DMD gRNA under the control of a promoter, wherein the gRNA targets a dystrophin splice acceptor site.

The subject-matter of claim 4 therefore differs from this known expression construct in that it comprises a second gRNA under the control of a promoter, wherein the gRNA targets the same dystrophin splice acceptor site as the first gRNA; and is therefore new.

The problem to be solved by the present invention may therefore be regarded as to provide an alternative.

The solution proposed in claim 4 of the present application cannot be considered as involving an inventive step because the skilled person has no motivation to add a second gRNA targeting the same dystrophin splice acceptor site as the first gRNA to the expression construct. Furthermore, a triple gRNA expression construct is shown in the present application to give better results in vivo compared to a single gRNA expression construct (p. 117, par. 2).

The same reasoning applies to claims 9, 14, 19, 37, 38, 55 and 79.

5.4 Document D3, as described above, is regarded as being the prior art closest to the subject-matter of claim 89.

The subject-matter of claim 89 therefore differs from this known nucleic acid in that the muscle specific promoter is CK8e.

The problem to be solved by the present invention may therefore be regarded as to provide an alternative.

The solution proposed in claim 89 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

It is to be noted that the term "CK8e" promoter has no well-defined meaning in the technical field and that therefore claim 89 is not clear (see section 7.4 below). According to the present application the sequence of the CK8e promoter is SEQ ID NO:875 (see p. 96). In the following reasoning, it is therefore assumed that the sequence of the CK8e promoter is SEQ ID NO: 875 of the present application.

Document D7 discloses a muscle specific CK8 promoter (SEQ ID NO:19) which comprises the sequence of SEQ ID NO:875 of the present application. It is not inventive to use the CK8 promoter of document D7 as an alternative to the CK8 promoter in the vector of document D3.

Re Item VI

Certain documents cited

6 The following document are intermediate documents published between the priority date and the filing date of the present application and/or are potentially conflicting patent applications:

6.1 Document D5, which discloses the present invention, was published on 29/11/2017. It is therefore prior art for subject-matter which is not entitled to the priority dates of 05/01/2017 and/or 11/08/2017.

6.2 Document D8, which discloses a nucleic encoding a Cas9 protein and the muscle-specific CK8e promoter, has a filing date of 30/11/2016 and is a potentially conflicting patent application, regardless of the validity of the priority of the present application.

6.3 Document D9, which discloses a nucleic encoding a Cas9 protein and the muscle-specific CK8e promoter, was published on 21/12/2017. It is therefore prior art for subject-matter which is not entitled to the priority dates of 05/01/2017 and/or 11/08/2017.

Re Item VIII

Certain observations on the international application

7 The application does not meet the requirements of Article 6 PCT, as follows:

7.1 It is clear from the description that the invention relates to a single-cut strategy using one gRNA that targets a dystrophin splice acceptor site. The feature of claim 4 is therefore essential to the definition of the invention.

Since independent claim 1 does not contain this feature it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

7.2 It appears that the second nucleic acid in the composition of claim 141 should be a nucleic acid comprising a sequence encoding a muscle-specific promoter and a sequence encoding a Cas9 protein or a nuclease domain thereof (i.e. the subject-matter of claim 87). However, this is not the case for all embodiments of said second nucleic acid because claims 96, 97, 102 and 106 all refer back to claims relating to other subject-matter.

7.3 Claim 91 appears to be an erroneous duplication of part of claim 90.

7.4 The term "CK8e promoter" used in claim 89 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.

7.5 The term "mini polyA sequence" used in claim 95 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.

7.6 Claim 132 erroneously refers to itself (claim 132).

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(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, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, 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.

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— *with international search report (Art. 21(3))*
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(54) Title: OPTIMIZED STRATEGY FOR EXON SKIPPING MODIFICATIONS USING CRISPR/CAS9 WITH TRIPLE GUIDE SEQUENCES



FIGS. 9A-B

(57) Abstract: CRISPR/Cas9-mediated genome editing holds clinical potential for treating genetic diseases, such as Duchenne muscular dystrophy (DMD), which is caused by mutations in the dystrophin gene. Here, using three promoters to drive expression of the same DMD guide RNA, a more robust and safe form of genome editing was achieved in a humanized mouse model for DMD with a deletion in exon 50, and in a ΔEx50-MD Dog.

WO 2018/129296 A1

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35 40 45

```
Arg Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Gln Lys Leu Pro Lys
    50                  55                  60

Glu Lys Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Lys Ala
65                  70                  75                  80

Leu Arg Val Leu Gln Asn Asn Asn Val Asp Leu Val Asn Ile Gly Ser
                85                  90                  95

Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Ile Trp
            100                 105                 110

Asn Ile Ile Leu His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met
        115                 120                 125

Ala Gly Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
    130                 135                 140

Arg Gln Ser Thr Arg Asn Tyr Pro Gln Val Asn Val Ile Asn Phe Thr
145                 150                 155                 160

Thr Ser Trp Ser Asp Gly Leu Ala Leu Asn Ala Leu Ile His Ser His
                165                 170                 175

Arg Pro Asp Leu Phe Asp Trp Asn Ser Val Val Cys Gln Gln Ser Ala
            180                 185                 190

Thr Gln Arg Leu Glu His Ala Phe Asn Ile Ala Arg Tyr Gln Leu Gly
        195                 200                 205

Ile Glu Lys Leu Leu Asp Pro Glu Asp Val Asp Thr Thr Tyr Pro Asp
    210                 215                 220

Lys Lys Ser Ile Leu Met Tyr Ile Thr Ser Leu Phe Gln Val Leu Pro
225                 230                 235                 240

Gln Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg
                245                 250                 255

Pro Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met
            260                 265                 270
```

```
His Tyr Ser Gln Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg
        275                 280                 285

Thr Ser Ser Pro Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala
    290                 295                 300

Ala Tyr Val Thr Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln
305                 310                 315                 320

His Leu Glu Ala Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu
                325                 330                 335

Ser Glu Val Asn Leu Asp Arg Tyr Gln Thr Ala Leu Glu Glu Val Leu
            340                 345                 350

Ser Trp Leu Leu Ser Ala Glu Asp Thr Leu Gln Ala Gln Gly Glu Ile
        355                 360                 365

Ser Asn Asp Val Glu Val Val Lys Asp Gln Phe His Thr His Glu Gly
    370                 375                 380

Tyr Met Met Asp Leu Thr Ala His Gln Gly Arg Val Gly Asn Ile Leu
385                 390                 395                 400

Gln Leu Gly Ser Lys Leu Ile Gly Thr Gly Lys Leu Ser Glu Asp Glu
                405                 410                 415

Glu Thr Glu Val Gln Glu Gln Met Asn Leu Leu Asn Ser Arg Trp Glu
            420                 425                 430

Cys Leu Arg Val Ala Ser Met Glu Lys Gln Ser Asn Leu His Arg Val
        435                 440                 445

Leu Met Asp Leu Gln Asn Gln Lys Leu Lys Glu Leu Asn Asp Trp Leu
    450                 455                 460

Thr Lys Thr Glu Glu Arg Thr Arg Lys Met Glu Glu Glu Pro Leu Gly
465                 470                 475                 480
```

```
Pro Asp Leu Glu Asp Leu Lys Arg Gln Val Gln Gln His Lys Val Leu
                485                 490                 495

Gln Glu Asp Leu Glu Gln Glu Gln Val Arg Val Asn Ser Leu Thr His
            500                 505                 510

Met Val Val Val Val Asp Glu Ser Ser Gly Asp His Ala Thr Ala Ala
        515                 520                 525

Leu Glu Glu Gln Leu Lys Val Leu Gly Asp Arg Trp Ala Asn Ile Cys
    530                 535                 540

Arg Trp Thr Glu Asp Arg Trp Val Leu Leu Gln Asp Ile Leu Leu Lys
545                 550                 555                 560

Trp Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ala Trp Leu Ser
                565                 570                 575

Glu Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp
            580                 585                 590

Gln Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala
        595                 600                 605

Asp Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys
    610                 615                 620

Gln Asp Leu Leu Ser Thr Leu Lys Asn Lys Ser Val Thr Gln Lys Thr
625                 630                 635                 640

Glu Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln
                645                 650                 655

Lys Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr
            660                 665                 670

Gln Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val
        675                 680                 685

Thr Thr Arg Glu Gln Ile Leu Val Lys His Ala Gln Glu Glu Leu Pro
    690                 695                 700
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Arg Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr
                725                 730                 735

Arg Ser Glu Ala Val Leu Gln Ser Pro Glu Phe Ala Ile Phe Arg Lys
            740                 745                 750

Glu Gly Asn Phe Ser Asp Leu Lys Glu Lys Val Asn Ala Ile Glu Arg
        755                 760                 765

Glu Lys Ala Glu Lys Phe Arg Lys Leu Gln Asp Ala Ser Arg Ser Ala
    770                 775                 780

Gln Ala Leu Val Glu Gln Met Val Asn Glu Gly Val Asn Ala Asp Ser
785                 790                 795                 800

Ile Lys Gln Ala Ser Glu Gln Leu Asn Ser Arg Trp Ile Glu Phe Cys
                805                 810                 815

Gln Leu Leu Ser Glu Arg Leu Asn Trp Leu Glu Tyr Gln Asn Asn Ile
            820                 825                 830

Ile Ala Phe Tyr Asn Gln Leu Gln Gln Leu Glu Gln Met Thr Thr Thr
        835                 840                 845

Ala Glu Asn Trp Leu Lys Ile Gln Pro Thr Thr Pro Ser Glu Pro Thr
    850                 855                 860

Ala Ile Lys Ser Gln Leu Lys Ile Cys Lys Asp Glu Val Asn Arg Leu
865                 870                 875                 880

Ser Gly Leu Gln Pro Gln Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala
                885                 890                 895

Leu Lys Glu Lys Gly Gln Gly Pro Met Phe Leu Asp Ala Asp Phe Val
            900                 905                 910
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```
Ala Phe Thr Asn His Phe Lys Gln Val Phe Ser Asp Val Gln Ala Arg
        915                 920                 925

Glu Lys Glu Leu Gln Thr Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr
    930                 935                 940

Gln Glu Thr Met Ser Ala Ile Arg Thr Trp Val Gln Gln Ser Glu Thr
945                 950                 955                 960

Lys Leu Ser Ile Pro Gln Leu Ser Val Thr Asp Tyr Glu Ile Met Glu
                965                 970                 975

Gln Arg Leu Gly Glu Leu Gln Ala Leu Gln Ser Ser Leu Gln Glu Gln
            980                 985                 990

Gln Ser Gly Leu Tyr Tyr Leu Ser  Thr Thr Val Lys Glu  Met Ser Lys
        995                 1000                1005

Lys Ala  Pro Ser Glu Ile Ser  Arg Lys Tyr Gln Ser  Glu Phe Glu
    1010                1015                1020

Glu Ile  Glu Gly Arg Trp Lys  Lys Leu Ser Ser Gln  Leu Val Glu
    1025                1030                1035

His Cys  Gln Lys Leu Glu Glu  Gln Met Asn Lys Leu  Arg Lys Ile
    1040                1045                1050

Gln Asn  His Ile Gln Thr Leu  Lys Lys Trp Met Ala  Glu Val Asp
    1055                1060                1065

Val Phe  Leu Lys Glu Glu Trp  Pro Ala Leu Gly Asp  Ser Glu Ile
    1070                1075                1080

Leu Lys  Lys Gln Leu Lys Gln  Cys Arg Leu Leu Val  Ser Asp Ile
    1085                1090                1095

Gln Thr  Ile Gln Pro Ser Leu  Asn Ser Val Asn Glu  Gly Gly Gln
    1100                1105                1110

Lys Ile  Lys Asn Glu Ala Glu  Pro Glu Phe Ala Ser  Arg Leu Glu
    1115                1120                1125
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```
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    1145                1150                1155

Thr Val  Ser Leu Gln Lys Asp  Leu Ser Glu Met His  Glu Trp Met
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Thr Gln  Ala Glu Glu Glu Tyr  Leu Glu Arg Asp Phe  Glu Tyr Lys
    1175                1180                1185

Thr Pro  Asp Glu Leu Gln Lys  Ala Val Glu Glu Met  Lys Arg Ala
    1190                1195                1200

Lys Glu  Glu Ala Gln Gln Lys  Glu Ala Lys Val Lys  Leu Leu Thr
    1205                1210                1215

Glu Ser  Val Asn Ser Val Ile  Ala Gln Ala Pro Pro  Val Ala Gln
    1220                1225                1230

Glu Ala  Leu Lys Lys Glu Leu  Glu Thr Leu Thr Thr  Asn Tyr Gln
    1235                1240                1245

Trp Leu  Cys Thr Arg Leu Asn  Gly Lys Cys Lys Thr  Leu Glu Glu
    1250                1255                1260

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    1265                1270                1275

Asn Lys  Trp Leu Asn Glu Val  Glu Phe Lys Leu Lys  Thr Thr Glu
    1280                1285                1290

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    1295                1300                1305

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    1340                1345                1350

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Lys His  Asn Gln Gly Lys Glu  Ala Ala Gln Arg Val  Leu Ser Gln
    1430                1435                1440

Ile Asp  Val Ala Gln Lys Lys  Leu Gln Asp Val Ser  Met Lys Phe
    1445                1450                1455

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    1460                1465                1470

Ser Lys  Met Ile Leu Asp Glu  Val Lys Met His Leu  Pro Ala Leu
    1475                1480                1485

Glu Thr  Lys Ser Val Glu Gln  Glu Val Val Gln Ser  Gln Leu Asn
    1490                1495                1500

His Cys  Val Asn Leu Tyr Lys  Ser Leu Ser Glu Val  Lys Ser Glu
    1505                1510                1515

Val Glu  Met Val Ile Lys Thr  Gly Arg Gln Ile Val  Gln Lys Lys
    1520                1525                1530
```

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Lys Leu  His Tyr Asn Glu Leu  Gly Ala Lys Val Thr  Glu Arg Lys
    1550                1555                1560

Gln Gln  Leu Glu Lys Cys Leu  Lys Leu Ser Arg Lys  Met Arg Lys
    1565                1570                1575

Glu Met  Asn Val Leu Thr Glu  Trp Leu Ala Ala Thr  Asp Met Glu
    1580                1585                1590

Leu Thr  Lys Arg Ser Ala Val  Glu Gly Met Pro Ser  Asn Leu Asp
    1595                1600                1605

Ser Glu  Val Ala Trp Gly Lys  Ala Thr Gln Lys Glu  Ile Glu Lys
    1610                1615                1620

Gln Lys  Val His Leu Lys Ser  Ile Thr Glu Val Gly  Glu Ala Leu
    1625                1630                1635

Lys Thr  Val Leu Gly Lys Lys  Glu Thr Leu Val Glu  Asp Lys Leu
    1640                1645                1650

Ser Leu  Leu Asn Ser Asn Trp  Ile Ala Val Thr Ser  Arg Ala Glu
    1655                1660                1665

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    1670                1675                1680

Phe Asp  Gln Asn Val Asp His  Ile Thr Lys Trp Ile  Ile Gln Ala
    1685                1690                1695

Asp Thr  Leu Leu Asp Glu Ser  Glu Lys Lys Lys Pro  Gln Gln Lys
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Pro Lys  Val Asp Ser Thr Arg  Asp Gln Ala Ala Asn  Leu Met Ala
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    1745                1750                1755

Glu Leu  Asn His Arg Phe Ala  Ala Ile Ser His Arg  Ile Lys Thr
    1760                1765                1770

Gly Lys  Ala Ser Ile Pro Leu  Lys Glu Leu Glu Gln  Phe Asn Ser
    1775                1780                1785

Asp Ile  Gln Lys Leu Leu Glu  Pro Leu Glu Ala Glu  Ile Gln Gln
    1790                1795                1800

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    1925                1930                1935
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    1955                1960                1965

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    1970                1975                1980

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    1985                1990                1995

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Ser Leu  Gln Gln Ser Ser Gly  Arg Ile Asp Ile Ile  His Ser Lys
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Lys Thr  Ala Ala Leu Gln Ser  Ala Thr Pro Val Glu  Arg Val Lys
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Leu Gln  Glu Ala Leu Ser Gln  Leu Asp Phe Gln Trp  Glu Lys Val
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Asn Lys  Met Tyr Lys Asp Arg  Gln Gly Arg Phe Asp  Arg Ser Val
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Ala Thr Gly Glu Glu Ile Ile Gln Gln Ser Ser Lys Thr Asp Ala
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Gln Leu Asn Glu Thr Gly Gly Pro Val Leu Val Ser Ala Pro Ile
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Lys Leu Glu Asp Leu Glu Glu Gln Leu Asn His Leu Leu Leu Trp
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Ala Lys  Gln Pro Asp Val Glu  Glu Ile Leu Ser Lys  Gly Gln His
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Leu Tyr  Lys Glu Lys Pro Ala  Thr Gln Pro Val Lys  Arg Lys Leu
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Glu Asp  Leu Ser Ser Glu Trp  Lys Ala Val Asn Arg  Leu Leu Gln
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Glu Leu  Arg Ala Lys Gln Pro  Asp Leu Ala Pro Gly  Leu Thr Thr
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Lys Ser  Gln Arg Val Met Val  Gly Asp Leu Glu Asp  Ile Asn Glu
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Met Ile  Ile Lys Gln Lys Ala  Thr Met Gln Asp Leu  Glu Gln Arg
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Ala Arg  Ala Lys Leu Glu Ser  Trp Lys Glu Gly Pro  Tyr Thr Val
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Asp Ala  Ile Gln Lys Lys Ile  Thr Glu Thr Lys Gln  Leu Ala Lys
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Val His  Met Ile Thr Glu Asn  Ile Asn Ala Ser Trp  Arg Ser Ile
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His Lys  Arg Val Ser Glu Arg  Glu Ala Ala Leu Glu  Glu Thr His
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Arg Leu  Leu Gln Gln Phe Pro  Leu Asp Leu Glu Lys  Phe Leu Ala
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Arg Leu  His Leu Ser Leu Gln  Glu Leu Leu Val Trp  Leu Gln Leu
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Gln Leu  His Arg Leu Arg Gln  Leu Leu Glu Gln Pro  Gln Ala Glu
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Ala Lys  Val Asn Gly Thr Thr  Val Ser Ser Pro Ser  Thr Ser Leu
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Ser Gln  Thr Ser Asp Ser Met  Gly Glu Glu Asp Leu  Leu Ser Pro
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Pro Gln  Asp Thr Ser Thr Gly  Leu Glu Glu Val Met  Glu Gln Leu
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Phe Ser Asp Leu Gln Asp Gly Arg Arg Leu Leu Asp Leu Leu Glu Gly
        35                  40                  45

Leu Thr Gly Gln Lys Leu Pro Lys Glu Lys Gly Ser Thr Arg Val His
    50                  55                  60

Ala Leu Asn Asn Val Asn Lys Ala Leu Arg Val Leu Gln Asn Asn Asn
65                  70                  75                  80

Val Asp Leu Val Asn Ile Gly Ser Thr Asp Ile Val Asp Gly Asn His
                85                  90                  95

Lys Leu Thr Leu Gly Leu Ile Trp Asn Ile Ile Leu His Trp Gln Val
            100                 105                 110

Lys Asn Val Met Lys Asn Ile Met Ala Gly Leu Gln Gln Thr Asn Ser
        115                 120                 125

Glu Lys Ile Leu Leu Ser Trp Val Arg Gln Ser Thr Arg Asn Tyr Pro
    130                 135                 140

Gln Val Asn Val Ile Asn Phe Thr Thr Ser Trp Ser Asp Gly Leu Ala
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Leu Asn Ala Leu Ile His Ser His Arg Pro Asp Leu Phe Asp Trp Asn
                165                 170                 175

Ser Val Val Cys Gln Gln Ser Ala Thr Gln Arg Leu Glu His Ala Phe
            180                 185                 190

Asn Ile Ala Arg Tyr Gln Leu Gly Ile Glu Lys Leu Leu Asp Pro Glu
        195                 200                 205

Asp Val Asp Thr Thr Tyr Pro Asp Lys Lys Ser Ile Leu Met Tyr Ile
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Thr Ser Leu Phe Gln Val Leu Pro Gln Gln Val Ser Ile Glu Ala Ile
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Gln Glu Val Glu Met Leu Pro Arg Pro Pro Lys Val Thr Lys Glu Glu
                245                 250                 255

His Phe Gln Leu His His Gln Met His Tyr Ser Gln Gln Ile Thr Val
            260                 265                 270

Ser Leu Ala Gln Gly Tyr Glu Arg Thr Ser Ser Pro Lys Pro Arg Phe
        275                 280                 285

Lys Ser Tyr Ala Tyr Thr Gln Ala Ala Tyr Val Thr Thr Ser Asp Pro
    290                 295                 300

Thr Arg Ser Pro Phe Pro Ser Gln His Leu Glu Ala Pro Glu Asp Lys
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Ser Phe Gly Ser Ser Leu Met Glu Ser Glu Val Asn Leu Asp Arg Tyr
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Gln Thr Ala Leu Glu Glu Val Leu Ser Trp Leu Leu Ser Ala Glu Asp
            340                 345                 350

Thr Leu Gln Ala Gln Gly Glu Ile Ser Asn Asp Val Glu Val Val Lys
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Asp Gln Phe His Thr His Glu Gly Tyr Met Met Asp Leu Thr Ala His
    370                 375                 380

Gln Gly Arg Val Gly Asn Ile Leu Gln Leu Gly Ser Lys Leu Ile Gly
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Thr Gly Lys Leu Ser Glu Asp Glu Glu Thr Glu Val Gln Glu Gln Met
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Asn Leu Leu Asn Ser Arg Trp Glu Cys Leu Arg Val Ala Ser Met Glu
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Lys Gln Ser Asn Leu His Arg Val Leu Met Asp Leu Gln Asn Gln Lys
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Leu Lys Glu Leu Asn Asp Trp Leu Thr Lys Thr Glu Glu Arg Thr Arg
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Lys Met Glu Glu Glu Pro Leu Gly Pro Asp Leu Glu Asp Leu Lys Arg
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Gln Val Gln Gln His Lys Val Leu Gln Glu Asp Leu Glu Gln Glu Gln
                485                 490                 495

Val Arg Val Asn Ser Leu Thr His Met Val Val Val Val Asp Glu Ser
            500                 505                 510

Ser Gly Asp His Ala Thr Ala Ala Leu Glu Glu Gln Leu Lys Val Leu
        515                 520                 525

Gly Asp Arg Trp Ala Asn Ile Cys Arg Trp Thr Glu Asp Arg Trp Val
    530                 535                 540

Leu Leu Gln Asp Ile Leu Leu Lys Trp Gln Arg Leu Thr Glu Glu Gln
545                 550                 555                 560

Cys Leu Phe Ser Ala Trp Leu Ser Glu Lys Glu Asp Ala Val Asn Lys
                565                 570                 575

Ile His Thr Thr Gly Phe Lys Asp Gln Asn Glu Met Leu Ser Ser Leu
            580                 585                 590

Gln Lys Leu Ala Val Leu Lys Ala Asp Leu Glu Lys Lys Lys Gln Ser
        595                 600                 605

Met Gly Lys Leu Tyr Ser Leu Lys Gln Asp Leu Leu Ser Thr Leu Lys
    610                 615                 620

Asn Lys Ser Val Thr Gln Lys Thr Glu Ala Trp Leu Asp Asn Phe Ala
625                 630                 635                 640

Arg Cys Trp Asp Asn Leu Val Gln Lys Leu Glu Lys Ser Thr Ala Gln
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                645                 650                 655

Ile Ser Gln Ala Val Thr Thr Thr Gln Pro Ser Leu Thr Gln Thr Thr
            660                 665                 670

Val Met Glu Thr Val Thr Thr Val Thr Thr Arg Glu Gln Ile Leu Val
        675                 680                 685

Lys His Ala Gln Glu Glu Leu Pro Pro Pro Pro Pro Gln Lys Lys Arg
    690                 695                 700

Gln Ile Thr Val Asp Ser Glu Ile Arg Lys Arg Leu Asp Val Asp Ile
705                 710                 715                 720

Thr Glu Leu His Ser Trp Ile Thr Arg Ser Glu Ala Val Leu Gln Ser
                725                 730                 735

Pro Glu Phe Ala Ile Phe Arg Lys Glu Gly Asn Phe Ser Asp Leu Lys
            740                 745                 750

Glu Lys Val Asn Ala Ile Glu Arg Glu Lys Ala Glu Lys Phe Arg Lys
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Leu Gln Asp Ala Ser Arg Ser Ala Gln Ala Leu Val Glu Gln Met Val
    770                 775                 780

Asn Glu Gly Val Asn Ala Asp Ser Ile Lys Gln Ala Ser Glu Gln Leu
785                 790                 795                 800

Asn Ser Arg Trp Ile Glu Phe Cys Gln Leu Leu Ser Glu Arg Leu Asn
                805                 810                 815

Trp Leu Glu Tyr Gln Asn Asn Ile Ile Ala Phe Tyr Asn Gln Leu Gln
            820                 825                 830

Gln Leu Glu Gln Met Thr Thr Thr Ala Glu Asn Trp Leu Lys Ile Gln
        835                 840                 845

Pro Thr Thr Pro Ser Glu Pro Thr Ala Ile Lys Ser Gln Leu Lys Ile
    850                 855                 860
```

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Cys Lys Asp Glu Val Asn Arg Leu Ser Gly Leu Gln Pro Gln Ile Glu
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Arg Leu Lys Ile Gln Ser Ile Ala Leu Lys Glu Lys Gly Gln Gly Pro
                885                 890                 895

Met Phe Leu Asp Ala Asp Phe Val Ala Phe Thr Asn His Phe Lys Gln
            900                 905                 910

Val Phe Ser Asp Val Gln Ala Arg Glu Lys Glu Leu Gln Thr Ile Phe
        915                 920                 925

Asp Thr Leu Pro Pro Met Arg Tyr Gln Glu Thr Met Ser Ala Ile Arg
    930                 935                 940

Thr Trp Val Gln Gln Ser Glu Thr Lys Leu Ser Ile Pro Gln Leu Ser
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Val Thr Asp Tyr Glu Ile Met Glu Gln Arg Leu Gly Glu Leu Gln Ala
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Leu Gln Ser Ser Leu Gln Glu Gln Gln Ser Gly Leu Tyr Tyr Leu Ser
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Thr Thr Val Lys Glu Met Ser Lys  Lys Ala Pro Ser Glu  Ile Ser Arg
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Lys Tyr  Gln Ser Glu Phe Glu  Glu Ile Glu Gly Arg  Trp Lys Lys
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Leu Ser  Ser Gln Leu Val Glu  His Cys Gln Lys Leu  Glu Glu Gln
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Met Asn  Lys Leu Arg Lys Ile  Gln Asn His Ile Gln  Thr Leu Lys
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Lys Trp  Met Ala Glu Val Asp  Val Phe Leu Lys Glu  Glu Trp Pro
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Ala Leu  Gly Asp Ser Glu Ile  Leu Lys Lys Gln Leu  Lys Gln Cys
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Arg Leu  Leu Val Ser Asp Ile  Gln Thr Ile Gln Pro  Ser Leu Asn
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Ser Val  Asn Glu Gly Gly Gln  Lys Ile Lys Asn Glu  Ala Glu Pro
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Glu Phe  Ala Ser Arg Leu Glu  Thr Glu Leu Lys Glu  Leu Asn Thr
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Gln Trp  Asp His Met Cys Gln  Gln Val Tyr Ala Arg  Lys Glu Ala
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Leu Lys  Gly Gly Leu Glu Lys  Thr Val Ser Leu Gln  Lys Asp Leu
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Ser Glu  Met His Glu Trp Met  Thr Gln Ala Glu Glu  Glu Tyr Leu
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Glu Arg  Asp Phe Glu Tyr Lys  Thr Pro Asp Glu Leu  Gln Lys Ala
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Val Glu  Glu Met Lys Arg Ala  Lys Glu Glu Ala Gln  Gln Lys Glu
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Ala Lys  Val Lys Leu Leu Thr  Glu Ser Val Asn Ser  Val Ile Ala
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Gln Ala  Pro Pro Val Ala Gln  Glu Ala Leu Lys Lys  Glu Leu Glu
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Thr Leu  Thr Thr Asn Tyr Gln  Trp Leu Cys Thr Arg  Leu Asn Gly
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Lys Cys  Lys Thr Leu Glu Glu  Val Trp Ala Cys Trp  His Glu Leu
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Leu Ser  Tyr Leu Glu Lys Ala  Asn Lys Trp Leu Asn  Glu Val Glu
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Ile Ser  Glu Val Leu Asp Ser  Leu Glu Asn Leu Met  Arg His Ser
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Glu Asp  Asn Pro Asn Gln Ile  Arg Ile Leu Ala Gln  Thr Leu Thr
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Asp Gly  Gly Val Met Asp Glu  Leu Ile Asn Glu Glu  Leu Glu Thr
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Phe Asn  Ser Arg Trp Arg Glu  Leu His Glu Glu Ala  Val Arg Arg
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Gln Lys  Leu Leu Glu Gln Ser  Ile Gln Ser Ala Gln  Glu Thr Glu
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Lys Ser  Leu His Leu Ile Gln  Glu Ser Leu Thr Phe  Ile Asp Lys
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Pro Gln  Glu Ala Gln Lys Ile  Gln Ser Asp Leu Thr  Ser His Glu
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Lys Met  His Leu Pro Ala Leu  Glu Thr Lys Ser Val  Glu Gln Glu
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Leu Ala  Ala Thr Asp Met Glu  Leu Thr Lys Arg Ser  Ala Val Glu
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Thr Leu  Val Glu Asp Lys Leu  Ser Leu Leu Asn Ser  Asn Trp Ile
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Ala Val  Thr Ser Arg Ala Glu  Glu Trp Leu Asn Leu  Leu Leu Glu
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Tyr Gln  Lys His Met Glu Thr  Phe Asp Gln Asn Val  Asp His Ile
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Lys Lys  Lys Pro Gln Gln Lys  Glu Asp Val Leu Lys  Arg Leu Lys
    1700                1705                1710

Ala Glu  Leu Asn Asp Ile Arg  Pro Lys Val Asp Ser  Thr Arg Asp
    1715                1720                1725

Gln Ala  Ala Asn Leu Met Ala  Asn Arg Gly Asp His  Cys Arg Lys
    1730                1735                1740

Leu Val  Glu Pro Gln Ile Ser  Glu Leu Asn His Arg  Phe Ala Ala
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Ile Ser  His Arg Ile Lys Thr  Gly Lys Ala Ser Ile  Pro Leu Lys
    1760                1765                1770

Glu Leu  Glu Gln Phe Asn Ser  Asp Ile Gln Lys Leu  Leu Glu Pro
    1775                1780                1785

Leu Glu  Ala Glu Ile Gln Gln  Gly Val Asn Leu Lys  Glu Glu Asp
    1790                1795                1800

Phe Asn  Lys Asp Met Asn Glu  Asp Asn Glu Gly Thr  Val Lys Glu
    1805                1810                1815

Leu Leu  Gln Arg Gly Asp Asn  Leu Gln Gln Arg Ile  Thr Asp Glu
    1820                1825                1830

Arg Lys  Arg Glu Glu Ile Lys  Ile Lys Gln Gln Leu  Leu Gln Thr
    1835                1840                1845

Lys His  Asn Ala Leu Lys Asp  Leu Arg Ser Gln Arg  Arg Lys Lys
    1850                1855                1860

Ala Leu  Glu Ile Ser His Gln  Trp Tyr Gln Tyr Lys  Arg Gln Ala
    1865                1870                1875

Asp Asp  Leu Leu Lys Cys Leu  Asp Asp Ile Glu Lys  Lys Leu Ala
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1880 1885 1890

Ser Leu Pro Glu Pro Arg Asp Glu Arg Lys Ile Lys Glu Ile Asp
1895 1900 1905

Arg Glu Leu Gln Lys Lys Lys Glu Glu Leu Asn Ala Val Arg Arg
1910 1915 1920

Gln Ala Glu Gly Leu Ser Glu Asp Gly Ala Ala Met Ala Val Glu
1925 1930 1935

Pro Thr Gln Ile Gln Leu Ser Lys Arg Trp Arg Glu Ile Glu Ser
1940 1945 1950

Lys Phe Ala Gln Phe Arg Arg Leu Asn Phe Ala Gln Ile His Thr
1955 1960 1965

Val Arg Glu Glu Thr Met Met Val Met Thr Glu Asp Met Pro Leu
1970 1975 1980

Glu Ile Ser Tyr Val Pro Ser Thr Tyr Leu Thr Glu Ile Thr His
1985 1990 1995

Val Ser Gln Ala Leu Leu Glu Val Glu Gln Leu Leu Asn Ala Pro
2000 2005 2010

Asp Leu Cys Ala Lys Asp Phe Glu Asp Leu Phe Lys Gln Glu Glu
2015 2020 2025

Ser Leu Lys Asn Ile Lys Asp Ser Leu Gln Gln Ser Ser Gly Arg
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Ile Asp Ile Ile His Ser Lys Lys Thr Ala Ala Leu Gln Ser Ala
2045 2050 2055

Thr Pro Val Glu Arg Val Lys Leu Gln Glu Ala Leu Ser Gln Leu
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Asp Phe Gln Trp Glu Lys Val Asn Lys Met Tyr Lys Asp Arg Gln
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Gly Arg  Phe Asp Arg Ser Val  Glu Lys Trp Arg Arg  Phe His Tyr
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Leu Arg  Lys Thr Gln Ile Pro  Glu Asn Trp Glu His  Ala Lys Tyr
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Lys Trp  Tyr Leu Lys Glu Leu  Gln Asp Gly Ile Gly  Gln Arg Gln
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Thr Val  Val Arg Thr Leu Asn  Ala Thr Gly Glu Glu  Ile Ile Gln
    2150                2155                2160

Gln Ser  Ser Lys Thr Asp Ala  Ser Ile Leu Gln Glu  Lys Leu Gly
    2165                2170                2175

Ser Leu  Asn Leu Arg Trp Gln  Glu Val Cys Lys Gln  Leu Ser Asp
    2180                2185                2190

Arg Lys  Lys Arg Leu Glu Glu  Gln Lys Asn Ile Leu  Ser Glu Phe
    2195                2200                2205

Gln Arg  Asp Leu Asn Glu Phe  Val Leu Trp Leu Glu  Glu Ala Asp
    2210                2215                2220

Asn Ile  Ala Ser Ile Pro Leu  Glu Pro Gly Lys Glu  Gln Gln Leu
    2225                2230                2235

Lys Glu  Lys Leu Glu Gln Val  Lys Leu Leu Val Glu  Glu Leu Pro
    2240                2245                2250

Leu Arg  Gln Gly Ile Leu Lys  Gln Leu Asn Glu Thr  Gly Gly Pro
    2255                2260                2265

Val Leu  Val Ser Ala Pro Ile  Ser Pro Glu Glu Gln  Asp Lys Leu
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Glu Asn  Lys Leu Lys Gln Thr  Asn Leu Gln Trp Ile  Lys Val Ser
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Arg Ala  Leu Pro Glu Lys Gln  Gly Glu Ile Glu Ala  Gln Ile Lys
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Asp Leu  Gly Gln Leu Glu Lys  Lys Leu Glu Asp Leu  Glu Glu Gln
    2315                2320                2325

Leu Asn  His Leu Leu Leu Trp  Leu Ser Pro Ile Arg  Asn Gln Leu
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Glu Ile  Tyr Asn Gln Pro Asn  Gln Glu Gly Pro Phe  Asp Val Gln
    2345                2350                2355

Glu Thr  Glu Ile Ala Val Gln  Ala Lys Gln Pro Asp  Val Glu Glu
    2360                2365                2370

Ile Leu  Ser Lys Gly Gln His  Leu Tyr Lys Glu Lys  Pro Ala Thr
    2375                2380                2385

Gln Pro  Val Lys Arg Lys Leu  Glu Asp Leu Ser Ser  Glu Trp Lys
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Ala Val  Asn Arg Leu Leu Gln  Glu Leu Arg Ala Lys  Gln Pro Asp
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Leu Ala  Pro Gly Leu Thr Thr  Ile Gly Ala Ser Pro  Thr Gln Thr
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Val Thr  Leu Val Thr Gln Pro  Val Val Thr Lys Glu  Thr Ala Ile
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Ser Lys  Leu Glu Met Pro Ser  Ser Leu Met Leu Glu  Val Pro Ala
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Leu Ala  Asp Phe Asn Arg Ala  Trp Thr Glu Leu Thr  Asp Trp Leu
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Ser Leu  Leu Asp Gln Val Ile  Lys Ser Gln Arg Val  Met Val Gly
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Ser Ala Asp Asp Thr Arg Lys Val His Met Ile Thr Glu Asn Ile
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Ala Asn  Val Leu Gln Asp Ala  Thr Arg Lys Glu Arg  Leu Leu Glu
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Asp Ser  Lys Gly Val Lys Glu  Leu Met Lys Gln Trp  Gln Asp Leu
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Gln Gly  Glu Ile Glu Ala His  Thr Asp Val Tyr His  Asn Leu Asp
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Glu Asn  Ser Gln Lys Ile Leu  Arg Ser Leu Glu Gly  Ser Asp Asp
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Ala Val  Leu Leu Gln Arg Arg  Leu Asp Asn Met Asn  Phe Lys Trp
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Ser Glu  Leu Arg Lys Lys Ser  Leu Asn Ile Arg Ser  His Leu Glu
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Val His  Arg Ala Phe Lys Arg  Glu Leu Lys Thr Lys  Glu Pro Val
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Ile Met  Ser Thr Leu Glu Thr  Val Arg Ile Phe Leu  Thr Glu Gln
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Pro Leu  Glu Gly Leu Glu Lys  Leu Tyr Gln Glu Pro  Arg Glu Leu
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Pro Pro  Glu Glu Arg Ala Gln  Asn Val Thr Arg Leu  Leu Arg Lys
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Ser Ala  Asp Trp Gln Arg Lys  Ile Asp Glu Thr Leu  Glu Arg Leu
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Gln Ala  Glu Val Ile Lys Gly  Ser Trp Gln Pro Val  Gly Asp Leu
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Arg Gly  Glu Ile Ala Pro Leu  Lys Glu Asn Val Ser  His Val Asn
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Asp Leu  Ala Arg Gln Leu Thr  Thr Leu Gly Ile Gln  Leu Ser Pro
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Tyr Asn  Leu Ser Thr Leu Glu  Asp Leu Asn Thr Arg  Trp Lys Leu
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Leu Gln  Val Ala Val Glu Asp  Arg Val Arg Gln Leu  His Glu Ala
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His Arg  Asp Phe Gly Pro Ala  Ser Gln His Phe Leu  Ser Thr Ser
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Val Gln  Gly Pro Trp Glu Arg  Ala Ile Ser Pro Asn  Lys Val Pro
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Tyr Tyr  Ile Asn His Glu Thr  Gln Thr Thr Cys Trp  Asp His Pro
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Ser Pro  Leu Pro Ser Pro Pro  Glu Met Met Pro Thr  Ser Pro Gln
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Ser Pro  Arg Asp Ala Glu Leu  Ile Ala Glu Ala Lys  Leu Leu Arg
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Gln His  Lys Gly Arg Leu Glu  Ala Arg Met Gln Ile  Leu Glu Asp
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His Asn  Lys Gln Leu Glu Ser  Gln Leu His Arg Leu  Arg Gln Leu
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Leu Glu  Gln Pro Gln Ala Glu  Ala Lys Val Asn Gly  Thr Thr Val
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Met Leu  Leu Arg Val Val Gly  Ser Gln Thr Ser Asp  Ser Met Gly
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Glu Glu  Asp Leu Leu Ser Pro  Pro Gln Asp Thr Ser  Thr Gly Leu
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Gly Lys Gln His Ile Glu Asn Leu Phe Ser Asp Leu Gln Asp Gly Arg
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Arg Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Gln Lys Leu Pro Lys
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Glu Lys Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Lys Ala
65   70   75   80

Leu Arg Val Leu Gln Asn Asn Asn Val Asp Leu Val Asn Ile Gly Ser
                85   90   95

Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Ile Trp
            100   105   110

Asn Ile Ile Leu His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met
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Ala Gly Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
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Arg Gln Ser Thr Arg Asn Tyr Pro Gln Val Asn Val Ile Asn Phe Thr
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Thr Ser Trp Ser Asp Gly Leu Ala Leu Asn Ala Leu Ile His Ser His
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Arg Pro Asp Leu Phe Asp Trp Asn Ser Val Val Cys Gln Gln Ser Ala
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Lys Lys Ser Ile Leu Met Tyr Ile Thr Ser Leu Phe Gln Val Leu Pro
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Gln Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg
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Pro Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met
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His Tyr Ser Gln Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg
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Thr Ser Ser Pro Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala
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Ala Tyr Val Thr Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln
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His Leu Glu Ala Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu
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Ser Glu Val Asn Leu Asp Arg Tyr Gln Thr Ala Leu Glu Glu Val Leu
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Ser Trp Leu Leu Ser Ala Glu Asp Thr Leu Gln Ala Gln Gly Glu Ile
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Ser Asn Asp Val Glu Val Val Lys Asp Gln Phe His Thr His Glu Gly
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Tyr Met Met Asp Leu Thr Ala His Gln Gly Arg Val Gly Asn Ile Leu
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Cys Leu Arg Val Ala Ser Met Glu Lys Gln Ser Asn Leu His Arg Val
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Leu Met Asp Leu Gln Asn Gln Lys Leu Lys Glu Leu Asn Asp Trp Leu
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Pro Asp Leu Glu Asp Leu Lys Arg Gln Val Gln Gln His Lys Val Leu
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Gln Glu Asp Leu Glu Gln Glu Gln Val Arg Val Asn Ser Leu Thr His
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Met Val Val Val Val Asp Glu Ser Ser Gly Asp His Ala Thr Ala Ala
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Leu Glu Glu Gln Leu Lys Val Leu Gly Asp Arg Trp Ala Asn Ile Cys
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Arg Trp Thr Glu Asp Arg Trp Val Leu Leu Gln Asp Ile Leu Leu Lys
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Trp Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ala Trp Leu Ser
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Glu Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp
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Gln Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala
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Asp Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys
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Glu Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln
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Lys Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr
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Gln Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val
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Thr Thr Arg Glu Gln Ile Leu Val Lys His Ala Gln Glu Glu Leu Pro
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Pro Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile
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Arg Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr
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Arg Ser Glu Ala Val Leu Gln Ser Pro Glu Phe Ala Ile Phe Arg Lys
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Glu Gly Asn Phe Ser Asp Leu Lys Glu Lys Val Asn Ala Ile Glu Arg
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Glu Lys Ala Glu Lys Phe Arg Lys Leu Gln Asp Ala Ser Arg Ser Ala
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Gln Leu Leu Ser Glu Arg Leu Asn Trp Leu Glu Tyr Gln Asn Asn Ile
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Ile Ala Phe Tyr Asn Gln Leu Gln Gln Leu Glu Gln Met Thr Thr Thr
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Ser Gly Leu Gln Pro Gln Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala
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Glu Lys Glu Leu Gln Thr Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr
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Gln Glu Thr Met Ser Ala Ile Arg Thr Trp Val Gln Gln Ser Glu Thr
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Ile Asp Val Ala Gln Lys Lys Leu Gln Asp Val Ser Met Lys Phe
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Arg Leu Phe Gln Lys Pro Ala Asn Phe Glu Gln Arg Leu Gln Glu
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Ser Lys Met Ile Leu Asp Glu Val Lys Met His Leu Pro Ala Leu
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His Cys Val Asn Leu Tyr Lys Ser Leu Ser Glu Val Lys Ser Glu
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Val Glu Met Val Ile Lys Thr Gly Arg Gln Ile Val Gln Lys Lys
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Leu Thr Lys Arg Ser Ala Val Glu Gly Met Pro Ser Asn Leu Asp
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Pro Lys Val Asp Ser Thr Arg Asp Gln Ala Ala Asn Leu Met Ala
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Asn Arg Gly Asp His Cys Arg Lys Leu Val Glu Pro Gln Ile Ser
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Glu Leu Asn His Arg Phe Ala Ala Ile Ser His Arg Ile Lys Thr
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Gly Lys Ala Ser Ile Pro Leu Lys Glu Leu Glu Gln Phe Asn Ser
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Asp Asn Glu Gly Thr Val Lys Glu Leu Leu Gln Arg Gly Asp Asn
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Leu Gln Gln Arg Ile Thr Asp Glu Arg Lys Arg Glu Glu Ile Lys
1835 1840 1845

Ile Lys Gln Gln Leu Leu Gln Thr Lys His Asn Ala Leu Lys Asp
1850 1855 1860

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Leu Arg  Ser Gln Arg Arg Lys  Lys Ala Leu Glu Ile  Ser His Gln
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Trp Tyr  Gln Tyr Lys Arg Gln  Ala Asp Asp Leu Leu  Lys Cys Leu
    1880                1885                1890

Asp Asp  Ile Glu Lys Lys Leu  Ala Ser Leu Pro Glu  Pro Arg Asp
    1895                1900                1905

Glu Arg  Lys Ile Lys Glu Ile  Asp Arg Glu Leu Gln  Lys Lys Lys
    1910                1915                1920

Glu Glu  Leu Asn Ala Val Arg  Arg Gln Ala Glu Gly  Leu Ser Glu
    1925                1930                1935

Asp Gly  Ala Ala Met Ala Val  Glu Pro Thr Gln Ile  Gln Leu Ser
    1940                1945                1950

Lys Arg  Trp Arg Glu Ile Glu  Ser Lys Phe Ala Gln  Phe Arg Arg
    1955                1960                1965

Leu Asn  Phe Ala Gln Ile His  Thr Val Arg Glu Glu  Thr Met Met
    1970                1975                1980

Val Met  Thr Glu Asp Met Pro  Leu Glu Ile Ser Tyr  Val Pro Ser
    1985                1990                1995

Thr Tyr  Leu Thr Glu Ile Thr  His Val Ser Gln Ala  Leu Leu Glu
    2000                2005                2010

Val Glu  Gln Leu Leu Asn Ala  Pro Asp Leu Cys Ala  Lys Asp Phe
    2015                2020                2025

Glu Asp  Leu Phe Lys Gln Glu  Glu Ser Leu Lys Asn  Ile Lys Asp
    2030                2035                2040

Ser Leu  Gln Gln Ser Ser Gly  Arg Ile Asp Ile Ile  His Ser Lys
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Lys Thr  Ala Ala Leu Gln Ser  Ala Thr Pro Val Glu  Arg Val Lys
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Asn Lys Met Tyr Lys Asp Arg Gln Gly Arg Phe Asp Arg Ser Val
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Glu Lys Trp Arg Arg Phe His Tyr Asp Ile Lys Ile Phe Asn Gln
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Val Leu Trp Leu Glu Glu Ala Asp Asn Ile Ala Ser Ile Pro Leu
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Glu Pro Gly Lys Glu Gln Gln Leu Lys Glu Lys Leu Glu Gln Val
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Lys Leu Leu Val Glu Glu Leu Pro Leu Arg Gln Gly Ile Leu Lys
2255 2260 2265

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Ser Pro  Glu Glu Gln Asp Lys  Leu Glu Asn Lys Leu  Lys Gln Thr
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Asn Leu  Gln Trp Ile Lys Val  Ser Arg Ala Leu Pro  Glu Lys Gln
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Gly Glu  Ile Glu Ala Gln Ile  Lys Asp Leu Gly Gln  Leu Glu Lys
    2315                2320                2325

Lys Leu  Glu Asp Leu Glu Glu  Gln Leu Asn His Leu  Leu Leu Trp
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Leu Ser  Pro Ile Arg Asn Gln  Leu Glu Ile Tyr Asn  Gln Pro Asn
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Gln Glu  Gly Pro Phe Asp Val  Gln Glu Thr Glu Ile  Ala Val Gln
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Ala Lys  Gln Pro Asp Val Glu  Glu Ile Leu Ser Lys  Gly Gln His
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Leu Tyr  Lys Glu Lys Pro Ala  Thr Gln Pro Val Lys  Arg Lys Leu
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Glu Asp  Leu Ser Ser Glu Trp  Lys Ala Val Asn Arg  Leu Leu Gln
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Glu Leu  Arg Ala Lys Gln Pro  Asp Leu Ala Pro Gly  Leu Thr Thr
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Ile Gly  Ala Ser Pro Thr Gln  Thr Val Thr Leu Val  Thr Gln Pro
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Val Val  Thr Lys Glu Thr Ala  Ile Ser Lys Leu Glu  Met Pro Ser
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Ser Leu  Met Leu Glu Val Pro  Ala Leu Ala Asp Phe  Asn Arg Ala
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Lys Ser  Gln Arg Val Met Val  Gly Asp Leu Glu Asp  Ile Asn Glu
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Met Ile  Ile Lys Gln Lys Ala  Thr Met Gln Asp Leu  Glu Gln Arg
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Arg Pro  Gln Leu Glu Glu Leu  Ile Thr Ala Ala Gln  Asn Leu Lys
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Asn Lys  Thr Ser Asn Gln Glu  Ala Arg Thr Ile Ile  Thr Asp Arg
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Ile Glu  Arg Ile Gln Asn Gln  Trp Asp Glu Val Gln  Glu His Leu
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Gln Asn  Arg Arg Gln Gln Leu  Asn Glu Met Leu Lys  Asp Ser Thr
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Ala Arg  Ala Lys Leu Glu Ser  Trp Lys Glu Gly Pro  Tyr Thr Val
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Asp Ala  Ile Gln Lys Lys Ile  Thr Glu Thr Lys Gln  Leu Ala Lys
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Ala Leu  Lys Leu Leu Arg Asp  Tyr Ser Ala Asp Asp  Thr Arg Lys
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Val His  Met Ile Thr Glu Asn  Ile Asn Ala Ser Trp  Arg Ser Ile
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Arg Ser  Leu Glu Gly Ser Asp  Asp Ala Val Leu Leu  Gln Arg Arg
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Arg Leu  His Leu Ser Leu Gln  Glu Leu Leu Val Trp  Leu Gln Leu
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Lys Asp  Asp Glu Leu Ser Arg  Gln Ala Pro Ile Gly  Gly Asp Phe
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Pro Ala  Val Gln Lys Gln Asn  Asp Val His Arg Ala  Phe Lys Arg
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Val Arg  Ile Phe Leu Thr Glu  Gln Pro Leu Glu Gly  Leu Glu Lys
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Ala Ile Ser Pro Asn Lys Val Pro Tyr Tyr Ile Asn His Glu Thr
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Lys Gln  Asn Asp Gln Pro Met  Asp Ile Leu Gln Ile  Ile Asn Cys
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Leu Thr  Thr Ile Tyr Asp Arg  Leu Glu Gln Glu His  Asn Asn Leu
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Asn Val  Tyr Asp Thr Gly Arg  Thr Gly Arg Ile Arg  Val Leu Ser
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Cys Asp  Gln Arg Arg Leu Gly  Leu Leu Leu His Asp  Ser Ile Gln
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Cys Pro  Ile Ile Gly Phe Arg  Tyr Arg Ser Leu Lys  His Phe Asn
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Tyr Asp  Ile Cys Gln Ser Cys  Phe Phe Ser Gly Arg  Val Ala Lys
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Gly His  Lys Met His Tyr Pro  Met Val Glu Tyr Cys  Thr Pro Thr
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Thr Ser  Gly Glu Asp Val Arg  Asp Phe Ala Lys Val  Leu Lys Asn
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Lys Phe  Arg Thr Lys Arg Tyr  Phe Ala Lys His Pro  Arg Met Gly
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Tyr Leu  Pro Val Gln Thr Val  Leu Glu Gly Asp Asn  Met Glu Thr
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Pro Val  Thr Leu Ile Asn Phe  Trp Pro Val Asp Ser  Ala Pro Ala
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Ser Ser  Pro Gln Leu Ser His  Asp Asp Thr His Ser  Arg Ile Glu
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His Tyr  Ala Ser Arg Leu Ala  Glu Met Glu Asn Ser  Asn Gly Ser
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Tyr Leu  Asn Asp Ser Ile Ser  Pro Asn Glu Ser Ile  Asp Asp Glu
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His Leu  Leu Ile Gln His Tyr  Cys Gln Ser Leu Asn  Gln Asp Ser
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Gln Asn Asn Asn Val Asp Leu Val Asn Ile Gly Ser Thr Asp Ile Val
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Asp Gly Asn His Lys Leu Thr Leu Gly Leu Ile Trp Asn Ile Ile Leu
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His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met Ala Gly Leu Gln
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Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg Pro Pro Lys Val
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Thr Lys Glu Glu His Phe Gln Leu His His Gln Met His Tyr Ser Gln
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Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg Thr Ser Ser Pro
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Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala Ala Tyr Val Thr
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Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln His Leu Glu Ala
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Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu Ser Glu Val Asn
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Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp Gln Asn Glu Met
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Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln Lys Leu Glu Lys
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Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr Gln Pro Ser Leu
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Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val Thr Thr Arg Glu
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Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr Arg Ser Glu Ala
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Val Leu Gln Ser Pro Glu Phe Ala Ile Phe Arg Lys Glu Gly Asn Phe
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Ser Asp Leu Lys Glu Lys Val Asn Ala Ile Glu Arg Glu Lys Ala Glu
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Glu Glu  Tyr Leu Glu Arg Asp  Phe Glu Tyr Lys Thr  Pro Asp Glu
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Leu Gln  Lys Ala Val Glu Glu  Met Lys Arg Ala Lys  Glu Glu Ala
    1190                1195                1200

Gln Gln  Lys Glu Ala Lys Val  Lys Leu Leu Thr Glu  Ser Val Asn
    1205                1210                1215
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Ser Val Ile Ala Gln Ala Pro Pro Val Ala Gln Glu Ala Leu Lys
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Lys Glu Leu Glu Thr Leu Thr Thr Asn Tyr Gln Trp Leu Cys Thr
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Arg Leu Asn Gly Lys Cys Lys Thr Leu Glu Glu Val Trp Ala Cys
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Trp His Glu Leu Leu Ser Tyr Leu Glu Lys Ala Asn Lys Trp Leu
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Asn Glu Val Glu Phe Lys Leu Lys Thr Thr Glu Asn Ile Pro Gly
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Gly Ala Glu Glu Ile Ser Glu Val Leu Asp Ser Leu Glu Asn Leu
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Met Arg His Ser Glu Asp Asn Pro Asn Gln Ile Arg Ile Leu Ala
1310 1315 1320

Gln Thr Leu Thr Asp Gly Gly Val Met Asp Glu Leu Ile Asn Glu
1325 1330 1335

Glu Leu Glu Thr Phe Asn Ser Arg Trp Arg Glu Leu His Glu Glu
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Ala Val Arg Arg Gln Lys Leu Leu Glu Gln Ser Ile Gln Ser Ala
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Gln Glu Thr Glu Lys Ser Leu His Leu Ile Gln Glu Ser Leu Thr
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Phe Ile Asp Lys Gln Leu Ala Ala Tyr Ile Ala Asp Lys Val Asp
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Ala Ala Gln Met Pro Gln Glu Ala Gln Lys Ile Gln Ser Asp Leu
1400 1405 1410

Thr Ser His Glu Ile Ser Leu Glu Glu Met Lys Lys His Asn Gln
1415 1420 1425

```
Gly Lys  Glu Ala Ala Gln Arg  Val Leu Ser Gln Ile  Asp Val Ala
    1430                1435                1440

Gln Lys  Lys Leu Gln Asp Val  Ser Met Lys Phe Arg  Leu Phe Gln
    1445                1450                1455

Lys Pro  Ala Asn Phe Glu Gln  Arg Leu Gln Glu Ser  Lys Met Ile
    1460                1465                1470

Leu Asp  Glu Val Lys Met His  Leu Pro Ala Leu Glu  Thr Lys Ser
    1475                1480                1485

Val Glu  Gln Glu Val Val Gln  Ser Gln Leu Asn His  Cys Val Asn
    1490                1495                1500

Leu Tyr  Lys Ser Leu Ser Glu  Val Lys Ser Glu Val  Glu Met Val
    1505                1510                1515

Ile Lys  Thr Gly Arg Gln Ile  Val Gln Lys Lys Gln  Thr Glu Asn
    1520                1525                1530

Pro Lys  Glu Leu Asp Glu Arg  Val Thr Ala Leu Lys  Leu His Tyr
    1535                1540                1545

Asn Glu  Leu Gly Ala Lys Val  Thr Glu Arg Lys Gln  Gln Leu Glu
    1550                1555                1560

Lys Cys  Leu Lys Leu Ser Arg  Lys Met Arg Lys Glu  Met Asn Val
    1565                1570                1575

Leu Thr  Glu Trp Leu Ala Ala  Thr Asp Met Glu Leu  Thr Lys Arg
    1580                1585                1590

Ser Ala  Val Glu Gly Met Pro  Ser Asn Leu Asp Ser  Glu Val Ala
    1595                1600                1605

Trp Gly  Lys Ala Thr Gln Lys  Glu Ile Glu Lys Gln  Lys Val His
    1610                1615                1620
```

```
Leu Lys  Ser Ile Thr Glu Val  Gly Glu Ala Leu Lys  Thr Val Leu
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Gly Lys  Lys Glu Thr Leu Val  Glu Asp Lys Leu Ser  Leu Leu Asn
    1640                1645                1650

Ser Asn  Trp Ile Ala Val Thr  Ser Arg Ala Glu Glu  Trp Leu Asn
    1655                1660                1665

Leu Leu  Leu Glu Tyr Gln Lys  His Met Glu Thr Phe  Asp Gln Asn
    1670                1675                1680

Val Asp  His Ile Thr Lys Trp  Ile Ile Gln Ala Asp  Thr Leu Leu
    1685                1690                1695

Asp Glu  Ser Glu Lys Lys Lys  Pro Gln Gln Lys Glu  Asp Val Leu
    1700                1705                1710

Lys Arg  Leu Lys Ala Glu Leu  Asn Asp Ile Arg Pro  Lys Val Asp
    1715                1720                1725

Ser Thr  Arg Asp Gln Ala Ala  Asn Leu Met Ala Asn  Arg Gly Asp
    1730                1735                1740

His Cys  Arg Lys Leu Val Glu  Pro Gln Ile Ser Glu  Leu Asn His
    1745                1750                1755

Arg Phe  Ala Ala Ile Ser His  Arg Ile Lys Thr Gly  Lys Ala Ser
    1760                1765                1770

Ile Pro  Leu Lys Glu Leu Glu  Gln Phe Asn Ser Asp  Ile Gln Lys
    1775                1780                1785

Leu Leu  Glu Pro Leu Glu Ala  Glu Ile Gln Gln Gly  Val Asn Leu
    1790                1795                1800

Lys Glu  Glu Asp Phe Asn Lys  Asp Met Asn Glu Asp  Asn Glu Gly
    1805                1810                1815

Thr Val  Lys Glu Leu Leu Gln  Arg Gly Asp Asn Leu  Gln Gln Arg
    1820                1825                1830
```

```
Ile Thr  Asp Glu Arg Lys Arg  Glu Glu Ile Lys Ile  Lys Gln Gln
    1835                1840                1845

Leu Leu  Gln Thr Lys His Asn  Ala Leu Lys Asp Leu  Arg Ser Gln
    1850                1855                1860

Arg Arg  Lys Lys Ala Leu Glu  Ile Ser His Gln Trp  Tyr Gln Tyr
    1865                1870                1875

Lys Arg  Gln Ala Asp Asp Leu  Leu Lys Cys Leu Asp  Asp Ile Glu
    1880                1885                1890

Lys Lys  Leu Ala Ser Leu Pro  Glu Pro Arg Asp Glu  Arg Lys Ile
    1895                1900                1905

Lys Glu  Ile Asp Arg Glu Leu  Gln Lys Lys Lys Glu  Glu Leu Asn
    1910                1915                1920

Ala Val  Arg Arg Gln Ala Glu  Gly Leu Ser Glu Asp  Gly Ala Ala
    1925                1930                1935

Met Ala  Val Glu Pro Thr Gln  Ile Gln Leu Ser Lys  Arg Trp Arg
    1940                1945                1950

Glu Ile  Glu Ser Lys Phe Ala  Gln Phe Arg Arg Leu  Asn Phe Ala
    1955                1960                1965

Gln Ile  His Thr Val Arg Glu  Glu Thr Met Met Val  Met Thr Glu
    1970                1975                1980

Asp Met  Pro Leu Glu Ile Ser  Tyr Val Pro Ser Thr  Tyr Leu Thr
    1985                1990                1995

Glu Ile  Thr His Val Ser Gln  Ala Leu Leu Glu Val  Glu Gln Leu
    2000                2005                2010

Leu Asn  Ala Pro Asp Leu Cys  Ala Lys Asp Phe Glu  Asp Leu Phe
    2015                2020                2025
```

```
Lys Gln  Glu Glu Ser Leu Lys  Asn Ile Lys Asp Ser  Leu Gln Gln
    2030                2035                2040

Ser Ser  Gly Arg Ile Asp Ile  Ile His Ser Lys Lys  Thr Ala Ala
    2045                2050                2055

Leu Gln  Ser Ala Thr Pro Val  Glu Arg Val Lys Leu  Gln Glu Ala
    2060                2065                2070

Leu Ser  Gln Leu Asp Phe Gln  Trp Glu Lys Val Asn  Lys Met Tyr
    2075                2080                2085

Lys Asp  Arg Gln Gly Arg Phe  Asp Arg Ser Val Glu  Lys Trp Arg
    2090                2095                2100

Arg Phe  His Tyr Asp Ile Lys  Ile Phe Asn Gln Trp  Leu Thr Glu
    2105                2110                2115

Ala Glu  Gln Phe Leu Arg Lys  Thr Gln Ile Pro Glu  Asn Trp Glu
    2120                2125                2130

His Ala  Lys Tyr Lys Trp Tyr  Leu Lys Glu Leu Gln  Asp Gly Ile
    2135                2140                2145

Gly Gln  Arg Gln Thr Val Val  Arg Thr Leu Asn Ala  Thr Gly Glu
    2150                2155                2160

Glu Ile  Ile Gln Gln Ser Ser  Lys Thr Asp Ala Ser  Ile Leu Gln
    2165                2170                2175

Glu Lys  Leu Gly Ser Leu Asn  Leu Arg Trp Gln Glu  Val Cys Lys
    2180                2185                2190

Gln Leu  Ser Asp Arg Lys Lys  Arg Leu Glu Glu Gln  Lys Asn Ile
    2195                2200                2205

Leu Ser  Glu Phe Gln Arg Asp  Leu Asn Glu Phe Val  Leu Trp Leu
    2210                2215                2220

Glu Glu  Ala Asp Asn Ile Ala  Ser Ile Pro Leu Glu  Pro Gly Lys
    2225                2230                2235
```

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Glu Glu Leu Pro Leu Arg Gln Gly Ile Leu Lys Gln Leu Asn Glu
2255 2260 2265

Thr Gly Gly Pro Val Leu Val Ser Ala Pro Ile Ser Pro Glu Glu
2270 2275 2280

Gln Asp Lys Leu Glu Asn Lys Leu Lys Gln Thr Asn Leu Gln Trp
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Ile Lys Val Ser Arg Ala Leu Pro Glu Lys Gln Gly Glu Ile Glu
2300 2305 2310

Ala Gln Ile Lys Asp Leu Gly Gln Leu Glu Lys Lys Leu Glu Asp
2315 2320 2325

Leu Glu Glu Gln Leu Asn His Leu Leu Leu Trp Leu Ser Pro Ile
2330 2335 2340

Arg Asn Gln Leu Glu Ile Tyr Asn Gln Pro Asn Gln Glu Gly Pro
2345 2350 2355

Phe Asp Val Gln Glu Thr Glu Ile Ala Val Gln Ala Lys Gln Pro
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Asp Val Glu Glu Ile Leu Ser Lys Gly Gln His Leu Tyr Lys Glu
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Lys Pro Ala Thr Gln Pro Val Lys Arg Lys Leu Glu Asp Leu Ser
2390 2395 2400

Ser Glu Trp Lys Ala Val Asn Arg Leu Leu Gln Glu Leu Arg Ala
2405 2410 2415

Lys Gln Pro Asp Leu Ala Pro Gly Leu Thr Thr Ile Gly Ala Ser
2420 2425 2430

```
Pro Thr  Gln Thr Val Thr Leu  Val Thr Gln Pro Val  Val Thr Lys
    2435                2440                2445

Glu Thr  Ala Ile Ser Lys Leu  Glu Met Pro Ser Ser  Leu Met Leu
    2450                2455                2460

Glu Val  Pro Ala Leu Ala Asp  Phe Asn Arg Ala Trp  Thr Glu Leu
    2465                2470                2475

Thr Asp  Trp Leu Ser Leu Leu  Asp Gln Val Ile Lys  Ser Gln Arg
    2480                2485                2490

Val Met  Val Gly Asp Leu Glu  Asp Ile Asn Glu Met  Ile Ile Lys
    2495                2500                2505

Gln Lys  Ala Thr Met Gln Asp  Leu Glu Gln Arg Arg  Pro Gln Leu
    2510                2515                2520

Glu Glu  Leu Ile Thr Ala Ala  Gln Asn Leu Lys Asn  Lys Thr Ser
    2525                2530                2535

Asn Gln  Glu Ala Arg Thr Ile  Ile Thr Asp Arg Ile  Glu Arg Ile
    2540                2545                2550

Gln Asn  Gln Trp Asp Glu Val  Gln Glu His Leu Gln  Asn Arg Arg
    2555                2560                2565

Gln Gln  Leu Asn Glu Met Leu  Lys Asp Ser Thr Gln  Trp Leu Glu
    2570                2575                2580

Ala Lys  Glu Glu Ala Glu Gln  Val Leu Gly Gln Ala  Arg Ala Lys
    2585                2590                2595

Leu Glu  Ser Trp Lys Glu Gly  Pro Tyr Thr Val Asp  Ala Ile Gln
    2600                2605                2610

Lys Lys  Ile Thr Glu Thr Lys  Gln Leu Ala Lys Asp  Leu Arg Gln
    2615                2620                2625

Trp Gln  Thr Asn Val Asp Val  Ala Asn Asp Leu Ala  Leu Lys Leu
    2630                2635                2640
```

```
Leu Arg  Asp Tyr Ser Ala Asp  Asp Thr Arg Lys Val  His Met Ile
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Thr Glu  Asn Ile Asn Ala Ser  Trp Arg Ser Ile His  Lys Arg Val
    2660                2665                2670

Ser Glu  Arg Glu Ala Ala Leu  Glu Glu Thr His Arg  Leu Leu Gln
    2675                2680                2685

Gln Phe  Pro Leu Asp Leu Glu  Lys Phe Leu Ala Trp  Leu Thr Glu
    2690                2695                2700

Ala Glu  Thr Thr Ala Asn Val  Leu Gln Asp Ala Thr  Arg Lys Glu
    2705                2710                2715

Arg Leu  Leu Glu Asp Ser Lys  Gly Val Lys Glu Leu  Met Lys Gln
    2720                2725                2730

Trp Gln  Asp Leu Gln Gly Glu  Ile Glu Ala His Thr  Asp Val Tyr
    2735                2740                2745

His Asn  Leu Asp Glu Asn Ser  Gln Lys Ile Leu Arg  Ser Leu Glu
    2750                2755                2760

Gly Ser  Asp Asp Ala Val Leu  Leu Gln Arg Arg Leu  Asp Asn Met
    2765                2770                2775

Asn Phe  Lys Trp Ser Glu Leu  Arg Lys Lys Ser Leu  Asn Ile Arg
    2780                2785                2790

Ser His  Leu Glu Ala Ser Ser  Asp Gln Trp Lys Arg  Leu His Leu
    2795                2800                2805

Ser Leu  Gln Glu Leu Leu Val  Trp Leu Gln Leu Lys  Asp Asp Glu
    2810                2815                2820

Leu Ser  Arg Gln Ala Pro Ile  Gly Gly Asp Phe Pro  Ala Val Gln
    2825                2830                2835
```

```
Lys Gln  Asn Asp Val His Arg  Ala Phe Lys Arg Glu  Leu Lys Thr
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Lys Glu  Pro Val Ile Met Ser  Thr Leu Glu Thr Val  Arg Ile Phe
    2855                 2860                 2865

Leu Thr  Glu Gln Pro Leu Glu  Gly Leu Glu Lys Leu  Tyr Gln Glu
    2870                 2875                 2880

Pro Arg  Glu Leu Pro Pro Glu  Glu Arg Ala Gln Asn  Val Thr Arg
    2885                 2890                 2895

Leu Leu  Arg Lys Gln Ala Glu  Glu Val Asn Thr Glu  Trp Glu Lys
    2900                 2905                 2910

Leu Asn  Leu His Ser Ala Asp  Trp Gln Arg Lys Ile  Asp Glu Thr
    2915                 2920                 2925

Leu Glu  Arg Leu Gln Glu Leu  Gln Glu Ala Thr Asp  Glu Leu Asp
    2930                 2935                 2940

Leu Lys  Leu Arg Gln Ala Glu  Val Ile Lys Gly Ser  Trp Gln Pro
    2945                 2950                 2955

Val Gly  Asp Leu Leu Ile Asp  Ser Leu Gln Asp His  Leu Glu Lys
    2960                 2965                 2970

Val Lys  Ala Leu Arg Gly Glu  Ile Ala Pro Leu Lys  Glu Asn Val
    2975                 2980                 2985

Ser His  Val Asn Asp Leu Ala  Arg Gln Leu Thr Thr  Leu Gly Ile
    2990                 2995                 3000

Gln Leu  Ser Pro Tyr Asn Leu  Ser Thr Leu Glu Asp  Leu Asn Thr
    3005                 3010                 3015

Arg Trp  Lys Leu Leu Gln Val  Ala Val Glu Asp Arg  Val Arg Gln
    3020                 3025                 3030

Leu His  Glu Ala His Arg Asp  Phe Gly Pro Ala Ser  Gln His Phe
    3035                 3040                 3045
```

```
Leu Ser  Thr Ser Val Gln Gly  Pro Trp Glu Arg Ala  Ile Ser Pro
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Asn Lys  Val Pro Tyr Tyr Ile  Asn His Glu Thr Gln  Thr Thr Cys
    3065                3070                3075

Trp Asp  His Pro Lys Met Thr  Glu Leu Tyr Gln Ser  Leu Ala Asp
    3080                3085                3090

Leu Asn  Asn Val Arg Phe Ser  Ala Tyr Arg Thr Ala  Met Lys Leu
    3095                3100                3105

Arg Arg  Leu Gln Lys Ala Leu  Cys Leu Asp Leu Leu  Ser Leu Ser
    3110                3115                3120

Ala Ala  Cys Asp Ala Leu Asp  Gln His Asn Leu Lys  Gln Asn Asp
    3125                3130                3135

Gln Pro  Met Asp Ile Leu Gln  Ile Ile Asn Cys Leu  Thr Thr Ile
    3140                3145                3150

Tyr Asp  Arg Leu Glu Gln Glu  His Asn Asn Leu Val  Asn Val Pro
    3155                3160                3165

Leu Cys  Val Asp Met Cys Leu  Asn Trp Leu Leu Asn  Val Tyr Asp
    3170                3175                3180

Thr Gly  Arg Thr Gly Arg Ile  Arg Val Leu Ser Phe  Lys Thr Gly
    3185                3190                3195

Ile Ile  Ser Leu Cys Lys Ala  His Leu Glu Asp Lys  Tyr Arg Tyr
    3200                3205                3210

Leu Phe  Lys Gln Val Ala Ser  Ser Thr Gly Phe Cys  Asp Gln Arg
    3215                3220                3225

Arg Leu  Gly Leu Leu Leu His  Asp Ser Ile Gln Ile  Pro Arg Gln
    3230                3235                3240
```

```
Leu Gly  Glu Val Ala Ser Phe  Gly Gly Ser Asn Ile  Glu Pro Ser
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Val Arg  Ser Cys Phe Gln Phe  Ala Asn Asn Lys Pro  Glu Ile Glu
    3260                3265                3270

Ala Ala  Leu Phe Leu Asp Trp  Met Arg Leu Glu Pro  Gln Ser Met
    3275                3280                3285

Val Trp  Leu Pro Val Leu His  Arg Val Ala Ala Ala  Glu Thr Ala
    3290                3295                3300

Lys His  Gln Ala Lys Cys Asn  Ile Cys Lys Glu Cys  Pro Ile Ile
    3305                3310                3315

Gly Phe  Arg Tyr Arg Ser Leu  Lys His Phe Asn Tyr  Asp Ile Cys
    3320                3325                3330

Gln Ser  Cys Phe Phe Ser Gly  Arg Val Ala Lys Gly  His Lys Met
    3335                3340                3345

His Tyr  Pro Met Val Glu Tyr  Cys Thr Pro Thr Thr  Ser Gly Glu
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Asp Val  Arg Asp Phe Ala Lys  Val Leu Lys Asn Lys  Phe Arg Thr
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Lys Arg  Tyr Phe Ala Lys His  Pro Arg Met Gly Tyr  Leu Pro Val
    3380                3385                3390

Gln Thr  Val Leu Glu Gly Asp  Asn Met Glu Thr Pro  Val Thr Leu
    3395                3400                3405

Ile Asn  Phe Trp Pro Val Asp  Ser Ala Pro Ala Ser  Ser Pro Gln
    3410                3415                3420

Leu Ser  His Asp Asp Thr His  Ser Arg Ile Glu His  Tyr Ala Ser
    3425                3430                3435

Arg Leu  Ala Glu Met Glu Asn  Ser Asn Gly Ser Tyr  Leu Asn Asp
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Ser Ile Ser Pro Asn Glu Ser Ile Asp Asp Glu His Leu Leu Ile
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Gln His Tyr Cys Gln Ser Leu Asn Gln Asp Ser Pro Leu Ser Gln
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Arg Asn Leu Gln Ala Glu Tyr Asp Arg Leu Lys Gln Gln His Glu
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Lys Leu Leu Arg Gln His Lys Gly Arg Leu Glu Ala Arg Met Gln
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Asp Lys Gln Leu Ala Ala Tyr Ile Ala Asp Lys Val Asp Ala Ala Gln
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Met Pro Gln Glu Ala Gln Lys Ile Gln Ser Asp Leu Thr Ser His Glu
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Ile Ser Leu Glu Glu Met Lys Lys His Asn Gln Gly Lys Glu Ala Ala
85 90 95

Gln Arg Val Leu Ser Gln Ile Asp Val Ala Gln Lys Lys Leu Gln Asp
100 105 110

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Arg Leu Gln Glu Ser Lys Met Ile Leu Asp Glu Val Lys Met His Leu
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Pro Ala Leu Glu Thr Lys Ser Val Glu Gln Glu Val Val Gln Ser Gln
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Leu Asn His Cys Val Asn Leu Tyr Lys Ser Leu Ser Glu Val Lys Ser
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Glu Val Glu Met Val Ile Lys Thr Gly Arg Gln Ile Val Gln Lys Lys
            180                 185                 190

Gln Thr Glu Asn Pro Lys Glu Leu Asp Glu Arg Val Thr Ala Leu Lys
        195                 200                 205

Leu His Tyr Asn Glu Leu Gly Ala Lys Val Thr Glu Arg Lys Gln Gln
    210                 215                 220

Leu Glu Lys Cys Leu Lys Leu Ser Arg Lys Met Arg Lys Glu Met Asn
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Val Leu Thr Glu Trp Leu Ala Ala Thr Asp Met Glu Leu Thr Lys Arg
                245                 250                 255

Ser Ala Val Glu Gly Met Pro Ser Asn Leu Asp Ser Glu Val Ala Trp
            260                 265                 270

Gly Lys Ala Thr Gln Lys Glu Ile Glu Lys Gln Lys Val His Leu Lys
        275                 280                 285

Ser Ile Thr Glu Val Gly Glu Ala Leu Lys Thr Val Leu Gly Lys Lys
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Glu Thr Leu Val Glu Asp Lys Leu Ser Leu Leu Asn Ser Asn Trp Ile
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Ala Val Thr Ser Arg Ala Glu Glu Trp Leu Asn Leu Leu Leu Glu Tyr
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Gln Lys His Met Glu Thr Phe Asp Gln Asn Val Asp His Ile Thr Lys
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Trp Ile Ile Gln Ala Asp Thr Leu Leu Asp Glu Ser Glu Lys Lys Lys
        355                 360                 365

Pro Gln Gln Lys Glu Asp Val Leu Lys Arg Leu Lys Ala Glu Leu Asn
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Asp Ile Arg Pro Lys Val Asp Ser Thr Arg Asp Gln Ala Ala Asn Leu
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Met Ala Asn Arg Gly Asp His Cys Arg Lys Leu Val Glu Pro Gln Ile
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Ser Glu Leu Asn His Arg Phe Ala Ala Ile Ser His Arg Ile Lys Thr
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Gly Lys Ala Ser Ile Pro Leu Lys Glu Leu Glu Gln Phe Asn Ser Asp
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Ile Gln Lys Leu Leu Glu Pro Leu Glu Ala Glu Ile Gln Gln Gly Val
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Asn Leu Lys Glu Glu Asp Phe Asn Lys Asp Met Asn Glu Asp Asn Glu
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Gly Thr Val Lys Glu Leu Leu Gln Arg Gly Asp Asn Leu Gln Gln Arg
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Ile Thr Asp Glu Arg Lys Arg Glu Glu Ile Lys Ile Lys Gln Gln Leu
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Leu Gln Thr Lys His Asn Ala Leu Lys Asp Leu Arg Ser Gln Arg Arg
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Lys Lys Ala Leu Glu Ile Ser His Gln Trp Tyr Gln Tyr Lys Arg Gln
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Ala Asp Asp Leu Leu Lys Cys Leu Asp Asp Ile Glu Lys Lys Leu Ala
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Ser Leu Pro Glu Pro Arg Asp Glu Arg Lys Ile Lys Glu Ile Asp Arg
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Glu Leu Gln Lys Lys Lys Glu Glu Leu Asn Ala Val Arg Arg Gln Ala
            580                 585                 590

Glu Gly Leu Ser Glu Asp Gly Ala Ala Met Ala Val Glu Pro Thr Gln
        595                 600                 605

Ile Gln Leu Ser Lys Arg Trp Arg Glu Ile Glu Ser Lys Phe Ala Gln
    610                 615                 620

Phe Arg Arg Leu Asn Phe Ala Gln Ile His Thr Val Arg Glu Glu Thr
625                 630                 635                 640

Met Met Val Met Thr Glu Asp Met Pro Leu Glu Ile Ser Tyr Val Pro
                645                 650                 655

Ser Thr Tyr Leu Thr Glu Ile Thr His Val Ser Gln Ala Leu Leu Glu
            660                 665                 670

Val Glu Gln Leu Leu Asn Ala Pro Asp Leu Cys Ala Lys Asp Phe Glu
        675                 680                 685

Asp Leu Phe Lys Gln Glu Glu Ser Leu Lys Asn Ile Lys Asp Ser Leu
    690                 695                 700

Gln Gln Ser Ser Gly Arg Ile Asp Ile Ile His Ser Lys Lys Thr Ala
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Ala Leu Gln Ser Ala Thr Pro Val Glu Arg Val Lys Leu Gln Glu Ala
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Leu Ser Gln Leu Asp Phe Gln Trp Glu Lys Val Asn Lys Met Tyr Lys
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```

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Asp Arg Gln Gly Arg Phe Asp Arg Ser Val Glu Lys Trp Arg Arg Phe
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His Tyr Asp Ile Lys Ile Phe Asn Gln Trp Leu Thr Glu Ala Glu Gln
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Phe Leu Arg Lys Thr Gln Ile Pro Glu Asn Trp Glu His Ala Lys Tyr
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Lys Trp Tyr Leu Lys Glu Leu Gln Asp Gly Ile Gly Gln Arg Gln Thr
                805                 810                 815

Val Val Arg Thr Leu Asn Ala Thr Gly Glu Glu Ile Ile Gln Gln Ser
            820                 825                 830

Ser Lys Thr Asp Ala Ser Ile Leu Gln Glu Lys Leu Gly Ser Leu Asn
        835                 840                 845

Leu Arg Trp Gln Glu Val Cys Lys Gln Leu Ser Asp Arg Lys Lys Arg
    850                 855                 860

Leu Glu Glu Gln Lys Asn Ile Leu Ser Glu Phe Gln Arg Asp Leu Asn
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Glu Phe Val Leu Trp Leu Glu Glu Ala Asp Asn Ile Ala Ser Ile Pro
                885                 890                 895

Leu Glu Pro Gly Lys Glu Gln Gln Leu Lys Glu Lys Leu Glu Gln Val
            900                 905                 910

Lys Leu Leu Val Glu Glu Leu Pro Leu Arg Gln Gly Ile Leu Lys Gln
        915                 920                 925

Leu Asn Glu Thr Gly Gly Pro Val Leu Val Ser Ala Pro Ile Ser Pro
    930                 935                 940

Glu Glu Gln Asp Lys Leu Glu Asn Lys Leu Lys Gln Thr Asn Leu Gln
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Trp Ile Lys Val Ser Arg Ala Leu Pro Glu Lys Gln Gly Glu Ile Glu
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Ala Gln Ile Lys Asp Leu Gly Gln Leu Glu Lys Lys Leu Glu Asp Leu
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Glu Glu Gln Leu Asn His Leu Leu  Leu Trp Leu Ser Pro  Ile Arg Asn
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Gln Leu  Glu Ile Tyr Asn Gln  Pro Asn Gln Glu Gly  Pro Phe Asp
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Val Gln  Glu Thr Glu Ile Ala  Val Gln Ala Lys Gln  Pro Asp Val
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Glu Glu  Ile Leu Ser Lys Gly  Gln His Leu Tyr Lys  Glu Lys Pro
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Trp Lys  Ala Val Asn Arg Leu  Leu Gln Glu Leu Arg  Ala Lys Gln
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Pro Asp  Leu Ala Pro Gly Leu  Thr Thr Ile Gly Ala  Ser Pro Thr
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Gln Thr  Val Thr Leu Val Thr  Gln Pro Val Val Thr  Lys Glu Thr
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Ala Ile  Ser Lys Leu Glu Met  Pro Ser Ser Leu Met  Leu Glu Val
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Pro Ala  Leu Ala Asp Phe Asn  Arg Ala Trp Thr Glu  Leu Thr Asp
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Trp Leu  Ser Leu Leu Asp Gln  Val Ile Lys Ser Gln  Arg Val Met
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Val Gly  Asp Leu Glu Asp Ile  Asn Glu Met Ile Ile  Lys Gln Lys
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Glu Ala  Arg Thr Ile Ile Thr  Asp Arg Ile Glu Arg  Ile Gln Asn
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Gln Trp  Asp Glu Val Gln Glu  His Leu Gln Asn Arg  Arg Gln Gln
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Leu Asn  Glu Met Leu Lys Asp  Ser Thr Gln Trp Leu  Glu Ala Lys
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Glu Glu  Ala Glu Gln Val Leu  Gly Gln Ala Arg Ala  Lys Leu Glu
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Ser Trp  Lys Glu Gly Pro Tyr  Thr Val Asp Ala Ile  Gln Lys Lys
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Ile Thr  Glu Thr Lys Gln Leu  Ala Lys Asp Leu Arg  Gln Trp Gln
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Thr Asn  Val Asp Val Ala Asn  Asp Leu Ala Leu Lys  Leu Leu Arg
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Asp Tyr  Ser Ala Asp Asp Thr  Arg Lys Val His Met  Ile Thr Glu
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Asn Ile  Asn Ala Ser Trp Arg  Ser Ile His Lys Arg  Val Ser Glu
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Arg Glu  Ala Ala Leu Glu Glu  Thr His Arg Leu Leu  Gln Gln Phe
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Pro Leu  Asp Leu Glu Lys Phe  Leu Ala Trp Leu Thr  Glu Ala Glu
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Thr Thr  Ala Asn Val Leu Gln  Asp Ala Thr Arg Lys  Glu Arg Leu
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Asp Asp  Ala Val Leu Leu Gln  Arg Arg Leu Asp Asn  Met Asn Phe
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Lys Trp  Ser Glu Leu Arg Lys  Lys Ser Leu Asn Ile  Arg Ser His
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Leu Glu  Ala Ser Ser Asp Gln  Trp Lys Arg Leu His  Leu Ser Leu
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Arg Gln  Ala Pro Ile Gly Gly  Asp Phe Pro Ala Val  Gln Lys Gln
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Asn Asp  Val His Arg Ala Phe  Lys Arg Glu Leu Lys  Thr Lys Glu
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Glu Leu  Pro Pro Glu Glu Arg  Ala Gln Asn Val Thr  Arg Leu Leu
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Arg Lys  Gln Ala Glu Glu Val  Asn Thr Glu Trp Glu  Lys Leu Asn
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Leu His  Ser Ala Asp Trp Gln  Arg Lys Ile Asp Glu  Thr Leu Glu
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Asp Leu  Leu Ile Asp Ser Leu  Gln Asp His Leu Glu  Lys Val Lys
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Ala Leu  Arg Gly Glu Ile Ala  Pro Leu Lys Glu Asn  Val Ser His
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Val Asn  Asp Leu Ala Arg Gln  Leu Thr Thr Leu Gly  Ile Gln Leu
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Ser Pro  Tyr Asn Leu Ser Thr  Leu Glu Asp Leu Asn  Thr Arg Trp
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Ser Leu  Cys Lys Ala His Leu  Glu Asp Lys Tyr Arg  Tyr Leu Phe
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Gly Leu  Leu Leu His Asp Ser  Ile Gln Ile Pro Arg  Gln Leu Gly
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Glu Val  Ala Ser Phe Gly Gly  Ser Asn Ile Glu Pro  Ser Val Arg
    1910                 1915                 1920

Ser Cys  Phe Gln Phe Ala Asn  Asn Lys Pro Glu Ile  Glu Ala Ala
    1925                 1930                 1935

Leu Phe  Leu Asp Trp Met Arg  Leu Glu Pro Gln Ser  Met Val Trp
    1940                 1945                 1950

Leu Pro  Val Leu His Arg Val  Ala Ala Ala Glu Thr  Ala Lys His
    1955                 1960                 1965

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    1970                 1975                 1980
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Arg Tyr  Arg Ser Leu Lys His  Phe Asn Tyr Asp Ile  Cys Gln Ser
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Cys Phe  Phe Ser Gly Arg Val  Ala Lys Gly His Lys  Met His Tyr
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Pro Met  Val Glu Tyr Cys Thr  Pro Thr Thr Ser Gly  Glu Asp Val
    2015                2020                2025

Arg Asp  Phe Ala Lys Val Leu  Lys Asn Lys Phe Arg  Thr Lys Arg
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Tyr Phe  Ala Lys His Pro Arg  Met Gly Tyr Leu Pro  Val Gln Thr
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Val Leu  Glu Gly Asp Asn Met  Glu Thr Pro Val Thr  Leu Ile Asn
    2060                2065                2070

Phe Trp  Pro Val Asp Ser Ala  Pro Ala Ser Ser Pro  Gln Leu Ser
    2075                2080                2085

His Asp  Asp Thr His Ser Arg  Ile Glu His Tyr Ala  Ser Arg Leu
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Ala Glu  Met Glu Asn Ser Asn  Gly Ser Tyr Leu Asn  Asp Ser Ile
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Ser Pro  Asn Glu Ser Ile Asp  Asp Glu His Leu Leu  Ile Gln His
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Tyr Cys  Gln Ser Leu Asn Gln  Asp Ser Pro Leu Ser  Gln Pro Arg
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Ser Pro  Ala Gln Ile Leu Ile  Ser Leu Glu Ser Glu  Glu Arg Gly
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Glu Leu  Glu Arg Ile Leu Ala  Asp Leu Glu Glu Glu  Asn Arg Asn
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Leu Gln  Ala Glu Tyr Asp Arg  Leu Lys Gln Gln His  Glu His Lys
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Lys His Asn Ala Leu Lys Asp Leu Arg Ser Gln Arg Arg Lys Lys Ala
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Leu Glu Ile Ser His Gln Trp Tyr Gln Tyr Lys Arg Gln Ala Asp Asp
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Leu Leu Lys Cys Leu Asp Asp Ile Glu Lys Lys Leu Ala Ser Leu Pro
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Glu Pro Arg Asp Glu Arg Lys Ile Lys Glu Ile Asp Arg Glu Leu Gln
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Lys Lys Lys Glu Glu Leu Asn Ala Val Arg Arg Gln Ala Glu Gly Leu
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            580                 585                 590

Ser Glu Asp Gly Ala Ala Met Ala Val Glu Pro Thr Gln Ile Gln Leu
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Ser Lys Arg Trp Arg Glu Ile Glu Ser Lys Phe Ala Gln Phe Arg Arg
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Leu Asn Phe Ala Gln Ile His Thr Val Arg Glu Glu Thr Met Met Val
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Met Thr Glu Asp Met Pro Leu Glu Ile Ser Tyr Val Pro Ser Thr Tyr
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Leu Thr Glu Ile Thr His Val Ser Gln Ala Leu Leu Glu Val Glu Gln
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Leu Leu Asn Ala Pro Asp Leu Cys Ala Lys Asp Phe Glu Asp Leu Phe
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Lys Gln Glu Glu Ser Leu Lys Asn Ile Lys Asp Ser Leu Gln Gln Ser
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Ser Gly Arg Ile Asp Ile Ile His Ser Lys Lys Thr Ala Ala Leu Gln
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Ser Ala Thr Pro Val Glu Arg Val Lys Leu Gln Glu Ala Leu Ser Gln
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Leu Asp Phe Gln Trp Glu Lys Val Asn Lys Met Tyr Lys Asp Arg Gln
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Gly Arg Phe Asp Arg Ser Val Glu Lys Trp Arg Arg Phe His Tyr Asp
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Ile Lys Ile Phe Asn Gln Trp Leu Thr Glu Ala Glu Gln Phe Leu Arg
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Lys Thr Gln Ile Pro Glu Asn Trp Glu His Ala Lys Tyr Lys Trp Tyr
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Thr Leu Asn Ala Thr Gly Glu Glu Ile Ile Gln Gln Ser Ser Lys Thr
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Asp Ala Ser Ile Leu Gln Glu Lys Leu Gly Ser Leu Asn Leu Arg Trp
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Gln Glu Val Cys Lys Gln Leu Ser Asp Arg Lys Lys Arg Leu Glu Glu
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Gln Lys Asn Ile Leu Ser Glu Phe Gln Arg Asp Leu Asn Glu Phe Val
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Leu Trp Leu Glu Glu Ala Asp Asn Ile Ala Ser Ile Pro Leu Glu Pro
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Gly Lys Glu Gln Gln Leu Lys Glu Lys Leu Glu Gln Val Lys Leu Leu
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Val Glu Glu Leu Pro Leu Arg Gln Gly Ile Leu Lys Gln Leu Asn Glu
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Thr Gly Gly Pro Val Leu Val Ser Ala Pro Ile Ser Pro Glu Glu Gln
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Asp Lys Leu Glu Asn Lys Leu Lys Gln Thr Asn Leu Gln Trp Ile Lys
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Val Ser Arg Ala Leu Pro Glu Lys Gln Gly Glu Ile Glu Ala Gln Ile
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Lys Asp Leu Gly Gln Leu Glu Lys Lys Leu Glu Asp Leu Glu Glu Gln
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Leu Asn His Leu Leu Leu Trp Leu  Ser Pro Ile Arg Asn  Gln Leu Glu
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Ile Tyr  Asn Gln Pro Asn Gln  Glu Gly Pro Phe Asp  Val Gln Glu
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Thr Glu  Ile Ala Val Gln Ala  Lys Gln Pro Asp Val  Glu Glu Ile
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Leu Ser  Lys Gly Gln His Leu  Tyr Lys Glu Lys Pro  Ala Thr Gln
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Pro Val  Lys Arg Lys Leu Glu  Asp Leu Ser Ser Glu  Trp Lys Ala
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Val Asn  Arg Leu Leu Gln Glu  Leu Arg Ala Lys Gln  Pro Asp Leu
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Ala Pro  Gly Leu Thr Thr Ile  Gly Ala Ser Pro Thr  Gln Thr Val
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Thr Leu  Val Thr Gln Pro Val  Val Thr Lys Glu Thr  Ala Ile Ser
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Lys Leu  Glu Met Pro Ser Ser  Leu Met Leu Glu Val  Pro Ala Leu
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Ala Asp  Phe Asn Arg Ala Trp  Thr Glu Leu Thr Asp  Trp Leu Ser
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Leu Leu  Asp Gln Val Ile Lys  Ser Gln Arg Val Met  Val Gly Asp
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Leu Glu  Asp Ile Asn Glu Met  Ile Ile Lys Gln Lys  Ala Thr Met
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Gln Asp  Leu Glu Gln Arg Arg  Pro Gln Leu Glu Glu  Leu Ile Thr
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Ala Ala  Gln Asn Leu Lys Asn  Lys Thr Ser Asn Gln  Glu Ala Arg
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Thr Ile  Ile Thr Asp Arg Ile  Glu Arg Ile Gln Asn  Gln Trp Asp
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Met Leu  Lys Asp Ser Thr Gln  Trp Leu Glu Ala Lys  Glu Glu Ala
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Glu Gln  Val Leu Gly Gln Ala  Arg Ala Lys Leu Glu  Ser Trp Lys
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Glu Gly  Pro Tyr Thr Val Asp  Ala Ile Gln Lys Lys  Ile Thr Glu
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Thr Lys  Gln Leu Ala Lys Asp  Leu Arg Gln Trp Gln  Thr Asn Val
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Asp Val  Ala Asn Asp Leu Ala  Leu Lys Leu Leu Arg  Asp Tyr Ser
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Ala Asp  Asp Thr Arg Lys Val  His Met Ile Thr Glu  Asn Ile Asn
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Ala Ser  Trp Arg Ser Ile His  Lys Arg Val Ser Glu  Arg Glu Ala
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Ala Leu  Glu Glu Thr His Arg  Leu Leu Gln Gln Phe  Pro Leu Asp
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Leu Glu  Lys Phe Leu Ala Trp  Leu Thr Glu Ala Glu  Thr Thr Ala
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Asn Val  Leu Gln Asp Ala Thr  Arg Lys Glu Arg Leu  Leu Glu Asp
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Ser Lys  Gly Val Lys Glu Leu  Met Lys Gln Trp Gln  Asp Leu Gln
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Gly Glu  Ile Glu Ala His Thr  Asp Val Tyr His Asn  Leu Asp Glu
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Asn Ser  Gln Lys Ile Leu Arg  Ser Leu Glu Gly Ser  Asp Asp Ala
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Val Leu Leu Gln Arg Arg Leu Asp Asn Met Asn Phe Lys Trp Ser
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Glu Leu Arg Lys Lys Ser Leu Asn Ile Arg Ser His Leu Glu Ala
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Ser Ser Asp Gln Trp Lys Arg Leu His Leu Ser Leu Gln Glu Leu
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Glu Leu Gln Glu Ala Thr Asp Glu Leu Asp Leu Lys Leu Arg Gln
1595 1600 1605

Ala Glu Val Ile Lys Gly Ser Trp Gln Pro Val Gly Asp Leu Leu
1610 1615 1620

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Ile Asp  Ser Leu Gln Asp His  Leu Glu Lys Val Lys  Ala Leu Arg
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Gly Glu  Ile Ala Pro Leu Lys  Glu Asn Val Ser His  Val Asn Asp
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Leu Ala  Arg Gln Leu Thr Thr  Leu Gly Ile Gln Leu  Ser Pro Tyr
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Asn Leu  Ser Thr Leu Glu Asp  Leu Asn Thr Arg Trp  Lys Leu Leu
    1670                1675                1680

Gln Val  Ala Val Glu Asp Arg  Val Arg Gln Leu His  Glu Ala His
    1685                1690                1695

Arg Asp  Phe Gly Pro Ala Ser  Gln His Phe Leu Ser  Thr Ser Val
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Gln Gly  Pro Trp Glu Arg Ala  Ile Ser Pro Asn Lys  Val Pro Tyr
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Tyr Ile  Asn His Glu Thr Gln  Thr Thr Cys Trp Asp  His Pro Lys
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Met Thr  Glu Leu Tyr Gln Ser  Leu Ala Asp Leu Asn  Asn Val Arg
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Phe Ser  Ala Tyr Arg Thr Ala  Met Lys Leu Arg Arg  Leu Gln Lys
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Ala Leu  Cys Leu Asp Leu Leu  Ser Leu Ser Ala Ala  Cys Asp Ala
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Leu Asp  Gln His Asn Leu Lys  Gln Asn Asp Gln Pro  Met Asp Ile
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Leu Gln  Ile Ile Asn Cys Leu  Thr Thr Ile Tyr Asp  Arg Leu Glu
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Gln Glu  His Asn Asn Leu Val  Asn Val Pro Leu Cys  Val Asp Met
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Cys Leu  Asn Trp Leu Leu Asn  Val Tyr Asp Thr Gly  Arg Thr Gly
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Arg Ile  Arg Val Leu Ser Phe  Lys Thr Gly Ile Ile  Ser Leu Cys
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Lys Ala  His Leu Glu Asp Lys  Tyr Arg Tyr Leu Phe  Lys Gln Val
    1865                1870                1875

Ala Ser  Ser Thr Gly Phe Cys  Asp Gln Arg Arg Leu  Gly Leu Leu
    1880                1885                1890

Leu His  Asp Ser Ile Gln Ile  Pro Arg Gln Leu Gly  Glu Val Ala
    1895                1900                1905

Ser Phe  Gly Gly Ser Asn Ile  Glu Pro Ser Val Arg  Ser Cys Phe
    1910                1915                1920

Gln Phe  Ala Asn Asn Lys Pro  Glu Ile Glu Ala Ala  Leu Phe Leu
    1925                1930                1935

Asp Trp  Met Arg Leu Glu Pro  Gln Ser Met Val Trp  Leu Pro Val
    1940                1945                1950

Leu His  Arg Val Ala Ala Ala  Glu Thr Ala Lys His  Gln Ala Lys
    1955                1960                1965

Cys Asn  Ile Cys Lys Glu Cys  Pro Ile Ile Gly Phe  Arg Tyr Arg
    1970                1975                1980

Ser Leu  Lys His Phe Asn Tyr  Asp Ile Cys Gln Ser  Cys Phe Phe
    1985                1990                1995

Ser Gly  Arg Val Ala Lys Gly  His Lys Met His Tyr  Pro Met Val
    2000                2005                2010

Glu Tyr  Cys Thr Pro Thr Thr  Ser Gly Glu Asp Val  Arg Asp Phe
    2015                2020                2025
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Ala Lys  Val Leu Lys Asn Lys  Phe Arg Thr Lys Arg  Tyr Phe Ala
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Lys His  Pro Arg Met Gly Tyr  Leu Pro Val Gln Thr  Val Leu Glu
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Gly Asp  Asn Met Glu Thr Pro  Val Thr Leu Ile Asn  Phe Trp Pro
    2060                2065                2070

Val Asp  Ser Ala Pro Ala Ser  Ser Pro Gln Leu Ser  His Asp Asp
    2075                2080                2085

Thr His  Ser Arg Ile Glu His  Tyr Ala Ser Arg Leu  Ala Glu Met
    2090                2095                2100

Glu Asn  Ser Asn Gly Ser Tyr  Leu Asn Asp Ser Ile  Ser Pro Asn
    2105                2110                2115

Glu Ser  Ile Asp Asp Glu His  Leu Leu Ile Gln His  Tyr Cys Gln
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Ser Leu  Asn Gln Asp Ser Pro  Leu Ser Gln Pro Arg  Ser Pro Ala
    2135                2140                2145

Gln Ile  Leu Ile Ser Leu Glu  Ser Glu Glu Arg Gly  Glu Leu Glu
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Arg Ile  Leu Ala Asp Leu Glu  Glu Glu Asn Arg Asn  Leu Gln Ala
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Glu Tyr  Asp Arg Leu Lys Gln  Gln His Glu His Lys  Gly Leu Ser
    2180                2185                2190

Pro Leu  Pro Ser Pro Pro Glu  Met Met Pro Thr Ser  Pro Gln Ser
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Pro Arg  Asp Ala Glu Leu Ile  Ala Glu Ala Lys Leu  Leu Arg Gln
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His Lys  Gly Arg Leu Glu Ala  Arg Met Gln Ile Leu  Glu Asp His
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Met Ile Ile Lys Gln Lys Ala Thr Met Gln Asp Leu Glu Gln Arg Arg
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Pro Gln Leu Glu Glu Leu Ile Thr Ala Ala Gln Asn Leu Lys Asn Lys
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Thr Ser Asn Gln Glu Ala Arg Thr Ile Ile Thr Asp Arg Ile Glu Arg
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Ile Gln Asn Gln Trp Asp Glu Val Gln Glu His Leu Gln Asn Arg Arg
            100                 105                 110

Gln Gln Leu Asn Glu Met Leu Lys Asp Ser Thr Gln Trp Leu Glu Ala
        115                 120                 125

Lys Glu Glu Ala Glu Gln Val Leu Gly Gln Ala Arg Ala Lys Leu Glu
    130                 135                 140

Ser Trp Lys Glu Gly Pro Tyr Thr Val Asp Ala Ile Gln Lys Lys Ile
145                 150                 155                 160

Thr Glu Thr Lys Gln Leu Ala Lys Asp Leu Arg Gln Trp Gln Thr Asn
                165                 170                 175

Val Asp Val Ala Asn Asp Leu Ala Leu Lys Leu Leu Arg Asp Tyr Ser
            180                 185                 190

Ala Asp Asp Thr Arg Lys Val His Met Ile Thr Glu Asn Ile Asn Ala
        195                 200                 205

Ser Trp Arg Ser Ile His Lys Arg Val Ser Glu Arg Glu Ala Ala Leu
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Glu Glu Thr His Arg Leu Leu Gln Gln Phe Pro Leu Asp Leu Glu Lys
225                 230                 235                 240

Phe Leu Ala Trp Leu Thr Glu Ala Glu Thr Thr Ala Asn Val Leu Gln
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Asp Ala Thr Arg Lys Glu Arg Leu Leu Glu Asp Ser Lys Gly Val Lys
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Glu Leu Met Lys Gln Trp Gln Asp Leu Gln Gly Glu Ile Glu Ala His
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```

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Thr Asp Val Tyr His Asn Leu Asp Glu Asn Ser Gln Lys Ile Leu Arg
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Ser Leu Glu Gly Ser Asp Asp Ala Val Leu Leu Gln Arg Arg Leu Asp
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Asn Met Asn Phe Lys Trp Ser Glu Leu Arg Lys Lys Ser Leu Asn Ile
                325                 330                 335

Arg Ser His Leu Glu Ala Ser Ser Asp Gln Trp Lys Arg Leu His Leu
            340                 345                 350

Ser Leu Gln Glu Leu Leu Val Trp Leu Gln Leu Lys Asp Asp Glu Leu
        355                 360                 365

Ser Arg Gln Ala Pro Ile Gly Gly Asp Phe Pro Ala Val Gln Lys Gln
    370                 375                 380

Asn Asp Val His Arg Ala Phe Lys Arg Glu Leu Lys Thr Lys Glu Pro
385                 390                 395                 400

Val Ile Met Ser Thr Leu Glu Thr Val Arg Ile Phe Leu Thr Glu Gln
                405                 410                 415

Pro Leu Glu Gly Leu Glu Lys Leu Tyr Gln Glu Pro Arg Glu Leu Pro
            420                 425                 430

Pro Glu Glu Arg Ala Gln Asn Val Thr Arg Leu Leu Arg Lys Gln Ala
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Glu Glu Val Asn Thr Glu Trp Glu Lys Leu Asn Leu His Ser Ala Asp
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Trp Gln Arg Lys Ile Asp Glu Thr Leu Glu Arg Leu Gln Glu Leu Gln
465                 470                 475                 480

Glu Ala Thr Asp Glu Leu Asp Leu Lys Leu Arg Gln Ala Glu Val Ile
                485                 490                 495
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Lys Gly Ser Trp Gln Pro Val Gly Asp Leu Leu Ile Asp Ser Leu Gln
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Asp His Leu Glu Lys Val Lys Ala Leu Arg Gly Glu Ile Ala Pro Leu
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Lys Glu Asn Val Ser His Val Asn Asp Leu Ala Arg Gln Leu Thr Thr
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Leu Gly Ile Gln Leu Ser Pro Tyr Asn Leu Ser Thr Leu Glu Asp Leu
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Asn Thr Arg Trp Lys Leu Leu Gln Val Ala Val Glu Asp Arg Val Arg
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Gln Leu His Glu Ala His Arg Asp Phe Gly Pro Ala Ser Gln His Phe
            580                 585                 590

Leu Ser Thr Ser Val Gln Gly Pro Trp Glu Arg Ala Ile Ser Pro Asn
        595                 600                 605

Lys Val Pro Tyr Tyr Ile Asn His Glu Thr Gln Thr Thr Cys Trp Asp
    610                 615                 620

His Pro Lys Met Thr Glu Leu Tyr Gln Ser Leu Ala Asp Leu Asn Asn
625                 630                 635                 640

Val Arg Phe Ser Ala Tyr Arg Thr Ala Met Lys Leu Arg Arg Leu Gln
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Lys Ala Leu Cys Leu Asp Leu Leu Ser Leu Ser Ala Ala Cys Asp Ala
            660                 665                 670

Leu Asp Gln His Asn Leu Lys Gln Asn Asp Gln Pro Met Asp Ile Leu
        675                 680                 685

Gln Ile Ile Asn Cys Leu Thr Thr Ile Tyr Asp Arg Leu Glu Gln Glu
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His Asn Asn Leu Val Asn Val Pro Leu Cys Val Asp Met Cys Leu Asn
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```

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Trp Leu Leu Asn Val Tyr Asp Thr Gly Arg Thr Gly Arg Ile Arg Val
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Leu Ser Phe Lys Thr Gly Ile Ile Ser Leu Cys Lys Ala His Leu Glu
            740                 745                 750

Asp Lys Tyr Arg Tyr Leu Phe Lys Gln Val Ala Ser Ser Thr Gly Phe
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Cys Asp Gln Arg Arg Leu Gly Leu Leu Leu His Asp Ser Ile Gln Ile
    770                 775                 780

Pro Arg Gln Leu Gly Glu Val Ala Ser Phe Gly Gly Ser Asn Ile Glu
785                 790                 795                 800

Pro Ser Val Arg Ser Cys Phe Gln Phe Ala Asn Asn Lys Pro Glu Ile
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Glu Ala Ala Leu Phe Leu Asp Trp Met Arg Leu Glu Pro Gln Ser Met
            820                 825                 830

Val Trp Leu Pro Val Leu His Arg Val Ala Ala Ala Glu Thr Ala Lys
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His Gln Ala Lys Cys Asn Ile Cys Lys Glu Cys Pro Ile Ile Gly Phe
    850                 855                 860

Arg Tyr Arg Ser Leu Lys His Phe Asn Tyr Asp Ile Cys Gln Ser Cys
865                 870                 875                 880

Phe Phe Ser Gly Arg Val Ala Lys Gly His Lys Met His Tyr Pro Met
                885                 890                 895

Val Glu Tyr Cys Thr Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe
            900                 905                 910

Ala Lys Val Leu Lys Asn Lys Phe Arg Thr Lys Arg Tyr Phe Ala Lys
        915                 920                 925
```

```
His Pro Arg Met Gly Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp
    930                 935                 940

Asn Met Glu Thr Pro Val Thr Leu Ile Asn Phe Trp Pro Val Asp Ser
945                 950                 955                 960

Ala Pro Ala Ser Ser Pro Gln Leu Ser His Asp Asp Thr His Ser Arg
                965                 970                 975

Ile Glu His Tyr Ala Ser Arg Leu Ala Glu Met Glu Asn Ser Asn Gly
            980                 985                 990

Ser Tyr Leu Asn Asp Ser Ile Ser  Pro Asn Glu Ser Ile  Asp Asp Glu
        995                 1000                1005

His Leu  Leu Ile Gln His Tyr  Cys Gln Ser Leu Asn  Gln Asp Ser
    1010                1015                1020

Pro Leu  Ser Gln Pro Arg Ser  Pro Ala Gln Ile Leu  Ile Ser Leu
    1025                1030                1035

Glu Ser  Glu Glu Arg Gly Glu  Leu Glu Arg Ile Leu  Ala Asp Leu
    1040                1045                1050

Glu Glu  Glu Asn Arg Asn Leu  Gln Ala Glu Tyr Asp  Arg Leu Lys
    1055                1060                1065

Gln Gln  His Glu His Lys Gly  Leu Ser Pro Leu Pro  Ser Pro Pro
    1070                1075                1080

Glu Met  Met Pro Thr Ser Pro  Gln Ser Pro Arg Asp  Ala Glu Leu
    1085                1090                1095

Ile Ala  Glu Ala Lys Leu Leu  Arg Gln His Lys Gly  Arg Leu Glu
    1100                1105                1110

Ala Arg  Met Gln Ile Leu Glu  Asp His Asn Lys Gln  Leu Glu Ser
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Gln Leu  His Arg Leu Arg Gln  Leu Leu Glu Gln Pro  Gln Ala Glu
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Pro Gln Asp Thr Ser Thr Gly Leu Glu Glu Val Met Glu Gln Leu
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Ile Leu Arg Ser Leu Glu Gly Ser Asp Asp Ala Val Leu Leu Gln Arg
        35                  40                  45

Arg Leu Asp Asn Met Asn Phe Lys Trp Ser Glu Leu Arg Lys Lys Ser
    50                  55                  60

Leu Asn Ile Arg Ser His Leu Glu Ala Ser Ser Asp Gln Trp Lys Arg
65                  70                  75                  80

Leu His Leu Ser Leu Gln Glu Leu Leu Val Trp Leu Gln Leu Lys Asp
                85                  90                  95

Asp Glu Leu Ser Arg Gln Ala Pro Ile Gly Gly Asp Phe Pro Ala Val
            100                 105                 110

Gln Lys Gln Asn Asp Val His Arg Ala Phe Lys Arg Glu Leu Lys Thr
        115                 120                 125

Lys Glu Pro Val Ile Met Ser Thr Leu Glu Thr Val Arg Ile Phe Leu
    130                 135                 140

Thr Glu Gln Pro Leu Glu Gly Leu Glu Lys Leu Tyr Gln Glu Pro Arg
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Glu Leu Pro Pro Glu Glu Arg Ala Gln Asn Val Thr Arg Leu Leu Arg
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Lys Gln Ala Glu Glu Val Asn Thr Glu Trp Glu Lys Leu Asn Leu His
            180                 185                 190

Ser Ala Asp Trp Gln Arg Lys Ile Asp Glu Thr Leu Glu Arg Leu Gln
        195                 200                 205

Glu Leu Gln Glu Ala Thr Asp Glu Leu Asp Leu Lys Leu Arg Gln Ala
    210                 215                 220
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Glu Val Ile Lys Gly Ser Trp Gln Pro Val Gly Asp Leu Leu Ile Asp
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Ser Leu Gln Asp His Leu Glu Lys Val Lys Ala Leu Arg Gly Glu Ile
                245                 250                 255

Ala Pro Leu Lys Glu Asn Val Ser His Val Asn Asp Leu Ala Arg Gln
            260                 265                 270

Leu Thr Thr Leu Gly Ile Gln Leu Ser Pro Tyr Asn Leu Ser Thr Leu
        275                 280                 285

Glu Asp Leu Asn Thr Arg Trp Lys Leu Leu Gln Val Ala Val Glu Asp
    290                 295                 300

Arg Val Arg Gln Leu His Glu Ala His Arg Asp Phe Gly Pro Ala Ser
305                 310                 315                 320

Gln His Phe Leu Ser Thr Ser Val Gln Gly Pro Trp Glu Arg Ala Ile
                325                 330                 335

Ser Pro Asn Lys Val Pro Tyr Tyr Ile Asn His Glu Thr Gln Thr Thr
            340                 345                 350

Cys Trp Asp His Pro Lys Met Thr Glu Leu Tyr Gln Ser Leu Ala Asp
        355                 360                 365

Leu Asn Asn Val Arg Phe Ser Ala Tyr Arg Thr Ala Met Lys Leu Arg
    370                 375                 380

Arg Leu Gln Lys Ala Leu Cys Leu Asp Leu Leu Ser Leu Ser Ala Ala
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Cys Asp Ala Leu Asp Gln His Asn Leu Lys Gln Asn Asp Gln Pro Met
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Glu Gln Glu His Asn Asn Leu Val Asn Val Pro Leu Cys Val Asp Met
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His Leu Glu Asp Lys Tyr Arg Tyr Leu Phe Lys Gln Val Ala Ser Ser
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Asn Ile Glu Pro Ser Val Arg Ser Cys Phe Gln Phe Ala Asn Asn Lys
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Pro Glu Ile Glu Ala Ala Leu Phe Leu Asp Trp Met Arg Leu Glu Pro
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Gln Ser Met Val Trp Leu Pro Val Leu His Arg Val Ala Ala Ala Glu
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Thr Ala Lys His Gln Ala Lys Cys Asn Ile Cys Lys Glu Cys Pro Ile
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Ile Gly Phe Arg Tyr Arg Ser Leu Lys His Phe Asn Tyr Asp Ile Cys
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Gln Ser Cys Phe Phe Ser Gly Arg Val Ala Lys Gly His Lys Met His
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Tyr Pro Met Val Glu Tyr Cys Thr Pro Thr Thr Ser Gly Glu Asp Val
625                 630                 635                 640

Arg Asp Phe Ala Lys Val Leu Lys Asn Lys Phe Arg Thr Lys Arg Tyr
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Phe Ala Lys His Pro Arg Met Gly Tyr Leu Pro Val Gln Thr Val Leu
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Glu Gly Asp Asn Met Glu Thr Pro Val Thr Leu Ile Asn Phe Trp Pro
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Val Asp Ser Ala Pro Ala Ser Ser Pro Gln Leu Ser His Asp Asp Thr
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His Ser Arg Ile Glu His Tyr Ala Ser Arg Leu Ala Glu Met Glu Asn
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Ser Asn Gly Ser Tyr Leu Asn Asp Ser Ile Ser Pro Asn Glu Ser Ile
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Asp Asp Glu His Leu Leu Ile Gln His Tyr Cys Gln Ser Leu Asn Gln
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Asp Ser Pro Leu Ser Gln Pro Arg Ser Pro Ala Gln Ile Leu Ile Ser
        755                 760                 765

Leu Glu Ser Glu Glu Arg Gly Glu Leu Glu Arg Ile Leu Ala Asp Leu
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Glu Glu Glu Asn Arg Asn Leu Gln Ala Glu Tyr Asp Arg Leu Lys Gln
785                 790                 795                 800

Gln His Glu His Lys Gly Leu Ser Pro Leu Pro Ser Pro Pro Glu Met
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Met Pro Thr Ser Pro Gln Ser Pro Arg Asp Ala Glu Leu Ile Ala Glu
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Ala Lys Leu Leu Arg Gln His Lys Gly Arg Leu Glu Ala Arg Met Gln
        835                 840                 845

Ile Leu Glu Asp His Asn Lys Gln Leu Glu Ser Gln Leu His Arg Leu
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Arg Gln Leu Leu Glu Gln Pro Gln Ala Glu Ala Lys Val Asn Gly Thr
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Glu Glu Asp Leu Leu Ser Pro Pro Gln Asp Thr Ser Thr Gly Leu Glu
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Val Arg Phe Ser Ala Tyr Arg Thr Ala Met Lys Leu Arg Arg Leu Gln
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Lys Ala Leu Cys Leu Asp Leu Leu Ser Leu Ser Ala Ala Cys Asp Ala
    50                  55                  60

Leu Asp Gln His Asn Leu Lys Gln Asn Asp Gln Pro Met Asp Ile Leu
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Gln Ile Ile Asn Cys Leu Thr Thr Ile Tyr Asp Arg Leu Glu Gln Glu
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His Asn Asn Leu Val Asn Val Pro Leu Cys Val Asp Met Cys Leu Asn
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Trp Leu Leu Asn Val Tyr Asp Thr Gly Arg Thr Gly Arg Ile Arg Val
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Leu Ser Phe Lys Thr Gly Ile Ile Ser Leu Cys Lys Ala His Leu Glu
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Asp Lys Tyr Arg Tyr Leu Phe Lys Gln Val Ala Ser Ser Thr Gly Phe
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Cys Asp Gln Arg Arg Leu Gly Leu Leu Leu His Asp Ser Ile Gln Ile
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Pro Arg Gln Leu Gly Glu Val Ala Ser Phe Gly Gly Ser Asn Ile Glu
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Pro Ser Val Arg Ser Cys Phe Gln Phe Ala Asn Asn Lys Pro Glu Ile
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Glu Ala Ala Leu Phe Leu Asp Trp Met Arg Leu Glu Pro Gln Ser Met
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His Gln Ala Lys Cys Asn Ile Cys Lys Glu Cys Pro Ile Ile Gly Phe
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Arg Tyr Arg Ser Leu Lys His Phe Asn Tyr Asp Ile Cys Gln Ser Cys
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Phe Phe Ser Gly Arg Val Ala Lys Gly His Lys Met His Tyr Pro Met
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Val Glu Tyr Cys Thr Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe
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Ala Lys Val Leu Lys Asn Lys Phe Arg Thr Lys Arg Tyr Phe Ala Lys
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His Pro Arg Met Gly Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp
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Asn Met Glu Thr Pro Val Thr Leu Ile Asn Phe Trp Pro Val Asp Ser
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Ala Pro Ala Ser Ser Pro Gln Leu Ser His Asp Asp Thr His Ser Arg
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Ile Glu His Tyr Ala Ser Arg Leu Ala Glu Met Glu Asn Ser Asn Gly
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Ser Tyr Leu Asn Asp Ser Ile Ser Pro Asn Glu Ser Ile Asp Asp Glu
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His Leu Leu Ile Gln His Tyr Cys Gln Ser Leu Asn Gln Asp Ser Pro
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Asn Arg Asn Leu Gln Ala Glu Tyr Asp Arg Leu Lys Gln Gln His Glu
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Ser Pro Gln Ser Pro Arg Asp Ala Glu Leu Ile Ala Glu Ala Lys Leu
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Leu Arg Gln His Lys Gly Arg Leu Glu Ala Arg Met Gln Ile Leu Glu
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Asp His Asn Lys Gln Leu Glu Ser Gln Leu His Arg Leu Arg Gln Leu
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Leu Glu Gln Pro Gln Ala Glu Ala Lys Val Asn Gly Thr Thr Val Ser
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Ser Pro Ser Thr Ser Leu Gln Arg Ser Asp Ser Ser Gln Pro Met Leu
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Leu Arg Val Val Gly Ser Gln Thr Ser Asp Ser Met Gly Glu Glu Asp
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Leu Leu Ser Pro Pro Gln Asp Thr Ser Thr Gly Leu Glu Glu Val Met
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Glu Gln Leu Asn Asn Ser Phe Pro Ser Ser Arg Gly Arg Asn Thr Pro
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Gly Lys Pro Met Arg Glu Asp Thr Met
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Cys Asp Gln Arg Arg Leu Gly Leu Leu Leu His Asp Ser Ile Gln Ile
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            180                 185                 190

Pro Ser Val Arg Ser Cys Phe Gln Phe Ala Asn Asn Lys Pro Glu Ile
        195                 200                 205

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            260                 265                 270

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Ala Lys Val Leu Lys Asn Lys Phe Arg Thr Lys Arg Tyr Phe Ala Lys
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His Pro Arg Met Gly Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp
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Asn Met Glu Thr Pro Val Thr Leu Ile Asn Phe Trp Pro Val Asp Ser
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Ala Pro Ala Ser Ser Pro Gln Leu Ser His Asp Asp Thr His Ser Arg
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Ile Glu His Tyr Ala Ser Arg Leu Ala Glu Met Glu Asn Ser Asn Gly
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Ser Tyr Leu Asn Asp Ser Ile Ser Pro Asn Glu Ser Ile Asp Asp Glu
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His Leu Leu Ile Gln His Tyr Cys Gln Ser Leu Asn Gln Asp Ser Pro
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Leu Ser Gln Pro Arg Ser Pro Ala Gln Ile Leu Ile Ser Leu Glu Ser
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Glu Glu Arg Gly Glu Leu Glu Arg Ile Leu Ala Asp Leu Glu Glu Glu
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Asn Arg Asn Leu Gln Ala Glu Tyr Asp Arg Leu Lys Gln Gln His Glu
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His Lys Gly Leu Ser Pro Leu Pro Ser Pro Pro Glu Met Met Pro Thr
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Ser Pro Gln Ser Pro Arg Asp Ala Glu Leu Ile Ala Glu Ala Lys Leu
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Leu Arg Gln His Lys Gly Arg Leu Glu Ala Arg Met Gln Ile Leu Glu
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Asp His Asn Lys Gln Leu Glu Ser Gln Leu His Arg Leu Arg Gln Leu
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Ser Pro Ser Thr Ser Leu Gln Arg Ser Asp Ser Ser Gln Pro Met Leu
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Leu Leu Ser Pro Pro Gln Asp Thr Ser Thr Gly Leu Glu Glu Val Met
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Val Arg Phe Ser Ala Tyr Arg Thr Ala Met Lys Leu Arg Arg Leu Gln
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Lys Ala Leu Cys Leu Asp Leu Leu Ser Leu Ser Ala Ala Cys Asp Ala
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Leu Asp Gln His Asn Leu Lys Gln Asn Asp Gln Pro Met Asp Ile Leu
65                  70                  75                  80

Gln Ile Ile Asn Cys Leu Thr Thr Ile Tyr Asp Arg Leu Glu Gln Glu
                85                  90                  95

His Asn Asn Leu Val Asn Val Pro Leu Cys Val Asp Met Cys Leu Asn
            100                 105                 110

Trp Leu Leu Asn Val Tyr Asp Thr Gly Arg Thr Gly Arg Ile Arg Val
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Leu Ser Phe Lys Thr Gly Ile Ile Ser Leu Cys Lys Ala His Leu Glu
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Asp Lys Tyr Arg Tyr Leu Phe Lys Gln Val Ala Ser Ser Thr Gly Phe
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Cys Asp Gln Arg Arg Leu Gly Leu Leu Leu His Asp Ser Ile Gln Ile
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Pro Arg Gln Leu Gly Glu Val Ala Ser Phe Gly Gly Ser Asn Ile Glu
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Pro Ser Val Arg Ser Cys Phe Gln Phe Ala Asn Asn Lys Pro Glu Ile
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Glu Ala Ala Leu Phe Leu Asp Trp Met Arg Leu Glu Pro Gln Ser Met
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Val Trp Leu Pro Val Leu His Arg Val Ala Ala Ala Glu Thr Ala Lys
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His Gln Ala Lys Cys Asn Ile Cys Lys Glu Cys Pro Ile Ile Gly Phe
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Arg Tyr Arg Ser Leu Lys His Phe Asn Tyr Asp Ile Cys Gln Ser Cys
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Phe Phe Ser Gly Arg Val Ala Lys Gly His Lys Met His Tyr Pro Met
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Val Glu Tyr Cys Thr Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe
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Ala Lys Val Leu Lys Asn Lys Phe Arg Thr Lys Arg Tyr Phe Ala Lys
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His Pro Arg Met Gly Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp
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Asn Met Glu Thr Pro Ala Ser Ser Pro Gln Leu Ser His Asp Asp Thr
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His Ser Arg Ile Glu His Tyr Ala Ser Arg Leu Ala Glu Met Glu Asn
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Ser Asn Gly Ser Tyr Leu Asn Asp Ser Ile Ser Pro Asn Glu Ser Ile
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Asp Asp Glu His Leu Leu Ile Gln His Tyr Cys Gln Ser Leu Asn Gln
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Asp Ser Pro Leu Ser Gln Pro Arg Ser Pro Ala Gln Ile Leu Ile Ser
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Leu Glu Ser Glu Glu Arg Gly Glu Leu Glu Arg Ile Leu Ala Asp Leu
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Glu Glu Glu Asn Arg Asn Leu Gln Ala Glu Tyr Asp Arg Leu Lys Gln
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Gln His Glu His Lys Gly Leu Ser Pro Leu Pro Ser Pro Pro Glu Met
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Ile Leu Glu Asp His Asn Lys Gln Leu Glu Ser Gln Leu His Arg Leu
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Thr Val Ser Ser Pro Ser Thr Ser Leu Gln Arg Ser Asp Ser Ser Gln
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Pro Met Leu Leu Arg Val Val Gly Ser Gln Thr Ser Asp Ser Met Gly
545                 550                 555                 560

Glu Glu Asp Leu Leu Ser Pro Pro Gln Asp Thr Ser Thr Gly Leu Glu
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Cys Asp Gln Arg Arg Leu Gly Leu Leu Leu His Asp Ser Ile Gln Ile
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            260                 265                 270

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        275                 280                 285

Val Glu Tyr Cys Thr Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe
    290                 295                 300

Ala Lys Val Leu Lys Asn Lys Phe Arg Thr Lys Arg Tyr Phe Ala Lys
305                 310                 315                 320

His Pro Arg Met Gly Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp
                325                 330                 335

Asn Met Glu Thr Pro Ala Ser Ser Pro Gln Leu Ser His Asp Asp Thr
            340                 345                 350

His Ser Arg Ile Glu His Tyr Ala Ser Arg Leu Ala Glu Met Glu Asn
        355                 360                 365

Ser Asn Gly Ser Tyr Leu Asn Asp Ser Ile Ser Pro Asn Glu Ser Ile
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Asp Asp Glu His Leu Leu Ile Gln His Tyr Cys Gln Ser Leu Asn Gln
385                 390                 395                 400
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Asp Ser Pro Leu Ser Gln Pro Arg Ser Pro Ala Gln Ile Leu Ile Ser
                405                 410                 415

Leu Glu Ser Glu Glu Arg Gly Glu Leu Glu Arg Ile Leu Ala Asp Leu
            420                 425                 430

Glu Glu Glu Asn Arg Asn Leu Gln Ala Glu Tyr Asp Arg Leu Lys Gln
        435                 440                 445

Gln His Glu His Lys Gly Leu Ser Pro Leu Pro Ser Pro Pro Glu Met
    450                 455                 460

Met Pro Thr Ser Pro Gln Ser Pro Arg Asp Ala Glu Leu Ile Ala Glu
465                 470                 475                 480

Ala Lys Leu Leu Arg Gln His Lys Gly Arg Leu Glu Ala Arg Met Gln
                485                 490                 495

Ile Leu Glu Asp His Asn Lys Gln Leu Glu Ser Gln Leu His Arg Leu
            500                 505                 510

Arg Gln Leu Leu Glu Gln Pro Gln Ala Glu Ala Lys Val Asn Gly Thr
        515                 520                 525

Thr Val Ser Ser Pro Ser Thr Ser Leu Gln Arg Ser Asp Ser Ser Gln
    530                 535                 540

Pro Met Leu Leu Arg Val Val Gly Ser Gln Thr Ser Asp Ser Met Gly
545                 550                 555                 560

Glu Glu Asp Leu Leu Ser Pro Pro Gln Asp Thr Ser Thr Gly Leu Glu
                565                 570                 575

Glu Val Met Glu Gln Leu Asn Asn Ser Phe Pro Ser Ser Arg Gly His
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Asn Val Gly Ser Leu Phe His Met Ala Asp Asp Leu Gly Arg Ala Met
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120

tgggaccatc ccaaaatgac agagctctac cagtctttag ctgacctgaa taatgtcaga
180

ttctcagctt ataggactgc catgaaactc cgaagactgc agaaggccct ttgcttggat
240

ctcttgagcc tgtcagctgc atgtgatgcc ttggaccagc acaacctcaa gcaaaatgac
300

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caagagcaca acaatttggt caacgtccct ctctgcgtgg atatgtgtct gaactggctg
420

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480

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540

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1080

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His Pro Lys Met Thr Glu Leu Tyr Gln Ser Leu Ala Asp Leu Asn Asn
20 25 30

Val Arg Phe Ser Ala Tyr Arg Thr Ala Met Lys Leu Arg Arg Leu Gln
35 40 45

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Lys Ala Leu Cys Leu Asp Leu Leu Ser Leu Ser Ala Ala Cys Asp Ala
    50                  55                  60

Leu Asp Gln His Asn Leu Lys Gln Asn Asp Gln Pro Met Asp Ile Leu
65                  70                  75                  80

Gln Ile Ile Asn Cys Leu Thr Thr Ile Tyr Asp Arg Leu Glu Gln Glu
                85                  90                  95

His Asn Asn Leu Val Asn Val Pro Leu Cys Val Asp Met Cys Leu Asn
            100                 105                 110

Trp Leu Leu Asn Val Tyr Asp Thr Gly Arg Thr Gly Arg Ile Arg Val
        115                 120                 125

Leu Ser Phe Lys Thr Gly Ile Ile Ser Leu Cys Lys Ala His Leu Glu
    130                 135                 140

Asp Lys Tyr Arg Tyr Leu Phe Lys Gln Val Ala Ser Ser Thr Gly Phe
145                 150                 155                 160

Cys Asp Gln Arg Arg Leu Gly Leu Leu Leu His Asp Ser Ile Gln Ile
                165                 170                 175

Pro Arg Gln Leu Gly Glu Val Ala Ser Phe Gly Gly Ser Asn Ile Glu
            180                 185                 190

Pro Ser Val Arg Ser Cys Phe Gln Phe Ala Asn Asn Lys Pro Glu Ile
        195                 200                 205

Glu Ala Ala Leu Phe Leu Asp Trp Met Arg Leu Glu Pro Gln Ser Met
    210                 215                 220

Val Trp Leu Pro Val Leu His Arg Val Ala Ala Ala Glu Thr Ala Lys
225                 230                 235                 240

His Gln Ala Lys Cys Asn Ile Cys Lys Glu Cys Pro Ile Ile Gly Phe
                245                 250                 255
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Arg Tyr Arg Ser Leu Lys His Phe Asn Tyr Asp Ile Cys Gln Ser Cys
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Phe Phe Ser Gly Arg Val Ala Lys Gly His Lys Met His Tyr Pro Met
        275                 280                 285

Val Glu Tyr Cys Thr Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe
    290                 295                 300

Ala Lys Val Leu Lys Asn Lys Phe Arg Thr Lys Arg Tyr Phe Ala Lys
305                 310                 315                 320

His Pro Arg Met Gly Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp
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Asn Met Glu Thr
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120

cagcggcaaa ctgttgtcag aacattgaat gcaactgggg aagaaataat tcagcaatcc
180

tcaaaaacag atgccagtat tctacaggaa aaattgggaa gcctgaatct gcggtggcag
240

gaggtctgca aacagctgtc agacagaaaa aagaggctag aagaacaaaa gaatatcttg
300

tcagaatttc aaagagattt aaatgaattt gttttatggt tggaggaagc agataacatt
360

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420

aagttactgg tggaagagtt gcccctgcgc cagggaattc tcaaacaatt aaatgaaact
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720

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35 40 45

Met Ile Ile Lys Gln Lys Ala Thr Met Gln Asp Leu Glu Gln Arg Arg
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Pro Gln Leu Glu Glu Leu Ile Thr Ala Ala Gln Asn Leu Lys Asn Lys
65 70 75 80

Thr Ser Asn Gln Glu Ala Arg Thr Ile Ile Thr Asp Arg Ile Glu Arg
85 90 95

Ile Gln Asn Gln Trp Asp Glu Val Gln Glu His Leu Gln Asn Arg Arg
100 105 110

Gln Gln Leu Asn Glu Met Leu Lys Asp Ser Thr Gln Trp Leu Glu Ala
115 120 125

Lys Glu Glu Ala Glu Gln Val Leu Gly Gln Ala Arg Ala Lys Leu Glu
130 135 140

Ser Trp Lys Glu Gly Pro Tyr Thr Val Asp Ala Ile Gln Lys Lys Ile
145 150 155 160

Thr Glu Thr Lys Gln Leu Ala Lys Asp Leu Arg Gln Trp Gln Thr Asn

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Val Asp Val Ala Asn Asp Leu Ala Leu Lys Leu Leu Arg Asp Tyr Ser
            180                 185                 190

Ala Asp Asp Thr Arg Lys Val His Met Ile Thr Glu Asn Ile Asn Ala
        195                 200                 205

Ser Trp Arg Ser Ile His Lys Arg Val Ser Glu Arg Glu Ala Ala Leu
    210                 215                 220

Glu Glu Thr His Arg Leu Leu Gln Gln Phe Pro Leu Asp Leu Glu Lys
225                 230                 235                 240

Phe Leu Ala Trp Leu Thr Glu Ala Glu Thr Thr Ala Asn Val Leu Gln
                245                 250                 255

Asp Ala Thr Arg Lys Glu Arg Leu Leu Glu Asp Ser Lys Gly Val Lys
            260                 265                 270

Glu Leu Met Lys Gln Trp Gln Asp Leu Gln Gly Glu Ile Glu Ala His
        275                 280                 285

Thr Asp Val Tyr His Asn Leu Asp Glu Asn Ser Gln Lys Ile Leu Arg
    290                 295                 300

Ser Leu Glu Gly Ser Asp Asp Ala Val Leu Leu Gln Arg Arg Leu Asp
305                 310                 315                 320

Asn Met Asn Phe Lys Trp Ser Glu Leu Arg Lys Lys Ser Leu Asn Ile
                325                 330                 335

Arg Ser His Leu Glu Ala Ser Ser Asp Gln Trp Lys Arg Leu His Leu
            340                 345                 350

Ser Leu Gln Glu Leu Leu Val Trp Leu Gln Leu Lys Asp Asp Glu Leu
        355                 360                 365

Ser Arg Gln Ala Pro Ile Gly Gly Asp Phe Pro Ala Val Gln Lys Gln
    370                 375                 380
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Asn Asp Val His Arg Ala Phe Lys Arg Glu Leu Lys Thr Lys Glu Pro
385                 390                 395                 400

Val Ile Met Ser Thr Leu Glu Thr Val Arg Ile Phe Leu Thr Glu Gln
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Pro Leu Glu Gly Leu Glu Lys Leu Tyr Gln Glu Pro Arg Glu Leu Pro
            420                 425                 430

Pro Glu Glu Arg Ala Gln Asn Val Thr Arg Leu Leu Arg Lys Gln Ala
        435                 440                 445

Glu Glu Val Asn Thr Glu Trp Glu Lys Leu Asn Leu His Ser Ala Asp
    450                 455                 460

Trp Gln Arg Lys Ile Asp Glu Thr Leu Glu Arg Leu Gln Glu Leu Gln
465                 470                 475                 480

Glu Ala Thr Asp Glu Leu Asp Leu Lys Leu Arg Gln Ala Glu Val Ile
                485                 490                 495

Lys Gly Ser Trp Gln Pro Val Gly Asp Leu Leu Ile Asp Ser Leu Gln
            500                 505                 510

Asp His Leu Glu Lys Val Lys Ala Leu Arg Gly Glu Ile Ala Pro Leu
        515                 520                 525

Lys Glu Asn Val Ser His Val Asn Asp Leu Ala Arg Gln Leu Thr Thr
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Leu Gly Ile Gln Leu Ser Pro Tyr Asn Leu Ser Thr Leu Glu Asp Leu
545                 550                 555                 560

Asn Thr Arg Trp Lys Leu Leu Gln Val Ala Val Glu Asp Arg Val Arg
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Gln Leu His Glu Ala His Arg Asp Phe Gly Pro Ala Ser Gln His Phe
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Leu Ser Thr Ser Val Gln Gly Pro Trp Glu Arg Ala Ile Ser Pro Asn
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595 600 605

Lys Val Pro Tyr Tyr Ile Asn His Glu Thr Gln Thr Thr Cys Trp Asp
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His Pro Lys Met Thr Glu Leu Tyr Gln Ser Leu Ala Asp Leu Asn Asn
625 630 635 640

Val Arg Phe Ser Ala Tyr Arg Thr Ala Met Lys Leu Arg Arg Leu Gln
645 650 655

Lys Ala Leu Cys Leu Asp Leu Leu Ser Leu Ser Ala Ala Cys Asp Ala
660 665 670

Leu Asp Gln His Asn Leu Lys Gln Asn Asp Gln Pro Met Asp Ile Leu
675 680 685

Gln Ile Ile Asn Cys Leu Thr Thr Ile Tyr Asp Arg Leu Glu Gln Glu
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Asp Lys Tyr Arg Tyr Leu Phe Lys Gln Val Ala Ser Ser Thr Gly Phe
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Cys Asp Gln Arg Arg Leu Gly Leu Leu Leu His Asp Ser Ile Gln Ile
770 775 780

Pro Arg Gln Leu Gly Glu Val Ala Ser Phe Gly Gly Ser Asn Ile Glu
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Pro Ser Val Arg Ser Cys Phe Gln Phe Ala Asn Asn Lys Pro Glu Ile
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Glu Ala Ala Leu Phe Leu Asp Trp Met Arg Leu Glu Pro Gln Ser Met
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Val Trp Leu Pro Val Leu His Arg Val Ala Ala Ala Glu Thr Ala Lys
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His Gln Ala Lys Cys Asn Ile Cys Lys Glu Cys Pro Ile Ile Gly Phe
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Arg Tyr Arg Ser Leu Lys His Phe Asn Tyr Asp Ile Cys Gln Ser Cys
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Phe Phe Ser Gly Arg Val Ala Lys Gly His Lys Met His Tyr Pro Met
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Val Glu Tyr Cys Thr Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe
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Ala Lys Val Leu Lys Asn Lys Phe Arg Thr Lys Arg Tyr Phe Ala Lys
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His Pro Arg Met Gly Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp
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Asn Met Glu Thr Asn Leu Gln Ala Glu Tyr Asp Arg Leu Lys Gln Gln
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His Glu His Lys Gly Leu Ser Pro Leu Pro Ser Pro Pro Glu Met Met
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Lys Leu Leu Arg Gln His Lys Gly  Arg Leu Glu Ala Arg  Met Gln Ile
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Ile Lys Ser Gln Arg Val Met Val Gly Asp Leu Glu Asp Ile Asn Glu
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Pro Gln Leu Glu Glu Leu Ile Thr Ala Ala Gln Asn Leu Lys Asn Lys
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Thr Ser Asn Gln Glu Ala Arg Thr Ile Ile Thr Asp Arg Ile Glu Arg
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Lys Glu Glu Ala Glu Gln Val Leu Gly Gln Ala Arg Ala Lys Leu Glu
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Ser Trp Lys Glu Gly Pro Tyr Thr Val Asp Ala Ile Gln Lys Lys Ile
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Thr Glu Thr Lys Gln Leu Ala Lys Asp Leu Arg Gln Trp Gln Thr Asn
                165                 170                 175

Val Asp Val Ala Asn Asp Leu Ala Leu Lys Leu Leu Arg Asp Tyr Ser
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Ala Asp Asp Thr Arg Lys Val His Met Ile Thr Glu Asn Ile Asn Ala
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Ser Trp Arg Ser Ile His Lys Arg Val Ser Glu Arg Glu Ala Ala Leu
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Glu Glu Thr His Arg Leu Leu Gln Gln Phe Pro Leu Asp Leu Glu Lys
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Phe Leu Ala Trp Leu Thr Glu Ala Glu Thr Thr Ala Asn Val Leu Gln
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Glu Leu Met Lys Gln Trp Gln Asp Leu Gln Gly Glu Ile Glu Ala His
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Thr Asp Val Tyr His Asn Leu Asp Glu Asn Ser Gln Lys Ile Leu Arg
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Glu Ala Thr Asp Glu Leu Asp Leu Lys Leu Arg Gln Ala Glu Val Ile
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Lys Glu Asn Val Ser His Val Asn Asp Leu Ala Arg Gln Leu Thr Thr
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Leu Gly Ile Gln Leu Ser Pro Tyr Asn Leu Ser Thr Leu Glu Asp Leu
545                 550                 555                 560

Asn Thr Arg Trp Lys Leu Leu Gln Val Ala Val Glu Asp Arg Val Arg
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Gln Leu His Glu Ala His Arg Asp Phe Gly Pro Ala Ser Gln His Phe
            580                 585                 590

Leu Ser Thr Ser Val Gln Gly Pro Trp Glu Arg Ala Ile Ser Pro Asn
        595                 600                 605

Lys Val Pro Tyr Tyr Ile Asn His Glu Thr Gln Thr Thr Cys Trp Asp
    610                 615                 620

His Pro Lys Met Thr Glu Leu Tyr Gln Ser Leu Ala Asp Leu Asn Asn
625                 630                 635                 640

Val Arg Phe Ser Ala Tyr Arg Thr Ala Met Lys Leu Arg Arg Leu Gln
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Lys Ala Leu Cys Leu Asp Leu Leu Ser Leu Ser Ala Ala Cys Asp Ala
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Leu Asp Gln His Asn Leu Lys Gln Asn Asp Gln Pro Met Asp Ile Leu
        675                 680                 685

Gln Ile Ile Asn Cys Leu Thr Thr Ile Tyr Asp Arg Leu Glu Gln Glu
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His Asn Asn Leu Val Asn Val Pro Leu Cys Val Asp Met Cys Leu Asn
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Trp Leu Leu Asn Val Tyr Asp Thr Gly Arg Thr Gly Arg Ile Arg Val
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Leu Ser Phe Lys Thr Gly Ile Ile Ser Leu Cys Lys Ala His Leu Glu
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Cys Asp Gln Arg Arg Leu Gly Leu Leu Leu His Asp Ser Ile Gln Ile
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Pro Arg Gln Leu Gly Glu Val Ala Ser Phe Gly Gly Ser Asn Ile Glu
785                 790                 795                 800

Pro Ser Val Arg Ser Cys Phe Gln Phe Ala Asn Asn Lys Pro Glu Ile
                805                 810                 815

Glu Ala Ala Leu Phe Leu Asp Trp Met Arg Leu Glu Pro Gln Ser Met
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Val Trp Leu Pro Val Leu His Arg Val Ala Ala Ala Glu Thr Ala Lys
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His Gln Ala Lys Cys Asn Ile Cys Lys Glu Cys Pro Ile Ile Gly Phe
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Arg Tyr Arg Ser Leu Lys His Phe Asn Tyr Asp Ile Cys Gln Ser Cys
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Phe Phe Ser Gly Arg Val Ala Lys Gly His Lys Met His Tyr Pro Met
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Ala Lys Val Leu Lys Asn Lys Phe Arg Thr Lys Arg Tyr Phe Ala Lys
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His Pro Arg Met Gly Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp
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Asn Met Glu Thr Pro Val Thr Leu Ile Asn Phe Trp Pro Val Asp Ser
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Ser Tyr Leu Asn Asp Ser Ile Ser  Pro Asn Glu Ser Ile  Asp Asp Glu
        995                 1000                1005

His Leu  Leu Ile Gln His Tyr  Cys Gln Ser Leu Asn  Gln Asp Ser
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Pro Leu  Ser Gln Pro Arg Ser  Pro Ala Gln Ile Leu  Ile Ser Leu
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Glu Ser  Glu Glu Arg Gly Glu  Leu Glu Arg Ile Leu  Ala Asp Leu
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Glu Glu  Glu Asn Arg Asn Leu  Gln Ala Glu Tyr Asp  Arg Leu Lys
    1055                1060                1065

Gln Gln  His Glu His Lys Gly  Leu Ser Pro Leu Pro  Ser Pro Pro
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Glu Met  Met Pro Thr Ser Pro  Gln Ser Pro Arg Asp  Ala Glu Leu
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Ile Ala  Glu Ala Lys Leu Leu  Arg Gln His Lys Gly  Arg Leu Glu
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Ala Arg  Met Gln Ile Leu Glu  Asp His Asn Lys Gln  Leu Glu Ser
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Thr Glu Thr Lys Gln Leu Ala Lys Asp Leu Arg Gln Trp Gln Thr Asn
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Val Asp Val Ala Asn Asp Leu Ala Leu Lys Leu Leu Arg Asp Tyr Ser
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Ala Asp Asp Thr Arg Lys Val His Met Ile Thr Glu Asn Ile Asn Ala
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Ser Trp Arg Ser Ile His Lys Arg Val Ser Glu Arg Glu Ala Ala Leu
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Glu Glu Thr His Arg Leu Leu Gln Gln Phe Pro Leu Asp Leu Glu Lys
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Phe Leu Ala Trp Leu Thr Glu Ala Glu Thr Thr Ala Asn Val Leu Gln
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Asp Ala Thr Arg Lys Glu Arg Leu Leu Glu Asp Ser Lys Gly Val Lys
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Thr Asp Val Tyr His Asn Leu Asp Glu Asn Ser Gln Lys Ile Leu Arg
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Ser Leu Glu Gly Ser Asp Asp Ala Val Leu Leu Gln Arg Arg Leu Asp
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Lys Gly Ser Trp Gln Pro Val Gly Asp Leu Leu Ile Asp Ser Leu Gln
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Asp His Leu Glu Lys Val Lys Ala Leu Arg Gly Glu Ile Ala Pro Leu
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Lys Glu Asn Val Ser His Val Asn Asp Leu Ala Arg Gln Leu Thr Thr
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Gln Leu His Glu Ala His Arg Asp Phe Gly Pro Ala Ser Gln His Phe
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Leu Ser Thr Ser Val Gln Gly Pro Trp Glu Arg Ala Ile Ser Pro Asn
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Lys Val Pro Tyr Tyr Ile Asn His Glu Thr Gln Thr Thr Cys Trp Asp
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His Pro Lys Met Thr Glu Leu Tyr Gln Ser Leu Ala Asp Leu Asn Asn
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His Asn Asn Leu Val Asn Val Pro Leu Cys Val Asp Met Cys Leu Asn
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Trp Leu Leu Asn Val Tyr Asp Thr Gly Arg Thr Gly Arg Ile Arg Val
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Leu Ser Phe Lys Thr Gly Ile Ile Ser Leu Cys Lys Ala His Leu Glu
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Pro Arg Gln Leu Gly Glu Val Ala Ser Phe Gly Gly Ser Asn Ile Glu
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Pro Ser Val Arg Ser Cys Phe Gln Phe Ala Asn Asn Lys Pro Glu Ile
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Glu Ala Ala Leu Phe Leu Asp Trp Met Arg Leu Glu Pro Gln Ser Met
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Val Trp Leu Pro Val Leu His Arg Val Ala Ala Ala Glu Thr Ala Lys
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His Gln Ala Lys Cys Asn Ile Cys Lys Glu Cys Pro Ile Ile Gly Phe
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Arg Tyr Arg Ser Leu Lys His Phe Asn Tyr Asp Ile Cys Gln Ser Cys
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Phe Phe Ser Gly Arg Val Ala Lys Gly His Lys Met His Tyr Pro Met
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Val Glu Tyr Cys Thr Pro Thr Thr Ser Gly Glu Asp Val Arg Asp Phe
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Ala Lys Val Leu Lys Asn Lys Phe Arg Thr Lys Arg Tyr Phe Ala Lys
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His Pro Arg Met Gly Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp
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Asn Met Glu Thr Pro Ala Ser Ser Pro Gln Leu Ser His Asp Asp Thr
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His Ser Arg Ile Glu His Tyr Ala Ser Arg Leu Ala Glu Met Glu Asn
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Val Asp Leu Val Asn Ile Gly Ser Thr Asp Ile Val Asp Gly Asn His
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Asp Val Asp Thr Thr Tyr Pro Asp Lys Lys Ser Ile Leu Met Tyr Ile
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Gln Glu Val Glu Met Leu Pro Arg Pro Pro Lys Val Thr Lys Glu Glu
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His Phe Gln Leu His His Gln Met His Tyr Ser Gln Gln Ile Thr Val
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Ser Leu Ala Gln Gly Tyr Glu Arg Thr Ser Ser Pro Lys Pro Arg Phe
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Leu Ser  Ser Gln Leu Val Glu  His Cys Gln Lys Leu  Glu Glu Gln
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Met Asn  Lys Leu Arg Lys Ile  Gln Asn His Ile Gln  Thr Leu Lys
    1040                1045                1050

Lys Trp  Met Ala Glu Val Asp  Val Phe Leu Lys Glu  Glu Trp Pro
    1055                1060                1065

Ala Leu  Gly Asp Ser Glu Ile  Leu Lys Lys Gln Leu  Lys Gln Cys
    1070                1075                1080

Arg Leu  Leu Val Ser Asp Ile  Gln Thr Ile Gln Pro  Ser Leu Asn
    1085                1090                1095

Ser Val  Asn Glu Gly Gly Gln  Lys Ile Lys Asn Glu  Ala Glu Pro
    1100                1105                1110

Glu Phe  Ala Ser Arg Leu Glu  Thr Glu Leu Lys Glu  Leu Asn Thr
    1115                1120                1125

Gln Trp  Asp His Met Cys Gln  Gln Val Tyr Ala Arg  Lys Glu Ala
    1130                1135                1140

Leu Lys  Gly Gly Leu Glu Lys  Thr Val Ser Leu Gln  Lys Asp Leu
    1145                1150                1155

Ser Glu  Met His Glu Trp Met  Thr Gln Ala Glu Glu  Glu Tyr Leu
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    1160                1165                1170

Glu Arg  Asp Phe Glu Tyr Lys  Thr Pro Asp Glu Leu  Gln Lys Ala
    1175                1180                1185

Val Glu  Glu Met Lys Arg Ala  Lys Glu Glu Ala Gln  Gln Lys Glu
    1190                1195                1200

Ala Lys  Val Lys Leu Leu Thr  Glu Ser Val Asn Ser  Val Ile Ala
    1205                1210                1215

Gln Ala  Pro Pro Val Ala Gln  Glu Ala Leu Lys Lys  Glu Leu Glu
    1220                1225                1230

Thr Leu  Thr Thr Asn Tyr Gln  Trp Leu Cys Thr Arg  Leu Asn Gly
    1235                1240                1245

Lys Cys  Lys Thr Leu Glu Glu  Val Trp Ala Cys Trp  His Glu Leu
    1250                1255                1260

Leu Ser  Tyr Leu Glu Lys Ala  Asn Lys Trp Leu Asn  Glu Val Glu
    1265                1270                1275

Phe Lys  Leu Lys Thr Thr Glu  Asn Ile Pro Gly Gly  Ala Glu Glu
    1280                1285                1290

Ile Ser  Glu Val Leu Asp Ser  Leu Glu Asn Leu Met  Arg His Ser
    1295                1300                1305

Glu Asp  Asn Pro Asn Gln Ile  Arg Ile Leu Ala Gln  Thr Leu Thr
    1310                1315                1320

Asp Gly  Gly Val Met Asp Glu  Leu Ile Asn Glu Glu  Leu Glu Thr
    1325                1330                1335

Phe Asn  Ser Arg Trp Arg Glu  Leu His Glu Glu Ala  Val Arg Arg
    1340                1345                1350

Gln Lys  Leu Leu Glu Gln Ser  Ile Gln Ser Ala Gln  Glu Thr Glu
    1355                1360                1365
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Lys Ser  Leu His Leu Ile Gln  Glu Ser Leu Thr Phe  Ile Asp Lys
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Gln Leu  Ala Ala Tyr Ile Ala  Asp Lys Val Asp Ala  Ala Gln Met
    1385                1390                1395

Pro Gln  Glu Ala Gln Lys Ile  Gln Ser Asp Leu Thr  Ser His Glu
    1400                1405                1410

Ile Ser  Leu Glu Glu Met Lys  Lys His Asn Gln Gly  Lys Glu Ala
    1415                1420                1425

Ala Gln  Arg Val Leu Ser Gln  Ile Asp Val Ala Gln  Lys Lys Leu
    1430                1435                1440

Gln Asp  Val Ser Met Lys Phe  Arg Leu Phe Gln Lys  Pro Ala Asn
    1445                1450                1455

Phe Glu  Gln Arg Leu Gln Glu  Ser Lys Met Ile Leu  Asp Glu Val
    1460                1465                1470

Lys Met  His Leu Pro Ala Leu  Glu Thr Lys Ser Val  Glu Gln Glu
    1475                1480                1485

Val Val  Gln Ser Gln Leu Asn  His Cys Val Asn Leu  Tyr Lys Ser
    1490                1495                1500

Leu Ser  Glu Val Lys Ser Glu  Val Glu Met Val Ile  Lys Thr Gly
    1505                1510                1515

Arg Gln  Ile Val Gln Lys Lys  Gln Thr Glu Asn Pro  Lys Glu Leu
    1520                1525                1530

Asp Glu  Arg Val Thr Ala Leu  Lys Leu His Tyr Asn  Glu Leu Gly
    1535                1540                1545

Ala Lys  Val Thr Glu Arg Lys  Gln Gln Leu Glu Lys  Cys Leu Lys
    1550                1555                1560

Leu Ser  Arg Lys Met Arg Lys  Glu Met Asn Val Leu  Thr Glu Trp
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Leu Ala Ala Thr Asp Met Glu Leu Thr Lys Arg Ser Ala Val Glu
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Gly Met Pro Ser Asn Leu Asp Ser Glu Val Ala Trp Gly Lys Ala
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Thr Gln Lys Glu Ile Glu Lys Gln Lys Val His Leu Lys Ser Ile
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Thr Glu Val Gly Glu Ala Leu Lys Thr Val Leu Gly Lys Lys Glu
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Ala Val Thr Ser Arg Ala Glu Glu Trp Leu Asn Leu Leu Leu Glu
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Tyr Gln Lys His Met Glu Thr Phe Asp Gln Asn Val Asp His Ile
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Lys Lys Lys Pro Gln Gln Lys Glu Asp Val Leu Lys Arg Leu Lys
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Ala Glu Leu Asn Asp Ile Arg Pro Lys Val Asp Ser Thr Arg Asp
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Leu Val Glu Pro Gln Ile Ser Glu Leu Asn His Arg Phe Ala Ala
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Ile Ser His Arg Ile Lys Thr Gly Lys Ala Ser Ile Pro Leu Lys
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Glu Leu Glu Gln Phe Asn Ser Asp Ile Gln Lys Leu Leu Glu Pro
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Leu Glu Ala Glu Ile Gln Gln Gly Val Asn Leu Lys Glu Glu Asp
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Phe Asn Lys Asp Met Asn Glu Asp Asn Glu Gly Thr Val Lys Glu
1805 1810 1815

Leu Leu Gln Arg Gly Asp Asn Leu Gln Gln Arg Ile Thr Asp Glu
1820 1825 1830

Arg Lys Arg Glu Glu Ile Lys Ile Lys Gln Gln Leu Leu Gln Thr
1835 1840 1845

Lys His Asn Ala Leu Lys Asp Leu Arg Ser Gln Arg Arg Lys Lys
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Ala Leu Glu Ile Ser His Gln Trp Tyr Gln Tyr Lys Arg Gln Ala
1865 1870 1875

Asp Asp Leu Leu Lys Cys Leu Asp Asp Ile Glu Lys Lys Leu Ala
1880 1885 1890

Ser Leu Pro Glu Pro Arg Asp Glu Arg Lys Ile Lys Glu Ile Asp
1895 1900 1905

Arg Glu Leu Gln Lys Lys Lys Glu Glu Leu Asn Ala Val Arg Arg
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Gln Ala Glu Gly Leu Ser Glu Asp Gly Ala Ala Met Ala Val Glu
1925 1930 1935

Pro Thr Gln Ile Gln Leu Ser Lys Arg Trp Arg Glu Ile Glu Ser
1940 1945 1950

Lys Phe Ala Gln Phe Arg Arg Leu Asn Phe Ala Gln Ile His Thr
1955 1960 1965

Val Arg Glu Glu Thr Met Met Val Met Thr Glu Asp Met Pro Leu

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Glu Ile  Ser Tyr Val Pro Ser  Thr Tyr Leu Thr Glu  Ile Thr His
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Val Ser  Gln Ala Leu Leu Glu  Val Glu Gln Leu Leu  Asn Ala Pro
    2000                2005                2010

Asp Leu  Cys Ala Lys Asp Phe  Glu Asp Leu Phe Lys  Gln Glu Glu
    2015                2020                2025

Ser Leu  Lys Asn Ile Lys Asp  Ser Leu Gln Gln Ser  Ser Gly Arg
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Ile Asp  Ile Ile His Ser Lys  Lys Thr Ala Ala Leu  Gln Ser Ala
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Thr Pro  Val Glu Arg Val Lys  Leu Gln Glu Ala Leu  Ser Gln Leu
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Asp Phe  Gln Trp Glu Lys Val  Asn Lys Met Tyr Lys  Asp Arg Gln
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Gly Arg  Phe Asp Arg Ser Val  Glu Lys Trp Arg Arg  Phe His Tyr
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Asp Ile  Lys Ile Phe Asn Gln  Trp Leu Thr Glu Ala  Glu Gln Phe
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Leu Arg  Lys Thr Gln Ile Pro  Glu Asn Trp Glu His  Ala Lys Tyr
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Lys Trp  Tyr Leu Lys Glu Leu  Gln Asp Gly Ile Gly  Gln Arg Gln
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Thr Val  Val Arg Thr Leu Asn  Ala Thr Gly Glu Glu  Ile Ile Gln
    2150                2155                2160

Gln Ser  Ser Lys Thr Asp Ala  Ser Ile Leu Gln Glu  Lys Leu Gly
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Asn Ile Ala Ser Ile Pro Leu Glu Pro Gly Lys Glu Gln Gln Leu
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Val Thr Leu Val Thr Gln Pro Val Val Thr Lys Glu Thr Ala Ile
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Glu Thr  Lys Gln Leu Ala Lys  Asp Leu Arg Gln Trp  Gln Thr Asn
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Val Asp  Val Ala Asn Asp Leu  Ala Leu Lys Leu Leu  Arg Asp Tyr
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Ser Ala  Asp Asp Thr Arg Lys  Val His Met Ile Thr  Glu Asn Ile
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Asn Ala  Ser Trp Arg Ser Ile  His Lys Arg Val Ser  Glu Arg Glu
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Ala Ala  Leu Glu Glu Thr His  Arg Leu Leu Gln Gln  Phe Pro Leu
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Asp Leu  Glu Lys Phe Leu Ala  Trp Leu Thr Glu Ala  Glu Thr Thr
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Ala Asn  Val Leu Gln Asp Ala  Thr Arg Lys Glu Arg  Leu Leu Glu
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Asp Ser  Lys Gly Val Lys Glu  Leu Met Lys Gln Trp  Gln Asp Leu
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Gln Gly  Glu Ile Glu Ala His  Thr Asp Val Tyr His  Asn Leu Asp
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Glu Asn  Ser Gln Lys Ile Leu  Arg Ser Leu Glu Gly  Ser Asp Asp
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Gly Arg Ile Arg Val Leu Ser Phe Lys Thr Gly Ile Ile Ser Leu

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Cys Lys  Ala His Leu Glu Asp  Lys Tyr Arg Tyr Leu  Phe Lys Gln
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Ala Ser  Phe Gly Gly Ser Asn  Ile Glu Pro Ser Val  Arg Ser Cys
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Phe Gln  Phe Ala Asn Asn Lys  Pro Glu Ile Glu Ala  Ala Leu Phe
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Leu Asp  Trp Met Arg Leu Glu  Pro Gln Ser Met Val  Trp Leu Pro
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Val Leu  His Arg Val Ala Ala  Ala Glu Thr Ala Lys  His Gln Ala
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Lys Cys  Asn Ile Cys Lys Glu  Cys Pro Ile Ile Gly  Phe Arg Tyr
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Arg Ser  Leu Lys His Phe Asn  Tyr Asp Ile Cys Gln  Ser Cys Phe
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Phe Ser  Gly Arg Val Ala Lys  Gly His Lys Met His  Tyr Pro Met
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Val Glu  Tyr Cys Thr Pro Thr  Thr Ser Gly Glu Asp  Val Arg Asp
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Phe Ala  Lys Val Leu Lys Asn  Lys Phe Arg Thr Lys  Arg Tyr Phe
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Ala Lys  His Pro Arg Met Gly  Tyr Leu Pro Val Gln  Thr Val Leu
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Gly Lys Gln His Ile Glu Asn Leu Phe Ser Asp Leu Gln Asp Gly Arg
        35   40   45

Arg Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Gln Lys Leu Pro Lys
    50   55   60

Glu Lys Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Lys Ala
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Leu Arg Val Leu Gln Asn Asn Asn Val Asp Leu Val Asn Ile Gly Ser
                85   90   95

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Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Ile Trp
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Asn Ile Ile Leu His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met
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Ala Gly Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
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Arg Gln Ser Thr Arg Asn Tyr Pro Gln Val Asn Val Ile Asn Phe Thr
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Thr Ser Trp Ser Asp Gly Leu Ala Leu Asn Ala Leu Ile His Ser His
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Arg Pro Asp Leu Phe Asp Trp Asn Ser Val Val Cys Gln Gln Ser Ala
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Thr Gln Arg Leu Glu His Ala Phe Asn Ile Ala Arg Tyr Gln Leu Gly
        195                 200                 205

Ile Glu Lys Leu Leu Asp Pro Glu Asp Val Asp Thr Thr Tyr Pro Asp
    210                 215                 220

Lys Lys Ser Ile Leu Met Tyr Ile Thr Ser Leu Phe Gln Val Leu Pro
225                 230                 235                 240

Gln Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg
                245                 250                 255

Pro Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met
            260                 265                 270

His Tyr Ser Gln Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg
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Thr Ser Ser Pro Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala
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His Leu Glu Ala Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu
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Ser Glu Val Asn Leu Asp Arg Tyr Gln Thr Ala Leu Glu Glu Val Leu
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Ser Trp Leu Leu Ser Ala Glu Asp Thr Leu Gln Ala Gln Gly Glu Ile
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Ser Asn Asp Val Glu Val Val Lys Asp Gln Phe His Thr His Glu Gly
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Tyr Met Met Asp Leu Thr Ala His Gln Gly Arg Val Gly Asn Ile Leu
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Cys Leu Arg Val Ala Ser Met Glu Lys Gln Ser Asn Leu His Arg Val
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Leu Met Asp Leu Gln Asn Gln Lys Leu Lys Glu Leu Asn Asp Trp Leu
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Trp Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ala Trp Leu Ser
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Gln Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala
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Asp Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys
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Glu Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln
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Lys Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr
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Gln Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val
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Thr Thr Arg Glu Gln Ile Leu Val Lys His Ala Gln Glu Glu Leu Pro
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Pro Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile
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Arg Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr
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Gln Leu Leu Ser Glu Arg Leu Asn Trp Leu Glu Tyr Gln Asn Asn Ile
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Ala Glu Asn Trp Leu Lys Ile Gln Pro Thr Thr Pro Ser Glu Pro Thr
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Ala Ile Lys Ser Gln Leu Lys Ile Cys Lys Asp Glu Val Asn Arg Leu
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Ser Asp Leu Gln Pro Gln Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala
                885                 890                 895

Leu Lys Glu Lys Gly Gln Gly Pro Met Phe Leu Asp Ala Asp Phe Val
            900                 905                 910

Ala Phe Thr Asn His Phe Lys Gln Val Phe Ser Asp Val Gln Ala Arg
        915                 920                 925

Glu Lys Glu Leu Gln Thr Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr
    930                 935                 940

Gln Glu Thr Met Ser Ala Ile Arg Thr Trp Val Gln Gln Ser Glu Thr
945                 950                 955                 960
```

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Lys Leu Ser Ile Pro Gln Leu Ser Val Thr Asp Tyr Glu Ile Met Glu
               965                 970                 975

Gln Arg Leu Gly Glu Leu Gln Ala Leu Gln Ser Ser Leu Gln Glu Gln
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Gln Ser Gly Leu Tyr Tyr Leu Ser  Thr Thr Val Lys Glu  Met Ser Lys
        995                 1000                1005

Lys Ala  Pro Ser Glu Ile Ser  Arg Lys Tyr Gln Ser  Glu Phe Glu
    1010                1015                1020

Glu Ile  Glu Gly Arg Trp Lys  Lys Leu Ser Ser Gln  Leu Val Glu
    1025                1030                1035

His Cys  Gln Lys Leu Glu Glu  Gln Met Asn Lys Leu  Arg Lys Ile
    1040                1045                1050

Gln Asn  His Ile Gln Thr Leu  Lys Lys Trp Met Ala  Glu Val Asp
    1055                1060                1065

Val Phe  Leu Lys Glu Glu Trp  Pro Ala Leu Gly Asp  Ser Glu Ile
    1070                1075                1080

Leu Lys  Lys Gln Leu Lys Gln  Cys Arg Leu Leu Val  Ser Asp Ile
    1085                1090                1095

Gln Thr  Ile Gln Pro Ser Leu  Asn Ser Val Asn Glu  Gly Gly Gln
    1100                1105                1110

Lys Ile  Lys Asn Glu Ala Glu  Pro Glu Phe Ala Ser  Arg Leu Glu
    1115                1120                1125

Thr Glu  Leu Lys Glu Leu Asn  Thr Gln Trp Asp His  Met Cys Gln
    1130                1135                1140

Gln Val  Tyr Ala Arg Lys Glu  Ala Leu Lys Gly Gly  Leu Glu Lys
    1145                1150                1155
```

```
Thr Val  Ser Leu Gln Lys Asp  Leu Ser Glu Met His  Glu Trp Met
    1160                1165                1170

Thr Gln  Ala Glu Glu Glu Tyr  Leu Glu Arg Asp Phe  Glu Tyr Lys
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Thr Pro  Asp Glu Leu Gln Lys  Ala Val Glu Glu Met  Lys Arg Ala
    1190                1195                1200

Lys Glu  Glu Ala Gln Gln Lys  Glu Ala Lys Val Lys  Leu Leu Thr
    1205                1210                1215

Glu Ser  Val Asn Ser Val Ile  Ala Gln Ala Pro Pro  Val Ala Gln
    1220                1225                1230

Glu Ala  Leu Lys Lys Glu Leu  Glu Thr Leu Thr Thr  Asn Tyr Gln
    1235                1240                1245

Trp Leu  Cys Thr Arg Leu Asn  Gly Lys Cys Lys Thr  Leu Glu Glu
    1250                1255                1260

Val Trp  Ala Cys Trp His Glu  Leu Leu Ser Tyr Leu  Glu Lys Ala
    1265                1270                1275

Asn Lys  Trp Leu Asn Glu Val  Glu Phe Lys Leu Lys  Thr Thr Glu
    1280                1285                1290

Asn Ile  Pro Gly Gly Ala Glu  Glu Ile Ser Glu Val  Leu Asp Ser
    1295                1300                1305

Leu Glu  Asn Leu Met Arg His  Ser Glu Asp Asn Pro  Asn Gln Ile
    1310                1315                1320

Arg Ile  Leu Ala Gln Thr Leu  Thr Asp Gly Gly Val  Met Asp Glu
    1325                1330                1335

Leu Ile  Asn Glu Glu Leu Glu  Thr Phe Asn Ser Arg  Trp Arg Glu
    1340                1345                1350

Leu His  Glu Glu Ala Val Arg  Arg Gln Lys Leu Leu  Glu Gln Ser
    1355                1360                1365
```

```
Ile Gln  Ser Ala Gln Glu Thr  Glu Lys Ser Leu His  Leu Ile Gln
    1370                1375                1380

Glu Ser  Leu Thr Phe Ile Asp  Lys Gln Leu Ala Ala  Tyr Ile Ala
    1385                1390                1395

Asp Lys  Val Asp Ala Ala Gln  Met Pro Gln Glu Ala  Gln Lys Ile
    1400                1405                1410

Gln Ser  Asp Leu Thr Ser His  Glu Ile Ser Leu Glu  Glu Met Lys
    1415                1420                1425

Lys His  Asn Gln Gly Lys Glu  Ala Ala Gln Arg Val  Leu Ser Gln
    1430                1435                1440

Ile Asp  Val Ala Gln Lys Lys  Leu Gln Asp Val Ser  Met Lys Phe
    1445                1450                1455

Arg Leu  Phe Gln Lys Pro Ala  Asn Phe Glu Gln Arg  Leu Gln Glu
    1460                1465                1470

Ser Lys  Met Ile Leu Asp Glu  Val Lys Met His Leu  Pro Ala Leu
    1475                1480                1485

Glu Thr  Lys Ser Val Glu Gln  Glu Val Val Gln Ser  Gln Leu Asn
    1490                1495                1500

His Cys  Val Asn Leu Tyr Lys  Ser Leu Ser Glu Val  Lys Ser Glu
    1505                1510                1515

Val Glu  Met Val Ile Lys Thr  Gly Arg Gln Ile Val  Gln Lys Lys
    1520                1525                1530

Gln Thr  Glu Asn Pro Lys Glu  Leu Asp Glu Arg Val  Thr Ala Leu
    1535                1540                1545

Lys Leu  His Tyr Asn Glu Leu  Gly Ala Lys Val Thr  Glu Arg Lys
    1550                1555                1560
```

```
Gln Gln  Leu Glu Lys Cys Leu  Lys Leu Ser Arg Lys  Met Arg Lys
    1565                1570                1575

Glu Met  Asn Val Leu Thr Glu  Trp Leu Ala Ala Thr  Asp Met Glu
    1580                1585                1590

Leu Thr  Lys Arg Ser Ala Val  Glu Gly Met Pro Ser  Asn Leu Asp
    1595                1600                1605

Ser Glu  Val Ala Trp Gly Lys  Ala Thr Gln Lys Glu  Ile Glu Lys
    1610                1615                1620

Gln Lys  Val His Leu Lys Ser  Ile Thr Glu Val Gly  Glu Ala Leu
    1625                1630                1635

Lys Thr  Val Leu Gly Lys Lys  Glu Thr Leu Val Glu  Asp Lys Leu
    1640                1645                1650

Ser Leu  Leu Asn Ser Asn Trp  Ile Ala Val Thr Ser  Arg Ala Glu
    1655                1660                1665

Glu Trp  Leu Asn Leu Leu Leu  Glu Tyr Gln Lys His  Met Glu Thr
    1670                1675                1680

Phe Asp  Gln Asn Val Asp His  Ile Thr Lys Trp Ile  Ile Gln Ala
    1685                1690                1695

Asp Thr  Leu Leu Asp Glu Ser  Glu Lys Lys Lys Pro  Gln Gln Lys
    1700                1705                1710

Glu Asp  Val Leu Lys Arg Leu  Lys Ala Glu Leu Asn  Asp Ile Arg
    1715                1720                1725

Pro Lys  Val Asp Ser Thr Arg  Asp Gln Ala Ala Asn  Leu Met Ala
    1730                1735                1740

Asn Arg  Gly Asp His Cys Arg  Lys Leu Val Glu Pro  Gln Ile Ser
    1745                1750                1755

Glu Leu  Asn His Arg Phe Ala  Ala Ile Ser His Arg  Ile Lys Thr
    1760                1765                1770
```

```
Gly Lys  Asn Glu Asp Asn Glu  Gly Thr Val Lys Glu  Leu Leu Gln
    1775                1780                1785

Arg Gly  Asp Asn Leu Gln Gln  Arg Ile Thr Asp Glu  Arg Lys Arg
    1790                1795                1800

Glu Glu  Ile Lys Ile Lys Gln  Gln Leu Leu Gln Thr  Lys His Asn
    1805                1810                1815

Ala Leu  Lys Asp Leu Arg Ser  Gln Arg Arg Lys Lys  Ala Leu Glu
    1820                1825                1830

Ile Ser  His Gln Trp Tyr Gln  Tyr Lys Arg Gln Ala  Asp Asp Leu
    1835                1840                1845

Leu Lys  Cys Leu Asp Asp Ile  Glu Lys Lys Leu Ala  Ser Leu Pro
    1850                1855                1860

Glu Pro  Arg Asp Glu Arg Lys  Ile Lys Glu Ile Asp  Arg Glu Leu
    1865                1870                1875

Gln Lys  Lys Lys Glu Glu Leu  Asn Ala Val Arg Arg  Gln Ala Glu
    1880                1885                1890

Gly Leu  Ser Glu Asp Gly Ala  Ala Met Ala Val Glu  Pro Thr Gln
    1895                1900                1905

Ile Gln  Leu Ser Lys Arg Trp  Arg Glu Ile Glu Ser  Lys Phe Ala
    1910                1915                1920

Gln Phe  Arg Arg Leu Asn Phe  Ala Gln Ile His Thr  Val Arg Glu
    1925                1930                1935

Glu Thr  Met Met Val Met Thr  Glu Asp Met Pro Leu  Glu Ile Ser
    1940                1945                1950

Tyr Val  Pro Ser Thr Tyr Leu  Thr Glu Ile Thr His  Val Ser Gln
    1955                1960                1965
```

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Ala Leu  Leu Glu Val Glu Gln  Leu Leu Asn Ala Pro  Asp Leu Cys
    1970                1975                1980

Ala Lys  Asp Phe Glu Asp Leu  Phe Lys Gln Glu Glu  Ser Leu Lys
    1985                1990                1995

Asn Ile  Lys Asp Ser Leu Gln  Gln Ser Ser Gly Arg  Ile Asp Ile
    2000                2005                2010

Ile His  Ser Lys Lys Thr Ala  Ala Leu Gln Ser Ala  Thr Pro Val
    2015                2020                2025

Glu Arg  Val Lys Leu Gln Glu  Ala Leu Ser Gln Leu  Asp Phe Gln
    2030                2035                2040

Trp Glu  Lys Val Asn Lys Met  Tyr Lys Asp Arg Gln  Gly Arg Phe
    2045                2050                2055

Asp Arg  Ser Val Glu Lys Trp  Arg Arg Phe His Tyr  Asp Ile Lys
    2060                2065                2070

Ile Phe  Asn Gln Trp Leu Thr  Glu Ala Glu Gln Phe  Leu Arg Lys
    2075                2080                2085

Thr Gln  Ile Pro Glu Asn Trp  Glu His Ala Lys Tyr  Lys Trp Tyr
    2090                2095                2100

Leu Lys  Glu Leu Gln Asp Gly  Ile Gly Gln Arg Gln  Thr Val Val
    2105                2110                2115

Arg Thr  Leu Asn Ala Thr Gly  Glu Glu Ile Ile Gln  Gln Ser Ser
    2120                2125                2130

Lys Thr  Asp Ala Ser Ile Leu  Gln Glu Lys Leu Gly  Ser Leu Asn
    2135                2140                2145

Leu Arg  Trp Gln Glu Val Cys  Lys Gln Leu Ser Asp  Arg Lys Lys
    2150                2155                2160

Arg Leu  Glu Glu Gln Lys Asn  Ile Leu Ser Glu Phe  Gln Arg Asp
    2165                2170                2175
```

```
Leu Asn  Glu Phe Val Leu Trp  Leu Glu Glu Ala Asp  Asn Ile Ala
    2180                2185                2190

Ser Ile  Pro Leu Glu Pro Gly  Lys Glu Gln Gln Leu  Lys Glu Lys
    2195                2200                2205

Leu Glu  Gln Val Lys Leu Leu  Val Glu Glu Leu Pro  Leu Arg Gln
    2210                2215                2220

Gly Ile  Leu Lys Gln Leu Asn  Glu Thr Gly Gly Pro  Val Leu Val
    2225                2230                2235

Ser Ala  Pro Ile Ser Pro Glu  Glu Gln Asp Lys Leu  Glu Asn Lys
    2240                2245                2250

Leu Lys  Gln Thr Asn Leu Gln  Trp Ile Lys Val Ser  Arg Ala Leu
    2255                2260                2265

Pro Glu  Lys Gln Gly Glu Ile  Glu Ala Gln Ile Lys  Asp Leu Gly
    2270                2275                2280

Gln Leu  Glu Lys Lys Leu Glu  Asp Leu Glu Glu Gln  Leu Asn His
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Leu Leu  Leu Trp Leu Ser Pro  Ile Arg Asn Gln Leu  Glu Ile Tyr
    2300                2305                2310

Asn Gln  Pro Asn Gln Glu Gly  Pro Phe Asp Val Lys  Glu Thr Glu
    2315                2320                2325

Ile Ala  Val Gln Ala Lys Gln  Pro Asp Val Glu Glu  Ile Leu Ser
    2330                2335                2340

Lys Gly  Gln His Leu Tyr Lys  Glu Lys Pro Ala Thr  Gln Pro Val
    2345                2350                2355

Lys Arg  Lys Leu Glu Asp Leu  Ser Ser Glu Trp Lys  Ala Val Asn
    2360                2365                2370
```

```
Arg Leu  Leu Gln Glu Leu Arg  Ala Lys Gln Pro Asp  Leu Ala Pro
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Gly Leu  Thr Thr Ile Gly Ala  Ser Pro Thr Gln Thr  Val Thr Leu
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Val Thr  Gln Pro Val Val Thr  Lys Glu Thr Ala Ile  Ser Lys Leu
    2405                2410                2415

Glu Met  Pro Ser Ser Leu Met  Leu Glu Val Pro Ala  Leu Ala Asp
    2420                2425                2430

Phe Asn  Arg Ala Trp Thr Glu  Leu Thr Asp Trp Leu  Ser Leu Leu
    2435                2440                2445

Asp Gln  Val Ile Lys Ser Gln  Arg Val Met Val Gly  Asp Leu Glu
    2450                2455                2460

Asp Ile  Asn Glu Met Ile Ile  Lys Gln Lys Ala Thr  Met Gln Asp
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Leu Glu  Gln Arg Arg Pro Gln  Leu Glu Glu Leu Ile  Thr Ala Ala
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Gln Asn  Leu Lys Asn Lys Thr  Ser Asn Gln Glu Ala  Arg Thr Ile
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Ile Thr  Asp Arg Ile Glu Arg  Ile Gln Asn Gln Trp  Asp Glu Val
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Gln Glu  His Leu Gln Asn Arg  Arg Gln Gln Leu Asn  Glu Met Leu
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Lys Asp  Ser Thr Gln Trp Leu  Glu Ala Lys Glu Glu  Ala Glu Gln
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Val Leu  Gly Gln Ala Arg Ala  Lys Leu Glu Ser Trp  Lys Glu Gly
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Pro Tyr  Thr Val Asp Ala Ile  Gln Lys Lys Ile Thr  Glu Thr Lys
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```

```
Gln Leu  Ala Lys Asp Leu Arg  Gln Trp Gln Thr Asn  Val Asp Val
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Ala Asn  Asp Leu Ala Leu Lys  Leu Leu Arg Asp Tyr  Ser Ala Asp
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Asp Thr  Arg Lys Val His Met  Ile Thr Glu Asn Ile  Asn Ala Ser
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Trp Arg  Ser Ile His Lys Arg  Val Ser Glu Arg Glu  Ala Ala Leu
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Glu Glu  Thr His Arg Leu Leu  Gln Gln Phe Pro Leu  Asp Leu Glu
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Lys Phe  Leu Ala Trp Leu Thr  Glu Ala Glu Thr Thr  Ala Asn Val
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Leu Gln  Asp Ala Thr Arg Lys  Glu Arg Leu Leu Glu  Asp Ser Lys
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Gly Val  Lys Glu Leu Met Lys  Gln Trp Gln Asp Leu  Gln Gly Glu
    2690                2695                2700

Ile Glu  Ala His Thr Asp Val  Tyr His Asn Leu Asp  Glu Asn Ser
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Gln Lys  Ile Leu Arg Ser Leu  Glu Gly Ser Asp Asp  Ala Val Leu
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Leu Gln  Arg Arg Leu Asp Asn  Met Asn Phe Lys Trp  Ser Glu Leu
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Arg Lys  Lys Ser Leu Asn Ile  Arg Ser His Leu Glu  Ala Ser Ser
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Asp Gln  Trp Lys Arg Leu His  Leu Ser Leu Gln Glu  Leu Leu Val
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```

```
Trp Leu  Gln Leu Lys Asp Asp  Glu Leu Ser Arg Gln  Ala Pro Ile
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Gly Gly  Asp Phe Pro Ala Val  Gln Lys Gln Asn Asp  Val His Arg
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Ala Phe  Lys Arg Glu Leu Lys  Thr Lys Glu Pro Val  Ile Met Ser
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Thr Leu  Glu Thr Val Arg Ile  Phe Leu Thr Glu Gln  Pro Leu Glu
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Gly Leu  Glu Lys Leu Tyr Gln  Glu Pro Arg Glu Leu  Pro Pro Glu
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Glu Arg  Ala Gln Asn Val Thr  Arg Leu Leu Arg Lys  Gln Ala Glu
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Glu Val  Asn Thr Glu Trp Glu  Lys Leu Asn Leu His  Ser Ala Asp
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Trp Gln  Arg Lys Ile Asp Glu  Thr Leu Glu Arg Leu  Arg Glu Leu
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Gln Glu  Ala Thr Asp Glu Leu  Asp Leu Lys Leu Arg  Gln Ala Glu
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Val Ile  Lys Gly Ser Trp Gln  Pro Val Gly Asp Leu  Leu Ile Asp
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Ser Leu  Gln Asp His Leu Glu  Lys Val Lys Ala Leu  Arg Gly Glu
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Ile Ala  Pro Leu Lys Glu Asn  Val Ser His Val Asn  Asp Leu Ala
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Arg Gln  Leu Thr Thr Leu Gly  Ile Gln Leu Ser Pro  Tyr Asn Leu
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Ser Thr  Leu Glu Asp Leu Asn  Thr Arg Trp Lys Leu  Leu Gln Val
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```

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Ala Val  Glu Asp Arg Val Arg  Gln Leu His Glu Ala  His Arg Asp
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Phe Gly  Pro Ala Ser Gln His  Phe Leu Ser Thr Ser  Val Gln Gly
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Pro Trp  Glu Arg Ala Ile Ser  Pro Asn Lys Val Pro  Tyr Tyr Ile
    3020                3025                3030

Asn His  Glu Thr Gln Thr Thr  Cys Trp Asp His Pro  Lys Met Thr
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Glu Leu  Tyr Gln Ser Leu Ala  Asp Leu Asn Asn Val  Arg Phe Ser
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Ala Tyr  Arg Thr Ala Met Lys  Leu Arg Arg Leu Gln  Lys Ala Leu
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Cys Leu  Asp Leu Leu Ser Leu  Ser Ala Ala Cys Asp  Ala Leu Asp
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Gln His  Asn Leu Lys Gln Asn  Asp Gln Pro Met Asp  Ile Leu Gln
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Ile Ile  Asn Cys Leu Thr Thr  Ile Tyr Asp Arg Leu  Glu Gln Glu
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His Asn  Asn Leu Val Asn Val  Pro Leu Cys Val Asp  Met Cys Leu
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Asn Trp  Leu Leu Asn Val Tyr  Asp Thr Gly Arg Thr  Gly Arg Ile
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Arg Val  Leu Ser Phe Lys Thr  Gly Ile Ile Ser Leu  Cys Lys Ala
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His Leu  Glu Asp Lys Tyr Arg  Tyr Leu Phe Lys Gln  Val Ala Ser
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Arg Trp Thr Glu Asp Arg Trp Val Leu Leu Gln Asp Ile Leu Leu Lys
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```

```
Trp Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ala Trp Leu Ser
                565                 570                 575

Glu Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp
            580                 585                 590

Gln Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala
        595                 600                 605

Asp Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys
    610                 615                 620

Gln Asp Leu Leu Ser Thr Leu Lys Asn Lys Ser Val Thr Gln Lys Thr
625                 630                 635                 640

Glu Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln
                645                 650                 655

Lys Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr
            660                 665                 670

Gln Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val
        675                 680                 685

Thr Thr Arg Glu Gln Ile Leu Val Lys His Ala Gln Glu Glu Leu Pro
    690                 695                 700

Pro Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile
705                 710                 715                 720

Arg Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr
                725                 730                 735

Arg Ser Glu Ala Val Leu Gln Ser Pro Glu Phe Ala Ile Phe Arg Lys
            740                 745                 750

Glu Gly Asn Phe Ser Asp Leu Lys Glu Lys Val Asn Ala Ile Glu Arg
        755                 760                 765

Glu Lys Ala Glu Lys Phe Arg Lys Leu Gln Asp Ala Ser Arg Ser Ala
    770                 775                 780
```

```
Gln Ala Leu Val Glu Gln Met Val Asn Glu Gly Val Asn Ala Asp Ser
785                 790                 795                 800

Ile Lys Gln Ala Ser Glu Gln Leu Asn Ser Arg Trp Ile Glu Phe Cys
                805                 810                 815

Gln Leu Leu Ser Glu Arg Leu Asn Trp Leu Glu Tyr Gln Asn Asn Ile
            820                 825                 830

Ile Ala Phe Tyr Asn Gln Leu Gln Gln Leu Glu Gln Met Thr Thr Thr
        835                 840                 845

Ala Glu Asn Trp Leu Lys Ile Gln Pro Thr Thr Pro Ser Glu Pro Thr
    850                 855                 860

Ala Ile Lys Ser Gln Leu Lys Ile Cys Lys Asp Glu Val Asn Arg Leu
865                 870                 875                 880

Ser Asp Leu Gln Pro Gln Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala
                885                 890                 895

Leu Lys Glu Lys Gly Gln Gly Pro Met Phe Leu Asp Ala Asp Phe Val
            900                 905                 910

Ala Phe Thr Asn His Phe Lys Gln Val Phe Ser Asp Val Gln Ala Arg
        915                 920                 925

Glu Lys Glu Leu Gln Thr Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr
    930                 935                 940

Gln Glu Thr Met Ser Ala Ile Arg Thr Trp Val Gln Gln Ser Glu Thr
945                 950                 955                 960

Lys Leu Ser Ile Pro Gln Leu Ser Val Thr Asp Tyr Glu Ile Met Glu
                965                 970                 975

Gln Arg Leu Gly Glu Leu Gln Ala Leu Gln Ser Ser Leu Gln Glu Gln
            980                 985                 990
```

```
Gln Ser Gly Leu Tyr Tyr Leu Ser  Thr Thr Val Lys Glu  Met Ser Lys
       995                1000                1005

Lys Ala  Pro Ser Glu Ile Ser  Arg Lys Tyr Gln Ser  Glu Phe Glu
    1010                1015                1020

Glu Ile  Glu Gly Arg Trp Lys  Lys Leu Ser Ser Gln  Leu Val Glu
    1025                1030                1035

His Cys  Gln Lys Leu Glu Glu  Gln Met Asn Lys Leu  Arg Lys Ile
    1040                1045                1050

Gln Asn  His Ile Gln Thr Leu  Lys Lys Trp Met Ala  Glu Val Asp
    1055                1060                1065

Val Phe  Leu Lys Glu Glu Trp  Pro Ala Leu Gly Asp  Ser Glu Ile
    1070                1075                1080

Leu Lys  Lys Gln Leu Lys Gln  Cys Arg Leu Leu Val  Ser Asp Ile
    1085                1090                1095

Gln Thr  Ile Gln Pro Ser Leu  Asn Ser Val Asn Glu  Gly Gly Gln
    1100                1105                1110

Lys Ile  Lys Asn Glu Ala Glu  Pro Glu Phe Ala Ser  Arg Leu Glu
    1115                1120                1125

Thr Glu  Leu Lys Glu Leu Asn  Thr Gln Trp Asp His  Met Cys Gln
    1130                1135                1140

Gln Val  Tyr Ala Arg Lys Glu  Ala Leu Lys Gly Gly  Leu Glu Lys
    1145                1150                1155

Thr Val  Ser Leu Gln Lys Asp  Leu Ser Glu Met His  Glu Trp Met
    1160                1165                1170

Thr Gln  Ala Glu Glu Glu Tyr  Leu Glu Arg Asp Phe  Glu Tyr Lys
    1175                1180                1185

Thr Pro  Asp Glu Leu Gln Lys  Ala Val Glu Glu Met  Lys Arg Ala
    1190                1195                1200
```

```
Lys Glu  Glu Ala Gln Gln Lys  Glu Ala Lys Val Lys  Leu Leu Thr
    1205                 1210                 1215

Glu Ser  Val Asn Ser Val Ile  Ala Gln Ala Pro Pro  Val Ala Gln
    1220                 1225                 1230

Glu Ala  Leu Lys Lys Glu Leu  Glu Thr Leu Thr Thr  Asn Tyr Gln
    1235                 1240                 1245

Trp Leu  Cys Thr Arg Leu Asn  Gly Lys Cys Lys Thr  Leu Glu Glu
    1250                 1255                 1260

Val Trp  Ala Cys Trp His Glu  Leu Leu Ser Tyr Leu  Glu Lys Ala
    1265                 1270                 1275

Asn Lys  Trp Leu Asn Glu Val  Glu Phe Lys Leu Lys  Thr Thr Glu
    1280                 1285                 1290

Asn Ile  Pro Gly Gly Ala Glu  Glu Ile Ser Glu Val  Leu Asp Ser
    1295                 1300                 1305

Leu Glu  Asn Leu Met Arg His  Ser Glu Asp Asn Pro  Asn Gln Ile
    1310                 1315                 1320

Arg Ile  Leu Ala Gln Thr Leu  Thr Asp Gly Gly Val  Met Asp Glu
    1325                 1330                 1335

Leu Ile  Asn Glu Glu Leu Glu  Thr Phe Asn Ser Arg  Trp Arg Glu
    1340                 1345                 1350

Leu His  Glu Glu Ala Val Arg  Arg Gln Lys Leu Leu  Glu Gln Ser
    1355                 1360                 1365

Ile Gln  Ser Ala Gln Glu Thr  Glu Lys Ser Leu His  Leu Ile Gln
    1370                 1375                 1380

Glu Ser  Leu Thr Phe Ile Asp  Lys Gln Leu Ala Ala  Tyr Ile Ala
    1385                 1390                 1395
```

```
Asp Lys  Val Asp Ala Ala Gln  Met Pro Gln Glu Ala  Gln Lys Ile
    1400                 1405                 1410

Gln Ser  Asp Leu Thr Ser His  Glu Ile Ser Leu Glu  Glu Met Lys
    1415                 1420                 1425

Lys His  Asn Gln Gly Lys Glu  Ala Ala Gln Arg Val  Leu Ser Gln
    1430                 1435                 1440

Ile Asp  Val Ala Gln Lys Lys  Leu Gln Asp Val Ser  Met Lys Phe
    1445                 1450                 1455

Arg Leu  Phe Gln Lys Pro Ala  Asn Phe Glu Gln Arg  Leu Gln Glu
    1460                 1465                 1470

Ser Lys  Met Ile Leu Asp Glu  Val Lys Met His Leu  Pro Ala Leu
    1475                 1480                 1485

Glu Thr  Lys Ser Val Glu Gln  Glu Val Val Gln Ser  Gln Leu Asn
    1490                 1495                 1500

His Cys  Val Asn Leu Tyr Lys  Ser Leu Ser Glu Val  Lys Ser Glu
    1505                 1510                 1515

Val Glu  Met Val Ile Lys Thr  Gly Arg Gln Ile Val  Gln Lys Lys
    1520                 1525                 1530

Gln Thr  Glu Asn Pro Lys Glu  Leu Asp Glu Arg Val  Thr Ala Leu
    1535                 1540                 1545

Lys Leu  His Tyr Asn Glu Leu  Gly Ala Lys Val Thr  Glu Arg Lys
    1550                 1555                 1560

Gln Gln  Leu Glu Lys Cys Leu  Lys Leu Ser Arg Lys  Met Arg Lys
    1565                 1570                 1575

Glu Met  Asn Val Leu Thr Glu  Trp Leu Ala Ala Thr  Asp Met Glu
    1580                 1585                 1590

Leu Thr  Lys Arg Ser Ala Val  Glu Gly Met Pro Ser  Asn Leu Asp
    1595                 1600                 1605
```

Ser Glu Val Ala Trp Gly Lys Ala Thr Gln Lys Glu Ile Glu Lys
1610 1615 1620

Gln Lys Val His Leu Lys Ser Ile Thr Glu Val Gly Glu Ala Leu
1625 1630 1635

Lys Thr Val Leu Gly Lys Lys Glu Thr Leu Val Glu Asp Lys Leu
1640 1645 1650

Ser Leu Leu Asn Ser Asn Trp Ile Ala Val Thr Ser Arg Ala Glu
1655 1660 1665

Glu Trp Leu Asn Leu Leu Leu Glu Tyr Gln Lys His Met Glu Thr
1670 1675 1680

Phe Asp Gln Asn Val Asp His Ile Thr Lys Trp Ile Ile Gln Ala
1685 1690 1695

Asp Thr Leu Leu Asp Glu Ser Glu Lys Lys Lys Pro Gln Gln Lys
1700 1705 1710

Glu Asp Val Leu Lys Arg Leu Lys Ala Glu Leu Asn Asp Ile Arg
1715 1720 1725

Pro Lys Val Asp Ser Thr Arg Asp Gln Ala Ala Asn Leu Met Ala
1730 1735 1740

Asn Arg Gly Asp His Cys Arg Lys Leu Val Glu Pro Gln Ile Ser
1745 1750 1755

Glu Leu Asn His Arg Phe Ala Ala Ile Ser His Arg Ile Lys Thr
1760 1765 1770

Gly Lys Ala Ser Ile Pro Leu Lys Glu Leu Glu Gln Phe Asn Ser
1775 1780 1785

Asp Ile Gln Lys Leu Leu Glu Pro Leu Glu Ala Glu Ile Gln Gln
1790 1795 1800

```
Gly Val  Asn Leu Lys Glu Glu  Asp Phe Asn Lys Asp  Met Asp Leu
    1805                1810                1815

Arg Ser  Gln Arg Arg Lys Lys  Ala Leu Glu Ile Ser  His Gln Trp
    1820                1825                1830

Tyr Gln  Tyr Lys Arg Gln Ala  Asp Asp Leu Leu Lys  Cys Leu Asp
    1835                1840                1845

Asp Ile  Glu Lys Lys Leu Ala  Ser Leu Pro Glu Pro  Arg Asp Glu
    1850                1855                1860

Arg Lys  Ile Lys Glu Ile Asp  Arg Glu Leu Gln Lys  Lys Lys Glu
    1865                1870                1875

Glu Leu  Asn Ala Val Arg Arg  Gln Ala Glu Gly Leu  Ser Glu Asp
    1880                1885                1890

Gly Ala  Ala Met Ala Val Glu  Pro Thr Gln Ile Gln  Leu Ser Lys
    1895                1900                1905

Arg Trp  Arg Glu Ile Glu Ser  Lys Phe Ala Gln Phe  Arg Arg Leu
    1910                1915                1920

Asn Phe  Ala Gln Ile His Thr  Val Arg Glu Glu Thr  Met Met Val
    1925                1930                1935

Met Thr  Glu Asp Met Pro Leu  Glu Ile Ser Tyr Val  Pro Ser Thr
    1940                1945                1950

Tyr Leu  Thr Glu Ile Thr His  Val Ser Gln Ala Leu  Leu Glu Val
    1955                1960                1965

Glu Gln  Leu Leu Asn Ala Pro  Asp Leu Cys Ala Lys  Asp Phe Glu
    1970                1975                1980

Asp Leu  Phe Lys Gln Glu Glu  Ser Leu Lys Asn Ile  Lys Asp Ser
    1985                1990                1995

Leu Gln  Gln Ser Ser Gly Arg  Ile Asp Ile Ile His  Ser Lys Lys
    2000                2005                2010
```

```
Thr Ala  Ala Leu Gln Ser Ala  Thr Pro Val Glu Arg  Val Lys Leu
    2015                2020                2025

Gln Glu  Ala Leu Ser Gln Leu  Asp Phe Gln Trp Glu  Lys Val Asn
    2030                2035                2040

Lys Met  Tyr Lys Asp Arg Gln  Gly Arg Phe Asp Arg  Ser Val Glu
    2045                2050                2055

Lys Trp  Arg Arg Phe His Tyr  Asp Ile Lys Ile Phe  Asn Gln Trp
    2060                2065                2070

Leu Thr  Glu Ala Glu Gln Phe  Leu Arg Lys Thr Gln  Ile Pro Glu
    2075                2080                2085

Asn Trp  Glu His Ala Lys Tyr  Lys Trp Tyr Leu Lys  Glu Leu Gln
    2090                2095                2100

Asp Gly  Ile Gly Gln Arg Gln  Thr Val Val Arg Thr  Leu Asn Ala
    2105                2110                2115

Thr Gly  Glu Glu Ile Ile Gln  Gln Ser Ser Lys Thr  Asp Ala Ser
    2120                2125                2130

Ile Leu  Gln Glu Lys Leu Gly  Ser Leu Asn Leu Arg  Trp Gln Glu
    2135                2140                2145

Val Cys  Lys Gln Leu Ser Asp  Arg Lys Lys Arg Leu  Glu Glu Gln
    2150                2155                2160

Lys Asn  Ile Leu Ser Glu Phe  Gln Arg Asp Leu Asn  Glu Phe Val
    2165                2170                2175

Leu Trp  Leu Glu Glu Ala Asp  Asn Ile Ala Ser Ile  Pro Leu Glu
    2180                2185                2190

Pro Gly  Lys Glu Gln Gln Leu  Lys Glu Lys Leu Glu  Gln Val Lys
    2195                2200                2205
```

```
Leu Leu  Val Glu Glu Leu Pro  Leu Arg Gln Gly Ile  Leu Lys Gln
    2210                2215                2220

Leu Asn  Glu Thr Gly Gly Pro  Val Leu Val Ser Ala  Pro Ile Ser
    2225                2230                2235

Pro Glu  Glu Gln Asp Lys Leu  Glu Asn Lys Leu Lys  Gln Thr Asn
    2240                2245                2250

Leu Gln  Trp Ile Lys Val Ser  Arg Ala Leu Pro Glu  Lys Gln Gly
    2255                2260                2265

Glu Ile  Glu Ala Gln Ile Lys  Asp Leu Gly Gln Leu  Glu Lys Lys
    2270                2275                2280

Leu Glu  Asp Leu Glu Glu Gln  Leu Asn His Leu Leu  Leu Trp Leu
    2285                2290                2295

Ser Pro  Ile Arg Asn Gln Leu  Glu Ile Tyr Asn Gln  Pro Asn Gln
    2300                2305                2310

Glu Gly  Pro Phe Asp Val Lys  Glu Thr Glu Ile Ala  Val Gln Ala
    2315                2320                2325

Lys Gln  Pro Asp Val Glu Glu  Ile Leu Ser Lys Gly  Gln His Leu
    2330                2335                2340

Tyr Lys  Glu Lys Pro Ala Thr  Gln Pro Val Lys Arg  Lys Leu Glu
    2345                2350                2355

Asp Leu  Ser Ser Glu Trp Lys  Ala Val Asn Arg Leu  Leu Gln Glu
    2360                2365                2370

Leu Arg  Ala Lys Gln Pro Asp  Leu Ala Pro Gly Leu  Thr Thr Ile
    2375                2380                2385

Gly Ala  Ser Pro Thr Gln Thr  Val Thr Leu Val Thr  Gln Pro Val
    2390                2395                2400

Val Thr  Lys Glu Thr Ala Ile  Ser Lys Leu Glu Met  Pro Ser Ser
    2405                2410                2415
```

```
Leu Met  Leu Glu Val Pro Ala  Leu Ala Asp Phe Asn  Arg Ala Trp
    2420                2425                2430

Thr Glu  Leu Thr Asp Trp Leu  Ser Leu Leu Asp Gln  Val Ile Lys
    2435                2440                2445

Ser Gln  Arg Val Met Val Gly  Asp Leu Glu Asp Ile  Asn Glu Met
    2450                2455                2460

Ile Ile  Lys Gln Lys Ala Thr  Met Gln Asp Leu Glu  Gln Arg Arg
    2465                2470                2475

Pro Gln  Leu Glu Glu Leu Ile  Thr Ala Ala Gln Asn  Leu Lys Asn
    2480                2485                2490

Lys Thr  Ser Asn Gln Glu Ala  Arg Thr Ile Ile Thr  Asp Arg Ile
    2495                2500                2505

Glu Arg  Ile Gln Asn Gln Trp  Asp Glu Val Gln Glu  His Leu Gln
    2510                2515                2520

Asn Arg  Arg Gln Gln Leu Asn  Glu Met Leu Lys Asp  Ser Thr Gln
    2525                2530                2535

Trp Leu  Glu Ala Lys Glu Glu  Ala Glu Gln Val Leu  Gly Gln Ala
    2540                2545                2550

Arg Ala  Lys Leu Glu Ser Trp  Lys Glu Gly Pro Tyr  Thr Val Asp
    2555                2560                2565

Ala Ile  Gln Lys Lys Ile Thr  Glu Thr Lys Gln Leu  Ala Lys Asp
    2570                2575                2580

Leu Arg  Gln Trp Gln Thr Asn  Val Asp Val Ala Asn  Asp Leu Ala
    2585                2590                2595

Leu Lys  Leu Leu Arg Asp Tyr  Ser Ala Asp Asp Thr  Arg Lys Val
    2600                2605                2610
```

```
His Met  Ile Thr Glu Asn Ile  Asn Ala Ser Trp Arg  Ser Ile His
    2615                 2620                 2625

Lys Arg  Val Ser Glu Arg Glu  Ala Ala Leu Glu Glu  Thr His Arg
    2630                 2635                 2640

Leu Leu  Gln Gln Phe Pro Leu  Asp Leu Glu Lys Phe  Leu Ala Trp
    2645                 2650                 2655

Leu Thr  Glu Ala Glu Thr Thr  Ala Asn Val Leu Gln  Asp Ala Thr
    2660                 2665                 2670

Arg Lys  Glu Arg Leu Leu Glu  Asp Ser Lys Gly Val  Lys Glu Leu
    2675                 2680                 2685

Met Lys  Gln Trp Gln Asp Leu  Gln Gly Glu Ile Glu  Ala His Thr
    2690                 2695                 2700

Asp Val  Tyr His Asn Leu Asp  Glu Asn Ser Gln Lys  Ile Leu Arg
    2705                 2710                 2715

Ser Leu  Glu Gly Ser Asp Asp  Ala Val Leu Leu Gln  Arg Arg Leu
    2720                 2725                 2730

Asp Asn  Met Asn Phe Lys Trp  Ser Glu Leu Arg Lys  Lys Ser Leu
    2735                 2740                 2745

Asn Ile  Arg Ser His Leu Glu  Ala Ser Ser Asp Gln  Trp Lys Arg
    2750                 2755                 2760

Leu His  Leu Ser Leu Gln Glu  Leu Leu Val Trp Leu  Gln Leu Lys
    2765                 2770                 2775

Asp Asp  Glu Leu Ser Arg Gln  Ala Pro Ile Gly Gly  Asp Phe Pro
    2780                 2785                 2790

Ala Val  Gln Lys Gln Asn Asp  Val His Arg Ala Phe  Lys Arg Glu
    2795                 2800                 2805

Leu Lys  Thr Lys Glu Pro Val  Ile Met Ser Thr Leu  Glu Thr Val
    2810                 2815                 2820
```

```
Arg Ile  Phe Leu Thr Glu Gln  Pro Leu Glu Gly Leu  Glu Lys Leu
    2825                2830                2835

Tyr Gln  Glu Pro Arg Glu Leu  Pro Pro Glu Glu Arg  Ala Gln Asn
    2840                2845                2850

Val Thr  Arg Leu Leu Arg Lys  Gln Ala Glu Glu Val  Asn Thr Glu
    2855                2860                2865

Trp Glu  Lys Leu Asn Leu His  Ser Ala Asp Trp Gln  Arg Lys Ile
    2870                2875                2880

Asp Glu  Thr Leu Glu Arg Leu  Arg Glu Leu Gln Glu  Ala Thr Asp
    2885                2890                2895

Glu Leu  Asp Leu Lys Leu Arg  Gln Ala Glu Val Ile  Lys Gly Ser
    2900                2905                2910

Trp Gln  Pro Val Gly Asp Leu  Leu Ile Asp Ser Leu  Gln Asp His
    2915                2920                2925

Leu Glu  Lys Val Lys Ala Leu  Arg Gly Glu Ile Ala  Pro Leu Lys
    2930                2935                2940

Glu Asn  Val Ser His Val Asn  Asp Leu Ala Arg Gln  Leu Thr Thr
    2945                2950                2955

Leu Gly  Ile Gln Leu Ser Pro  Tyr Asn Leu Ser Thr  Leu Glu Asp
    2960                2965                2970

Leu Asn  Thr Arg Trp Lys Leu  Leu Gln Val Ala Val  Glu Asp Arg
    2975                2980                2985

Val Arg  Gln Leu His Glu Ala  His Arg Asp Phe Gly  Pro Ala Ser
    2990                2995                3000

Gln His  Phe Leu Ser Thr Ser  Val Gln Gly Pro Trp  Glu Arg Ala
    3005                3010                3015
```

Ile Ser Pro Asn Lys Val Pro Tyr Tyr Ile Asn His Glu Thr Gln
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Thr Thr Cys Trp Asp His Pro Lys Met Thr Glu Leu Tyr Gln Ser
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Leu Ala Asp Leu Asn Asn Val Arg Phe Ser Ala Tyr Arg Thr Ala
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Met Lys Leu Arg Arg Leu Gln Lys Ala Leu Cys Leu Asp Leu Leu
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Ser Leu Ser Ala Ala Cys Asp Ala Leu Asp Gln His Asn Leu Lys
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Gln Asn Asp Gln Pro Met Asp Ile Leu Gln Ile Ile Asn Cys Leu
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Thr Thr Ile Tyr Asp Arg Leu Glu Gln Glu His Asn Asn Leu Val
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Asn Val Pro Leu Cys Val Asp Met Cys Leu Asn Trp Leu Leu Asn
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Val Tyr Asp Thr Gly Arg Thr Gly Arg Ile Arg Val Leu Ser Phe
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Lys Thr Gly Ile Ile Ser Leu Cys Lys Ala His Leu Glu Asp Lys
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Tyr Arg Tyr Leu Phe Lys Gln Val Ala Ser Ser Thr Gly Phe Cys
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Asp Gln Arg Arg Leu Gly Leu Leu Leu His Asp Ser Ile Gln Ile
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Pro Arg Gln Leu Gly Glu Val Ala Ser Phe Gly Gly Ser Asn Ile
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Glu Pro Ser Val Arg Ser Cys Phe Gln Phe Ala Asn Asn Lys Pro
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```
Glu Ile  Glu Ala Ala Leu Phe  Leu Asp Trp Met Arg  Leu Glu Pro
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Gln Ser  Met Val Trp Leu Pro  Val Leu His Arg Val  Ala Ala Ala
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Glu Thr  Ala Lys His Gln Ala  Lys Cys Asn Ile Cys  Lys Glu Cys
    3260                3265                3270

Pro Ile  Ile Gly Phe Arg Tyr  Arg Ser Leu Lys His  Phe Asn Tyr
    3275                3280                3285

Asp Ile  Cys Gln Ser Cys Phe  Phe Ser Gly Arg Val  Ala Lys Gly
    3290                3295                3300

His Lys  Met His Tyr Pro Met  Val Glu Tyr Cys Thr  Pro Thr Thr
    3305                3310                3315

Ser Gly  Glu Asp Val Arg Asp  Phe Ala Lys Val Leu  Lys Asn Lys
    3320                3325                3330

Phe Arg  Thr Lys Arg Tyr Phe  Ala Lys His Pro Arg  Met Gly Tyr
    3335                3340                3345

Leu Pro  Val Gln Thr Val Leu  Glu Gly Asp Asn Met  Glu Thr Pro
    3350                3355                3360

Val Thr  Leu Ile Asn Phe Trp  Pro Val Asp Ser Ala  Pro Ala Ser
    3365                3370                3375

Ser Pro  Gln Leu Ser His Asp  Asp Thr His Ser Arg  Ile Glu His
    3380                3385                3390

Tyr Ala  Ser Arg Leu Ala Glu  Met Glu Asn Ser Asn  Gly Ser Tyr
    3395                3400                3405

Leu Asn  Asp Ser Ile Ser Pro  Asn Glu Ser Ile Asp  Asp Glu His
    3410                3415                3420
```

```
Leu Leu  Ile Gln His Tyr Cys  Gln Ser Leu Asn Gln  Asp Ser Pro
    3425                3430                3435

Leu Ser  Gln Pro Arg Ser Pro  Ala Gln Ile Leu Ile  Ser Leu Glu
    3440                3445                3450

Ser Glu  Glu Arg Gly Glu Leu  Glu Arg Ile Leu Ala  Asp Leu Glu
    3455                3460                3465

Glu Glu  Asn Arg Asn Leu Gln  Ala Glu Tyr Asp Arg  Leu Lys Gln
    3470                3475                3480

Gln His  Glu His Lys Gly Leu  Ser Pro Leu Pro Ser  Pro Pro Glu
    3485                3490                3495

Met Met  Pro Thr Ser Pro Gln  Ser Pro Arg Asp Ala  Glu Leu Ile
    3500                3505                3510

Ala Glu  Ala Lys Leu Leu Arg  Gln His Lys Gly Arg  Leu Glu Ala
    3515                3520                3525

Arg Met  Gln Ile Leu Glu Asp  His Asn Lys Gln Leu  Glu Ser Gln
    3530                3535                3540

Leu His  Arg Leu Arg Gln Leu  Leu Glu Gln Pro Gln  Ala Glu Ala
    3545                3550                3555

Lys Val  Asn Gly Thr Thr Val  Ser Ser Pro Ser Thr  Ser Leu Gln
    3560                3565                3570

Arg Ser  Asp Ser Ser Gln Pro  Met Leu Leu Arg Val  Val Gly Ser
    3575                3580                3585

Gln Thr  Ser Asp Ser Met Gly  Glu Glu Asp Leu Leu  Ser Pro Pro
    3590                3595                3600

Gln Asp  Thr Ser Thr Gly Leu  Glu Glu Val Met Glu  Gln Leu Asn
    3605                3610                3615

Asn Ser  Phe Pro Ser Ser Arg  Gly His Asn Val Gly  Ser Leu Phe
    3620                3625                3630
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His Met Ala Asp Asp Leu Gly Arg Ala Met Glu Ser Leu Val Ser
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Val Met Thr Asp Glu Glu Gly Ala Glu
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Gln Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg
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Pro Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met
            260                 265                 270

His Tyr Ser Gln Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg
        275                 280                 285

Thr Ser Ser Pro Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala
    290                 295                 300

Ala Tyr Val Thr Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln
305                 310                 315                 320

His Leu Glu Ala Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu
                325                 330                 335

Ser Glu Val Asn Leu Asp Arg Tyr Gln Thr Ala Leu Glu Glu Val Leu
            340                 345                 350

Ser Trp Leu Leu Ser Ala Glu Asp Thr Leu Gln Ala Gln Gly Glu Ile
        355                 360                 365

Ser Asn Asp Val Glu Val Val Lys Asp Gln Phe His Thr His Glu Gly
    370                 375                 380

Tyr Met Met Asp Leu Thr Ala His Gln Gly Arg Val Gly Asn Ile Leu
385                 390                 395                 400

Gln Leu Gly Ser Lys Leu Ile Gly Thr Gly Lys Leu Ser Glu Asp Glu
                405                 410                 415
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Glu Thr Glu Val Gln Glu Gln Met Asn Leu Leu Asn Ser Arg Trp Glu
            420                 425                 430

Cys Leu Arg Val Ala Ser Met Glu Lys Gln Ser Asn Leu His Arg Val
        435                 440                 445

Leu Met Asp Leu Gln Asn Gln Lys Leu Lys Glu Leu Asn Asp Trp Leu
    450                 455                 460

Thr Lys Thr Glu Glu Arg Thr Arg Lys Met Glu Glu Glu Pro Leu Gly
465                 470                 475                 480

Pro Asp Leu Glu Asp Leu Lys Arg Gln Val Gln Gln His Lys Val Leu
                485                 490                 495

Gln Glu Asp Leu Glu Gln Glu Gln Val Arg Val Asn Ser Leu Thr His
            500                 505                 510

Met Val Val Val Val Asp Glu Ser Ser Gly Asp His Ala Thr Ala Ala
        515                 520                 525

Leu Glu Glu Gln Leu Lys Val Leu Gly Asp Arg Trp Ala Asn Ile Cys
    530                 535                 540

Arg Trp Thr Glu Asp Arg Trp Val Leu Leu Gln Asp Ile Leu Leu Lys
545                 550                 555                 560

Trp Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ala Trp Leu Ser
                565                 570                 575

Glu Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp
            580                 585                 590

Gln Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala
        595                 600                 605

Asp Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys
    610                 615                 620

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

625 630 635 640

Glu Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln
645 650 655

Lys Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr
660 665 670

Gln Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val
675 680 685

Thr Thr Arg Glu Gln Ile Leu Val Lys His Ala Gln Glu Glu Leu Pro
690 695 700

Pro Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile
705 710 715 720

Arg Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr
725 730 735

Arg Ser Glu Ala Val Leu Gln Ser Pro Glu Phe Ala Ile Phe Arg Lys
740 745 750

Glu Gly Asn Phe Ser Asp Leu Lys Glu Lys Val Asn Ala Ile Glu Arg
755 760 765

Glu Lys Ala Glu Lys Phe Arg Lys Leu Gln Asp Ala Ser Arg Ser Ala
770 775 780

Gln Ala Leu Val Glu Gln Met Val Asn Glu Gly Val Asn Ala Asp Ser
785 790 795 800

Ile Lys Gln Ala Ser Glu Gln Leu Asn Ser Arg Trp Ile Glu Phe Cys
805 810 815

Gln Leu Leu Ser Glu Arg Leu Asn Trp Leu Glu Tyr Gln Asn Asn Ile
820 825 830

Ile Ala Phe Tyr Asn Gln Leu Gln Gln Leu Glu Gln Met Thr Thr Thr
835 840 845

```
Ala Glu Asn Trp Leu Lys Ile Gln Pro Thr Thr Pro Ser Glu Pro Thr
    850                 855                 860

Ala Ile Lys Ser Gln Leu Lys Ile Cys Lys Asp Glu Val Asn Arg Leu
865                 870                 875                 880

Ser Asp Leu Gln Pro Gln Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala
                885                 890                 895

Leu Lys Glu Lys Gly Gln Gly Pro Met Phe Leu Asp Ala Asp Phe Val
            900                 905                 910

Ala Phe Thr Asn His Phe Lys Gln Val Phe Ser Asp Val Gln Ala Arg
        915                 920                 925

Glu Lys Glu Leu Gln Thr Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr
    930                 935                 940

Gln Glu Thr Met Ser Ala Ile Arg Thr Trp Val Gln Gln Ser Glu Thr
945                 950                 955                 960

Lys Leu Ser Ile Pro Gln Leu Ser Val Thr Asp Tyr Glu Ile Met Glu
                965                 970                 975

Gln Arg Leu Gly Glu Leu Gln Ala Leu Gln Ser Ser Leu Gln Glu Gln
            980                 985                 990

Gln Ser Gly Leu Tyr Tyr Leu Ser  Thr Thr Val Lys Glu  Met Ser Lys
        995                 1000                1005

Lys Ala  Pro Ser Glu Ile Ser  Arg Lys Tyr Gln Ser  Glu Phe Glu
    1010                1015                1020

Glu Ile  Glu Gly Arg Trp Lys  Lys Leu Ser Ser Gln  Leu Val Glu
    1025                1030                1035

His Cys  Gln Lys Leu Glu Glu  Gln Met Asn Lys Leu  Arg Lys Ile
    1040                1045                1050

Gln Asn  His Ile Gln Thr Leu  Lys Lys Trp Met Ala  Glu Val Asp
```

```
    1055                1060                1065

Val Phe  Leu Lys Glu Glu Trp  Pro Ala Leu Gly Asp  Ser Glu Ile
    1070                1075                1080

Leu Lys  Lys Gln Leu Lys Gln  Cys Arg Leu Leu Val  Ser Asp Ile
    1085                1090                1095

Gln Thr  Ile Gln Pro Ser Leu  Asn Ser Val Asn Glu  Gly Gly Gln
    1100                1105                1110

Lys Ile  Lys Asn Glu Ala Glu  Pro Glu Phe Ala Ser  Arg Leu Glu
    1115                1120                1125

Thr Glu  Leu Lys Glu Leu Asn  Thr Gln Trp Asp His  Met Cys Gln
    1130                1135                1140

Gln Val  Tyr Ala Arg Lys Glu  Ala Leu Lys Gly Gly  Leu Glu Lys
    1145                1150                1155

Thr Val  Ser Leu Gln Lys Asp  Leu Ser Glu Met His  Glu Trp Met
    1160                1165                1170

Thr Gln  Ala Glu Glu Glu Tyr  Leu Glu Arg Asp Phe  Glu Tyr Lys
    1175                1180                1185

Thr Pro  Asp Glu Leu Gln Lys  Ala Val Glu Glu Met  Lys Arg Ala
    1190                1195                1200

Lys Glu  Glu Ala Gln Gln Lys  Glu Ala Lys Val Lys  Leu Leu Thr
    1205                1210                1215

Glu Ser  Val Asn Ser Val Ile  Ala Gln Ala Pro Pro  Val Ala Gln
    1220                1225                1230

Glu Ala  Leu Lys Lys Glu Leu  Glu Thr Leu Thr Thr  Asn Tyr Gln
    1235                1240                1245

Trp Leu  Cys Thr Arg Leu Asn  Gly Lys Cys Lys Thr  Leu Glu Glu
    1250                1255                1260
```

```
Val Trp  Ala Cys Trp His Glu  Leu Leu Ser Tyr Leu  Glu Lys Ala
    1265                1270                1275

Asn Lys  Trp Leu Asn Glu Val  Glu Phe Lys Leu Lys  Thr Thr Glu
    1280                1285                1290

Asn Ile  Pro Gly Gly Ala Glu  Glu Ile Ser Glu Val  Leu Asp Ser
    1295                1300                1305

Leu Glu  Asn Leu Met Arg His  Ser Glu Asp Asn Pro  Asn Gln Ile
    1310                1315                1320

Arg Ile  Leu Ala Gln Thr Leu  Thr Asp Gly Gly Val  Met Asp Glu
    1325                1330                1335

Leu Ile  Asn Glu Glu Leu Glu  Thr Phe Asn Ser Arg  Trp Arg Glu
    1340                1345                1350

Leu His  Glu Glu Ala Val Arg  Arg Gln Lys Leu Leu  Glu Gln Ser
    1355                1360                1365

Ile Gln  Ser Ala Gln Glu Thr  Glu Lys Ser Leu His  Leu Ile Gln
    1370                1375                1380

Glu Ser  Leu Thr Phe Ile Asp  Lys Gln Leu Ala Ala  Tyr Ile Ala
    1385                1390                1395

Asp Lys  Val Asp Ala Ala Gln  Met Pro Gln Glu Ala  Gln Lys Ile
    1400                1405                1410

Gln Ser  Asp Leu Thr Ser His  Glu Ile Ser Leu Glu  Glu Met Lys
    1415                1420                1425

Lys His  Asn Gln Gly Lys Glu  Ala Ala Gln Arg Val  Leu Ser Gln
    1430                1435                1440

Ile Asp  Val Ala Gln Lys Lys  Leu Gln Asp Val Ser  Met Lys Phe
    1445                1450                1455

Arg Leu  Phe Gln Lys Pro Ala  Asn Phe Glu Gln Arg  Leu Gln Glu
```

1460 1465 1470

Ser Lys Met Ile Leu Asp Glu Val Lys Met His Leu Pro Ala Leu
1475 1480 1485

Glu Thr Lys Ser Val Glu Gln Glu Val Val Gln Ser Gln Leu Asn
1490 1495 1500

His Cys Val Asn Leu Tyr Lys Ser Leu Ser Glu Val Lys Ser Glu
1505 1510 1515

Val Glu Met Val Ile Lys Thr Gly Arg Gln Ile Val Gln Lys Lys
1520 1525 1530

Gln Thr Glu Asn Pro Lys Glu Leu Asp Glu Arg Val Thr Ala Leu
1535 1540 1545

Lys Leu His Tyr Asn Glu Leu Gly Ala Lys Val Thr Glu Arg Lys
1550 1555 1560

Gln Gln Leu Glu Lys Cys Leu Lys Leu Ser Arg Lys Met Arg Lys
1565 1570 1575

Glu Met Asn Val Leu Thr Glu Trp Leu Ala Ala Thr Asp Met Glu
1580 1585 1590

Leu Thr Lys Arg Ser Ala Val Glu Gly Met Pro Ser Asn Leu Asp
1595 1600 1605

Ser Glu Val Ala Trp Gly Lys Ala Thr Gln Lys Glu Ile Glu Lys
1610 1615 1620

Gln Lys Val His Leu Lys Ser Ile Thr Glu Val Gly Glu Ala Leu
1625 1630 1635

Lys Thr Val Leu Gly Lys Lys Glu Thr Leu Val Glu Asp Lys Leu
1640 1645 1650

Ser Leu Leu Asn Ser Asn Trp Ile Ala Val Thr Ser Arg Ala Glu
1655 1660 1665

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Glu Trp  Leu Asn Leu Leu Leu  Glu Tyr Gln Lys His  Met Glu Thr
    1670                1675                1680

Phe Asp  Gln Asn Val Asp His  Ile Thr Lys Trp Ile  Ile Gln Ala
    1685                1690                1695

Asp Thr  Leu Leu Asp Glu Ser  Glu Lys Lys Lys Pro  Gln Gln Lys
    1700                1705                1710

Glu Asp  Val Leu Lys Arg Leu  Lys Ala Glu Leu Asn  Asp Ile Arg
    1715                1720                1725

Pro Lys  Val Asp Ser Thr Arg  Asp Gln Ala Ala Asn  Leu Met Ala
    1730                1735                1740

Asn Arg  Gly Asp His Cys Arg  Lys Leu Val Glu Pro  Gln Ile Ser
    1745                1750                1755

Glu Leu  Asn His Arg Phe Ala  Ala Ile Ser His Arg  Ile Lys Thr
    1760                1765                1770

Gly Lys  Ala Ser Ile Pro Leu  Lys Glu Leu Glu Gln  Phe Asn Ser
    1775                1780                1785

Asp Ile  Gln Lys Leu Leu Glu  Pro Leu Glu Ala Glu  Ile Gln Gln
    1790                1795                1800

Gly Val  Asn Leu Lys Glu Glu  Asp Phe Asn Lys Asp  Met Asn Glu
    1805                1810                1815

Asp Asn  Glu Gly Thr Val Lys  Glu Leu Leu Gln Arg  Gly Asp Asn
    1820                1825                1830

Leu Gln  Gln Arg Ile Thr Asp  Glu Arg Lys Arg Glu  Glu Ile Lys
    1835                1840                1845

Ile Lys  Gln Gln Leu Leu Gln  Thr Lys His Asn Ala  Leu Lys Asp
    1850                1855                1860

Leu Arg  Ser Gln Arg Arg Lys  Lys Ala Leu Glu Ile  Ser His Gln
```

1865 1870 1875

Trp Tyr Gln Tyr Lys Arg Gln Ala Asp Asp Leu Leu Lys Cys Leu
1880 1885 1890

Asp Asp Ile Glu Lys Lys Leu Ala Ser Leu Pro Glu Pro Arg Asp
1895 1900 1905

Glu Arg Lys Ile Lys Glu Ile Asp Arg Glu Leu Gln Lys Lys Lys
1910 1915 1920

Glu Glu Leu Asn Ala Val Arg Arg Gln Ala Glu Gly Leu Ser Glu
1925 1930 1935

Asp Gly Ala Ala Met Ala Val Glu Pro Thr Gln Ile Gln Leu Ser
1940 1945 1950

Lys Arg Trp Arg Glu Ile Glu Ser Lys Phe Ala Gln Phe Arg Arg
1955 1960 1965

Leu Asn Phe Ala Gln Ile His Thr Val Arg Glu Glu Thr Met Met
1970 1975 1980

Val Met Thr Glu Asp Met Pro Leu Glu Ile Ser Tyr Val Pro Ser
1985 1990 1995

Thr Tyr Leu Thr Glu Ile Thr His Val Ser Gln Ala Leu Leu Glu
2000 2005 2010

Val Glu Gln Leu Leu Asn Ala Pro Asp Leu Cys Ala Lys Asp Phe
2015 2020 2025

Glu Asp Leu Phe Lys Gln Glu Glu Ser Leu Lys Asn Ile Lys Asp
2030 2035 2040

Ser Leu Gln Gln Ser Ser Gly Arg Ile Asp Ile Ile His Ser Lys
2045 2050 2055

Lys Thr Ala Ala Leu Gln Ser Ala Thr Pro Val Glu Arg Val Lys
2060 2065 2070

Leu Gln Glu Ala Leu Ser Gln Leu Asp Phe Gln Trp Glu Lys Val
2075 2080 2085

Asn Lys Met Tyr Lys Asp Arg Gln Gly Arg Phe Asp Arg Ser Val
2090 2095 2100

Glu Lys Trp Arg Arg Phe His Tyr Asp Ile Lys Ile Phe Asn Gln
2105 2110 2115

Trp Leu Thr Glu Ala Glu Gln Phe Leu Arg Lys Thr Gln Ile Pro
2120 2125 2130

Glu Asn Trp Glu His Ala Lys Tyr Lys Trp Tyr Leu Lys Glu Leu
2135 2140 2145

Gln Asp Gly Ile Gly Gln Arg Gln Thr Val Val Arg Thr Leu Asn
2150 2155 2160

Ala Thr Gly Glu Glu Ile Ile Gln Gln Ser Ser Lys Thr Asp Ala
2165 2170 2175

Ser Ile Leu Gln Glu Lys Leu Gly Ser Leu Asn Leu Arg Trp Gln
2180 2185 2190

Glu Val Cys Lys Gln Leu Ser Asp Arg Lys Lys Arg Leu Glu Glu
2195 2200 2205

Gln Lys Asn Ile Leu Ser Glu Phe Gln Arg Asp Leu Asn Glu Phe
2210 2215 2220

Val Leu Trp Leu Glu Glu Ala Asp Asn Ile Ala Ser Ile Pro Leu
2225 2230 2235

Glu Pro Gly Lys Glu Gln Gln Leu Lys Glu Lys Leu Glu Gln Val
2240 2245 2250

Lys Leu Leu Val Glu Glu Leu Pro Leu Arg Gln Gly Ile Leu Lys
2255 2260 2265

Gln Leu Asn Glu Thr Gly Gly Pro Val Leu Val Ser Ala Pro Ile

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    2270                2275                2280

Ser Pro  Glu Glu Gln Asp Lys  Leu Glu Asn Lys Leu  Lys Gln Thr
    2285                2290                2295

Asn Leu  Gln Trp Ile Lys Val  Ser Arg Ala Leu Pro  Glu Lys Gln
    2300                2305                2310

Gly Glu  Ile Glu Ala Gln Ile  Lys Asp Leu Gly Gln  Leu Glu Lys
    2315                2320                2325

Lys Leu  Glu Asp Leu Glu Glu  Gln Leu Asn His Leu  Leu Leu Trp
    2330                2335                2340

Leu Ser  Pro Ile Arg Asn Gln  Leu Glu Ile Tyr Asn  Gln Pro Asn
    2345                2350                2355

Gln Glu  Gly Pro Phe Asp Val  Lys Glu Thr Glu Ile  Ala Val Gln
    2360                2365                2370

Ala Lys  Gln Pro Asp Val Glu  Glu Ile Leu Ser Lys  Gly Gln His
    2375                2380                2385

Leu Tyr  Lys Glu Lys Pro Ala  Thr Gln Pro Val Lys  Arg Lys Leu
    2390                2395                2400

Glu Asp  Leu Ser Ser Glu Trp  Lys Ala Val Asn Arg  Leu Leu Gln
    2405                2410                2415

Glu Leu  Arg Ala Lys Gln Pro  Asp Leu Ala Pro Gly  Leu Thr Thr
    2420                2425                2430

Ile Gly  Ala Ser Pro Thr Gln  Thr Val Thr Leu Val  Thr Gln Pro
    2435                2440                2445

Val Val  Thr Lys Glu Thr Ala  Ile Ser Lys Leu Glu  Met Pro Ser
    2450                2455                2460

Ser Leu  Met Leu Glu Val Pro  Ala Leu Ala Asp Phe  Asn Arg Ala
    2465                2470                2475
```

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Trp Thr  Glu Leu Thr Asp Trp  Leu Ser Leu Leu Asp  Gln Val Ile
    2480                2485                2490

Lys Ser  Gln Arg Val Met Val  Gly Asp Leu Glu Asp  Ile Asn Glu
    2495                2500                2505

Met Ile  Ile Lys Gln Lys Ala  Thr Met Gln Asp Leu  Glu Gln Arg
    2510                2515                2520

Arg Pro  Gln Leu Glu Glu Leu  Ile Thr Ala Ala Gln  Asn Leu Lys
    2525                2530                2535

Asn Lys  Thr Ser Asn Gln Glu  Ala Arg Thr Ile Ile  Thr Asp Arg
    2540                2545                2550

Ile Glu  Arg Ile Gln Asn Gln  Trp Asp Glu Val Gln  Glu His Leu
    2555                2560                2565

Gln Asn  Arg Arg Gln Gln Leu  Asn Glu Met Leu Lys  Asp Ser Thr
    2570                2575                2580

Gln Trp  Leu Glu Ala Lys Glu  Glu Ala Glu Gln Val  Leu Gly Gln
    2585                2590                2595

Ala Arg  Ala Lys Leu Glu Ser  Trp Lys Glu Gly Pro  Tyr Thr Val
    2600                2605                2610

Asp Ala  Ile Gln Lys Lys Ile  Thr Glu Thr Lys Gln  Leu Ala Lys
    2615                2620                2625

Asp Leu  Arg Gln Trp Gln Thr  Asn Val Asp Val Ala  Asn Asp Leu
    2630                2635                2640

Ala Leu  Lys Leu Leu Arg Asp  Tyr Ser Ala Asp Asp  Thr Arg Lys
    2645                2650                2655

Val His  Met Ile Thr Glu Asn  Ile Asn Ala Ser Trp  Arg Ser Ile
    2660                2665                2670

His Lys  Arg Val Ser Glu Arg  Glu Ala Ala Leu Glu  Glu Thr His
```

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    2675                2680                2685

Arg Leu  Leu Gln Gln Phe Pro  Leu Asp Leu Glu Lys  Phe Leu Ala
    2690                2695                2700

Trp Leu  Thr Glu Ala Glu Thr  Thr Ala Asn Val Leu  Gln Asp Ala
    2705                2710                2715

Thr Arg  Lys Glu Arg Leu Leu  Glu Asp Ser Lys Gly  Val Lys Glu
    2720                2725                2730

Leu Met  Lys Gln Trp Gln Asp  Leu Gln Gly Glu Ile  Glu Ala His
    2735                2740                2745

Thr Asp  Val Tyr His Asn Leu  Asp Glu Asn Ser Gln  Lys Ile Leu
    2750                2755                2760

Arg Ser  Leu Glu Gly Ser Asp  Asp Ala Val Leu Leu  Gln Arg Arg
    2765                2770                2775

Leu Asp  Asn Met Asn Phe Lys  Trp Ser Glu Leu Arg  Lys Lys Ser
    2780                2785                2790

Leu Asn  Ile Arg Ser His Leu  Glu Ala Ser Ser Asp  Gln Trp Lys
    2795                2800                2805

Arg Leu  His Leu Ser Leu Gln  Glu Leu Leu Val Trp  Leu Gln Leu
    2810                2815                2820

Lys Asp  Asp Glu Leu Ser Arg  Gln Ala Pro Ile Gly  Gly Asp Phe
    2825                2830                2835

Pro Ala  Val Gln Lys Gln Asn  Asp Val His Arg Ala  Phe Lys Arg
    2840                2845                2850

Glu Leu  Lys Thr Lys Glu Pro  Val Ile Met Ser Thr  Leu Glu Thr
    2855                2860                2865

Val Arg  Ile Phe Leu Thr Glu  Gln Pro Leu Glu Gly  Leu Glu Lys
    2870                2875                2880
```

Leu Tyr Gln Glu Pro Arg Glu Leu Pro Pro Glu Glu Arg Ala Gln
2885 2890 2895

Asn Val Thr Arg Leu Leu Arg Lys Gln Ala Glu Glu Val Asn Thr
2900 2905 2910

Glu Trp Glu Lys Leu Asn Leu His Ser Ala Asp Trp Gln Arg Lys
2915 2920 2925

Ile Asp Glu Thr Leu Glu Arg Leu Arg Glu Leu Gln Glu Ala Thr
2930 2935 2940

Asp Glu Leu Asp Leu Lys Leu Arg Gln Ala Glu Val Ile Lys Gly
2945 2950 2955

Ser Trp Gln Pro Val Gly Asp Leu Leu Ile Asp Ser Leu Gln Asp
2960 2965 2970

His Leu Glu Lys Val Lys Ala Leu Arg Gly Glu Ile Ala Pro Leu
2975 2980 2985

Lys Glu Asn Val Ser His Val Asn Asp Leu Ala Arg Gln Leu Thr
2990 2995 3000

Thr Leu Gly Ile Gln Leu Ser Pro Tyr Asn Leu Ser Thr Leu Glu
3005 3010 3015

Asp Leu Asn Thr Arg Trp Lys Leu Leu Gln Val Ala Val Glu Asp
3020 3025 3030

Arg Val Arg Gln Leu His Glu Ala His Arg Asp Phe Gly Pro Ala
3035 3040 3045

Ser Gln His Phe Leu Ser Thr Ser Val Gln Gly Pro Trp Glu Arg
3050 3055 3060

Ala Ile Ser Pro Asn Lys Val Pro Tyr Tyr Ile Asn His Glu Thr
3065 3070 3075

Gln Thr Thr Cys Trp Asp His Pro Lys Met Thr Glu Leu Tyr Gln

```
    3080                3085                3090

Ser Leu  Ala Asp Leu Asn Asn  Val Arg Phe Ser Ala  Tyr Arg Thr
    3095                3100                3105

Ala Met  Lys Leu Arg Arg Leu  Gln Lys Ala Leu Cys  Leu Asp Leu
    3110                3115                3120

Leu Ser  Leu Ser Ala Ala Cys  Asp Ala Leu Asp Gln  His Asn Leu
    3125                3130                3135

Lys Gln  Asn Asp Gln Pro Met  Asp Ile Leu Gln Ile  Ile Asn Cys
    3140                3145                3150

Leu Thr  Thr Ile Tyr Asp Arg  Leu Glu Gln Glu His  Asn Asn Leu
    3155                3160                3165

Val Asn  Val Pro Leu Cys Val  Asp Met Cys Leu Asn  Trp Leu Leu
    3170                3175                3180

Asn Val  Tyr Asp Thr Gly Arg  Thr Gly Arg Ile Arg  Val Leu Ser
    3185                3190                3195

Phe Lys  Thr Gly Ile Ile Ser  Leu Cys Lys Ala His  Leu Glu Asp
    3200                3205                3210

Lys Tyr  Arg Tyr Leu Phe Lys  Gln Val Ala Ser Ser  Thr Gly Phe
    3215                3220                3225

Cys Asp  Gln Arg Arg Leu Gly  Leu Leu Leu His Asp  Ser Ile Gln
    3230                3235                3240

Ile Pro  Arg Gln Leu Gly Glu  Val Ala Ser Phe Gly  Gly Ser Asn
    3245                3250                3255

Ile Glu  Pro Ser Val Arg Ser  Cys Phe Gln Phe Ala  Asn Asn Lys
    3260                3265                3270

Pro Glu  Ile Glu Ala Ala Leu  Phe Leu Asp Trp Met  Arg Leu Glu
    3275                3280                3285
```

Pro Gln Ser Met Val Trp Leu Pro Val Leu His Arg Val Ala Ala
3290 3295 3300

Ala Glu Thr Ala Lys His Gln Ala Lys Cys Asn Ile Cys Lys Glu
3305 3310 3315

Cys Pro Ile Ile Gly Phe Arg Tyr Arg Ser Leu Lys His Phe Asn
3320 3325 3330

Tyr Asp Ile Cys Gln Ser Cys Phe Phe Ser Gly Arg Val Ala Lys
3335 3340 3345

Gly His Lys Met His Tyr Pro Met Val Glu Tyr Cys Thr Pro Thr
3350 3355 3360

Thr Ser Gly Glu Asp Val Arg Asp Phe Ala Lys Val Leu Lys Asn
3365 3370 3375

Lys Phe Arg Thr Lys Arg Tyr Phe Ala Lys His Pro Arg Met Gly
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Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp Asn Met Glu Thr
3395 3400 3405

Asn Leu Gln Ala Glu Tyr Asp Arg Leu Lys Gln Gln His Glu His
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Lys Gly Leu Ser Pro Leu Pro Ser Pro Pro Glu Met Met Pro Thr
3425 3430 3435

Ser Pro Gln Ser Pro Arg Asp Ala Glu Leu Ile Ala Glu Ala Lys
3440 3445 3450

Leu Leu Arg Gln His Lys Gly Arg Leu Glu Ala Arg Met Gln Ile
3455 3460 3465

Leu Glu Asp His Asn Lys Gln Leu Glu Ser Gln Leu His Arg Leu
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Arg Gln Leu Leu Glu Gln Pro Gln Ala Glu Ala Lys Val Asn Gly

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Thr Thr Val Ser Ser Pro Ser Thr Ser Leu Gln Arg Ser Asp Ser
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Ser Gln Pro Met Leu Leu Arg Val Val Gly Ser Gln Thr Ser Asp
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Ser Met Gly Glu Glu Asp Leu Leu Ser Pro Pro Gln Asp Thr Ser
3530 3535 3540

Thr Gly Leu Glu Glu Val Met Glu Gln Leu Asn Asn Ser Phe Pro
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Ser Ser Arg Gly Arg Asn Thr Pro Gly Lys Pro Met Arg Glu Asp
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Asn Ile Ile Leu His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met
        115                 120                 125

Ala Gly Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
    130                 135                 140

Arg Gln Ser Thr Arg Asn Tyr Pro Gln Val Asn Val Ile Asn Phe Thr
145                 150                 155                 160

Thr Ser Trp Ser Asp Gly Leu Ala Leu Asn Ala Leu Ile His Ser His
                165                 170                 175

Arg Pro Asp Leu Phe Asp Trp Asn Ser Val Val Cys Gln Gln Ser Ala
            180                 185                 190

Thr Gln Arg Leu Glu His Ala Phe Asn Ile Ala Arg Tyr Gln Leu Gly
        195                 200                 205

Ile Glu Lys Leu Leu Asp Pro Glu Asp Val Asp Thr Thr Tyr Pro Asp
    210                 215                 220

Lys Lys Ser Ile Leu Met Tyr Ile Thr Ser Leu Phe Gln Val Leu Pro
225                 230                 235                 240

Gln Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg
                245                 250                 255

Pro Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met
            260                 265                 270

His Tyr Ser Gln Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg
        275                 280                 285

Thr Ser Ser Pro Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala
    290                 295                 300
```

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Ala Tyr Val Thr Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln
305                 310                 315                 320

His Leu Glu Ala Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu
                325                 330                 335

Ser Glu Val Asn Leu Asp Arg Tyr Gln Thr Ala Leu Glu Glu Val Leu
            340                 345                 350

Ser Trp Leu Leu Ser Ala Glu Asp Thr Leu Gln Ala Gln Gly Glu Ile
        355                 360                 365

Ser Asn Asp Val Glu Val Val Lys Asp Gln Phe His Thr His Glu Gly
    370                 375                 380

Tyr Met Met Asp Leu Thr Ala His Gln Gly Arg Val Gly Asn Ile Leu
385                 390                 395                 400

Gln Leu Gly Ser Lys Leu Ile Gly Thr Gly Lys Leu Ser Glu Asp Glu
                405                 410                 415

Glu Thr Glu Val Gln Glu Gln Met Asn Leu Leu Asn Ser Arg Trp Glu
            420                 425                 430

Cys Leu Arg Val Ala Ser Met Glu Lys Gln Ser Asn Leu His Arg Val
        435                 440                 445

Leu Met Asp Leu Gln Asn Gln Lys Leu Lys Glu Leu Asn Asp Trp Leu
    450                 455                 460

Thr Lys Thr Glu Glu Arg Thr Arg Lys Met Glu Glu Glu Pro Leu Gly
465                 470                 475                 480

Pro Asp Leu Glu Asp Leu Lys Arg Gln Val Gln Gln His Lys Val Leu
                485                 490                 495

Gln Glu Asp Leu Glu Gln Glu Gln Val Arg Val Asn Ser Leu Thr His
            500                 505                 510
```

```
Met Val Val Val Val Asp Glu Ser Ser Gly Asp His Ala Thr Ala Ala
        515                 520                 525

Leu Glu Glu Gln Leu Lys Val Leu Gly Asp Arg Trp Ala Asn Ile Cys
    530                 535                 540

Arg Trp Thr Glu Asp Arg Trp Val Leu Leu Gln Asp Ile Leu Leu Lys
545                 550                 555                 560

Trp Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ala Trp Leu Ser
                565                 570                 575

Glu Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp
            580                 585                 590

Gln Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala
        595                 600                 605

Asp Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys
    610                 615                 620

Gln Asp Leu Leu Ser Thr Leu Lys Asn Lys Ser Val Thr Gln Lys Thr
625                 630                 635                 640

Glu Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln
                645                 650                 655

Lys Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr
            660                 665                 670

Gln Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val
        675                 680                 685

Thr Thr Arg Glu Gln Ile Leu Val Lys His Ala Gln Glu Glu Leu Pro
    690                 695                 700

Pro Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile
705                 710                 715                 720

Arg Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr
                725                 730                 735
```

```
Arg Ser Glu Ala Val Leu Gln Ser Pro Glu Phe Ala Ile Phe Arg Lys
            740                 745                 750

Glu Gly Asn Phe Ser Asp Leu Lys Glu Lys Val Asn Ala Ile Glu Arg
        755                 760                 765

Glu Lys Ala Glu Lys Phe Arg Lys Leu Gln Asp Ala Ser Arg Ser Ala
    770                 775                 780

Gln Ala Leu Val Glu Gln Met Val Asn Glu Gly Val Asn Ala Asp Ser
785                 790                 795                 800

Ile Lys Gln Ala Ser Glu Gln Leu Asn Ser Arg Trp Ile Glu Phe Cys
                805                 810                 815

Gln Leu Leu Ser Glu Arg Leu Asn Trp Leu Glu Tyr Gln Asn Asn Ile
            820                 825                 830

Ile Ala Phe Tyr Asn Gln Leu Gln Gln Leu Glu Gln Met Thr Thr Thr
        835                 840                 845

Ala Glu Asn Trp Leu Lys Ile Gln Pro Thr Thr Pro Ser Glu Pro Thr
    850                 855                 860

Ala Ile Lys Ser Gln Leu Lys Ile Cys Lys Asp Glu Val Asn Arg Leu
865                 870                 875                 880

Ser Asp Leu Gln Pro Gln Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala
                885                 890                 895

Leu Lys Glu Lys Gly Gln Gly Pro Met Phe Leu Asp Ala Asp Phe Val
            900                 905                 910

Ala Phe Thr Asn His Phe Lys Gln Val Phe Ser Asp Val Gln Ala Arg
        915                 920                 925

Glu Lys Glu Leu Gln Thr Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr
    930                 935                 940
```

```
Gln Glu Thr Met Ser Ala Ile Arg Thr Trp Val Gln Gln Ser Glu Thr
945                 950                 955                 960

Lys Leu Ser Ile Pro Gln Leu Ser Val Thr Asp Tyr Glu Ile Met Glu
                965                 970                 975

Gln Arg Leu Gly Glu Leu Gln Ala Leu Gln Ser Ser Leu Gln Glu Gln
            980                 985                 990

Gln Ser Gly Leu Tyr Tyr Leu Ser  Thr Thr Val Lys Glu  Met Ser Lys
        995                 1000                1005

Lys Ala  Pro Ser Glu Ile Ser  Arg Lys Tyr Gln Ser  Glu Phe Glu
    1010                1015                1020

Glu Ile  Glu Gly Arg Trp Lys  Lys Leu Ser Ser Gln  Leu Val Glu
    1025                1030                1035

His Cys  Gln Lys Leu Glu Glu  Gln Met Asn Lys Leu  Arg Lys Ile
    1040                1045                1050

Gln Asn  His Ile Gln Thr Leu  Lys Lys Trp Met Ala  Glu Val Asp
    1055                1060                1065

Val Phe  Leu Lys Glu Glu Trp  Pro Ala Leu Gly Asp  Ser Glu Ile
    1070                1075                1080

Leu Lys  Lys Gln Leu Lys Gln  Cys Arg Leu Leu Val  Ser Asp Ile
    1085                1090                1095

Gln Thr  Ile Gln Pro Ser Leu  Asn Ser Val Asn Glu  Gly Gly Gln
    1100                1105                1110

Lys Ile  Lys Asn Glu Ala Glu  Pro Glu Phe Ala Ser  Arg Leu Glu
    1115                1120                1125

Thr Glu  Leu Lys Glu Leu Asn  Thr Gln Trp Asp His  Met Cys Gln
    1130                1135                1140

Gln Val  Tyr Ala Arg Lys Glu  Ala Leu Lys Gly Gly  Leu Glu Lys
    1145                1150                1155
```

```
Thr Val  Ser Leu Gln Lys Asp  Leu Ser Glu Met His  Glu Trp Met
    1160                1165                1170

Thr Gln  Ala Glu Glu Glu Tyr  Leu Glu Arg Asp Phe  Glu Tyr Lys
    1175                1180                1185

Thr Pro  Asp Glu Leu Gln Lys  Ala Val Glu Glu Met  Lys Arg Ala
    1190                1195                1200

Lys Glu  Glu Ala Gln Gln Lys  Glu Ala Lys Val Lys  Leu Leu Thr
    1205                1210                1215

Glu Ser  Val Asn Ser Val Ile  Ala Gln Ala Pro Pro  Val Ala Gln
    1220                1225                1230

Glu Ala  Leu Lys Lys Glu Leu  Glu Thr Leu Thr Thr  Asn Tyr Gln
    1235                1240                1245

Trp Leu  Cys Thr Arg Leu Asn  Gly Lys Cys Lys Thr  Leu Glu Glu
    1250                1255                1260

Val Trp  Ala Cys Trp His Glu  Leu Leu Ser Tyr Leu  Glu Lys Ala
    1265                1270                1275

Asn Lys  Trp Leu Asn Glu Val  Glu Phe Lys Leu Lys  Thr Thr Glu
    1280                1285                1290

Asn Ile  Pro Gly Gly Ala Glu  Glu Ile Ser Glu Val  Leu Asp Ser
    1295                1300                1305

Leu Glu  Asn Leu Met Arg His  Ser Glu Asp Asn Pro  Asn Gln Ile
    1310                1315                1320

Arg Ile  Leu Ala Gln Thr Leu  Thr Asp Gly Gly Val  Met Asp Glu
    1325                1330                1335

Leu Ile  Asn Glu Glu Leu Glu  Thr Phe Asn Ser Arg  Trp Arg Glu
    1340                1345                1350
```

```
Leu His  Glu Glu Ala Val Arg  Arg Gln Lys Leu Leu  Glu Gln Ser
    1355                1360                1365

Ile Gln  Ser Ala Gln Glu Thr  Glu Lys Ser Leu His  Leu Ile Gln
    1370                1375                1380

Glu Ser  Leu Thr Phe Ile Asp  Lys Gln Leu Ala Ala  Tyr Ile Ala
    1385                1390                1395

Asp Lys  Val Asp Ala Ala Gln  Met Pro Gln Glu Ala  Gln Lys Ile
    1400                1405                1410

Gln Ser  Asp Leu Thr Ser His  Glu Ile Ser Leu Glu  Glu Met Lys
    1415                1420                1425

Lys His  Asn Gln Gly Lys Glu  Ala Ala Gln Arg Val  Leu Ser Gln
    1430                1435                1440

Ile Asp  Val Ala Gln Lys Lys  Leu Gln Asp Val Ser  Met Lys Phe
    1445                1450                1455

Arg Leu  Phe Gln Lys Pro Ala  Asn Phe Glu Gln Arg  Leu Gln Glu
    1460                1465                1470

Ser Lys  Met Ile Leu Asp Glu  Val Lys Met His Leu  Pro Ala Leu
    1475                1480                1485

Glu Thr  Lys Ser Val Glu Gln  Glu Val Val Gln Ser  Gln Leu Asn
    1490                1495                1500

His Cys  Val Asn Leu Tyr Lys  Ser Leu Ser Glu Val  Lys Ser Glu
    1505                1510                1515

Val Glu  Met Val Ile Lys Thr  Gly Arg Gln Ile Val  Gln Lys Lys
    1520                1525                1530

Gln Thr  Glu Asn Pro Lys Glu  Leu Asp Glu Arg Val  Thr Ala Leu
    1535                1540                1545

Lys Leu  His Tyr Asn Glu Leu  Gly Ala Lys Val Thr  Glu Arg Lys
    1550                1555                1560
```

```
Gln Gln  Leu Glu Lys Cys Leu  Lys Leu Ser Arg Lys  Met Arg Lys
    1565                1570                1575

Glu Met  Asn Val Leu Thr Glu  Trp Leu Ala Ala Thr  Asp Met Glu
    1580                1585                1590

Leu Thr  Lys Arg Ser Ala Val  Glu Gly Met Pro Ser  Asn Leu Asp
    1595                1600                1605

Ser Glu  Val Ala Trp Gly Lys  Ala Thr Gln Lys Glu  Ile Glu Lys
    1610                1615                1620

Gln Lys  Val His Leu Lys Ser  Ile Thr Glu Val Gly  Glu Ala Leu
    1625                1630                1635

Lys Thr  Val Leu Gly Lys Lys  Glu Thr Leu Val Glu  Asp Lys Leu
    1640                1645                1650

Ser Leu  Leu Asn Ser Asn Trp  Ile Ala Val Thr Ser  Arg Ala Glu
    1655                1660                1665

Glu Trp  Leu Asn Leu Leu Leu  Glu Tyr Gln Lys His  Met Glu Thr
    1670                1675                1680

Phe Asp  Gln Asn Val Asp His  Ile Thr Lys Trp Ile  Ile Gln Ala
    1685                1690                1695

Asp Thr  Leu Leu Asp Glu Ser  Glu Lys Lys Lys Pro  Gln Gln Lys
    1700                1705                1710

Glu Asp  Val Leu Lys Arg Leu  Lys Ala Glu Leu Asn  Asp Ile Arg
    1715                1720                1725

Pro Lys  Val Asp Ser Thr Arg  Asp Gln Ala Ala Asn  Leu Met Ala
    1730                1735                1740

Asn Arg  Gly Asp His Cys Arg  Lys Leu Val Glu Pro  Gln Ile Ser
    1745                1750                1755
```

```
Glu Leu  Asn His Arg Phe Ala  Ala Ile Ser His Arg  Ile Lys Thr
    1760                1765                1770

Gly Lys  Ala Ser Ile Pro Leu  Lys Glu Leu Glu Gln  Phe Asn Ser
    1775                1780                1785

Asp Ile  Gln Lys Leu Leu Glu  Pro Leu Glu Ala Glu  Ile Gln Gln
    1790                1795                1800

Gly Val  Asn Leu Lys Glu Glu  Asp Phe Asn Lys Asp  Met Asn Glu
    1805                1810                1815

Asp Asn  Glu Gly Thr Val Lys  Glu Leu Leu Gln Arg  Gly Asp Asn
    1820                1825                1830

Leu Gln  Gln Arg Ile Thr Asp  Glu Arg Lys Arg Glu  Glu Ile Lys
    1835                1840                1845

Ile Lys  Gln Gln Leu Leu Gln  Thr Lys His Asn Ala  Leu Lys Asp
    1850                1855                1860

Leu Arg  Ser Gln Arg Arg Lys  Lys Ala Leu Glu Ile  Ser His Gln
    1865                1870                1875

Trp Tyr  Gln Tyr Lys Arg Gln  Ala Asp Asp Leu Leu  Lys Cys Leu
    1880                1885                1890

Asp Asp  Ile Glu Lys Lys Leu  Ala Ser Leu Pro Glu  Pro Arg Asp
    1895                1900                1905

Glu Arg  Lys Ile Lys Glu Ile  Asp Arg Glu Leu Gln  Lys Lys Lys
    1910                1915                1920

Glu Glu  Leu Asn Ala Val Arg  Arg Gln Ala Glu Gly  Leu Ser Glu
    1925                1930                1935

Asp Gly  Ala Ala Met Ala Val  Glu Pro Thr Gln Ile  Gln Leu Ser
    1940                1945                1950

Lys Arg  Trp Arg Glu Ile Glu  Ser Lys Phe Ala Gln  Phe Arg Arg
    1955                1960                1965
```

```
Leu Asn  Phe Ala Gln Ile His  Thr Val Arg Glu Glu  Thr Met Met
    1970                1975                1980

Val Met  Thr Glu Asp Met Pro  Leu Glu Ile Ser Tyr  Val Pro Ser
    1985                1990                1995

Thr Tyr  Leu Thr Glu Ile Thr  His Val Ser Gln Ala  Leu Leu Glu
    2000                2005                2010

Val Glu  Gln Leu Leu Asn Ala  Pro Asp Leu Cys Ala  Lys Asp Phe
    2015                2020                2025

Glu Asp  Leu Phe Lys Gln Glu  Glu Ser Leu Lys Asn  Ile Lys Asp
    2030                2035                2040

Ser Leu  Gln Gln Ser Ser Gly  Arg Ile Asp Ile Ile  His Ser Lys
    2045                2050                2055

Lys Thr  Ala Ala Leu Gln Ser  Ala Thr Pro Val Glu  Arg Val Lys
    2060                2065                2070

Leu Gln  Glu Ala Leu Ser Gln  Leu Asp Phe Gln Trp  Glu Lys Val
    2075                2080                2085

Asn Lys  Met Tyr Lys Asp Arg  Gln Gly Arg Phe Asp  Arg Ser Val
    2090                2095                2100

Glu Lys  Trp Arg Arg Phe His  Tyr Asp Ile Lys Ile  Phe Asn Gln
    2105                2110                2115

Trp Leu  Thr Glu Ala Glu Gln  Phe Leu Arg Lys Thr  Gln Ile Pro
    2120                2125                2130

Glu Asn  Trp Glu His Ala Lys  Tyr Lys Trp Tyr Leu  Lys Glu Leu
    2135                2140                2145

Gln Asp  Gly Ile Gly Gln Arg  Gln Thr Val Val Arg  Thr Leu Asn
    2150                2155                2160
```

```
Ala Thr  Gly Glu Glu Ile Ile  Gln Gln Ser Ser Lys  Thr Asp Ala
    2165                 2170                 2175

Ser Ile  Leu Gln Glu Lys Leu  Gly Ser Leu Asn Leu  Arg Trp Gln
    2180                 2185                 2190

Glu Val  Cys Lys Gln Leu Ser  Asp Arg Lys Lys Arg  Leu Glu Glu
    2195                 2200                 2205

Gln Lys  Asn Ile Leu Ser Glu  Phe Gln Arg Asp Leu  Asn Glu Phe
    2210                 2215                 2220

Val Leu  Trp Leu Glu Glu Ala  Asp Asn Ile Ala Ser  Ile Pro Leu
    2225                 2230                 2235

Glu Pro  Gly Lys Glu Gln Gln  Leu Lys Glu Lys Leu  Glu Gln Val
    2240                 2245                 2250

Lys Leu  Leu Val Glu Glu Leu  Pro Leu Arg Gln Gly  Ile Leu Lys
    2255                 2260                 2265

Gln Leu  Asn Glu Thr Gly Gly  Pro Val Leu Val Ser  Ala Pro Ile
    2270                 2275                 2280

Ser Pro  Glu Glu Gln Asp Lys  Leu Glu Asn Lys Leu  Lys Gln Thr
    2285                 2290                 2295

Asn Leu  Gln Trp Ile Lys Val  Ser Arg Ala Leu Pro  Glu Lys Gln
    2300                 2305                 2310

Gly Glu  Ile Glu Ala Gln Ile  Lys Asp Leu Gly Gln  Leu Glu Lys
    2315                 2320                 2325

Lys Leu  Glu Asp Leu Glu Glu  Gln Leu Asn His Leu  Leu Leu Trp
    2330                 2335                 2340

Leu Ser  Pro Ile Arg Asn Gln  Leu Glu Ile Tyr Asn  Gln Pro Asn
    2345                 2350                 2355

Gln Glu  Gly Pro Phe Asp Val  Lys Glu Thr Glu Ile  Ala Val Gln
    2360                 2365                 2370
```

```
Ala Lys  Gln Pro Asp Val Glu  Glu Ile Leu Ser Lys  Gly Gln His
    2375                2380                2385

Leu Tyr  Lys Glu Lys Pro Ala  Thr Gln Pro Val Lys  Arg Lys Leu
    2390                2395                2400

Glu Asp  Leu Ser Ser Glu Trp  Lys Ala Val Asn Arg  Leu Leu Gln
    2405                2410                2415

Glu Leu  Arg Ala Lys Gln Pro  Asp Leu Ala Pro Gly  Leu Thr Thr
    2420                2425                2430

Ile Gly  Ala Ser Pro Thr Gln  Thr Val Thr Leu Val  Thr Gln Pro
    2435                2440                2445

Val Val  Thr Lys Glu Thr Ala  Ile Ser Lys Leu Glu  Met Pro Ser
    2450                2455                2460

Ser Leu  Met Leu Glu Val Pro  Ala Leu Ala Asp Phe  Asn Arg Ala
    2465                2470                2475

Trp Thr  Glu Leu Thr Asp Trp  Leu Ser Leu Leu Asp  Gln Val Ile
    2480                2485                2490

Lys Ser  Gln Arg Val Met Val  Gly Asp Leu Glu Asp  Ile Asn Glu
    2495                2500                2505

Met Ile  Ile Lys Gln Lys Ala  Thr Met Gln Asp Leu  Glu Gln Arg
    2510                2515                2520

Arg Pro  Gln Leu Glu Glu Leu  Ile Thr Ala Ala Gln  Asn Leu Lys
    2525                2530                2535

Asn Lys  Thr Ser Asn Gln Glu  Ala Arg Thr Ile Ile  Thr Asp Arg
    2540                2545                2550

Ile Glu  Arg Ile Gln Asn Gln  Trp Asp Glu Val Gln  Glu His Leu
    2555                2560                2565
```

```
Gln Asn  Arg Arg Gln Gln Leu  Asn Glu Met Leu Lys  Asp Ser Thr
    2570                2575                2580

Gln Trp  Leu Glu Ala Lys Glu  Glu Ala Glu Gln Val  Leu Gly Gln
    2585                2590                2595

Ala Arg  Ala Lys Leu Glu Ser  Trp Lys Glu Gly Pro  Tyr Thr Val
    2600                2605                2610

Asp Ala  Ile Gln Lys Lys Ile  Thr Glu Thr Lys Gln  Leu Ala Lys
    2615                2620                2625

Asp Leu  Arg Gln Trp Gln Thr  Asn Val Asp Val Ala  Asn Asp Leu
    2630                2635                2640

Ala Leu  Lys Leu Leu Arg Asp  Tyr Ser Ala Asp Asp  Thr Arg Lys
    2645                2650                2655

Val His  Met Ile Thr Glu Asn  Ile Asn Ala Ser Trp  Arg Ser Ile
    2660                2665                2670

His Lys  Arg Val Ser Glu Arg  Glu Ala Ala Leu Glu  Glu Thr His
    2675                2680                2685

Arg Leu  Leu Gln Gln Phe Pro  Leu Asp Leu Glu Lys  Phe Leu Ala
    2690                2695                2700

Trp Leu  Thr Glu Ala Glu Thr  Thr Ala Asn Val Leu  Gln Asp Ala
    2705                2710                2715

Thr Arg  Lys Glu Arg Leu Leu  Glu Asp Ser Lys Gly  Val Lys Glu
    2720                2725                2730

Leu Met  Lys Gln Trp Gln Asp  Leu Gln Gly Glu Ile  Glu Ala His
    2735                2740                2745

Thr Asp  Val Tyr His Asn Leu  Asp Glu Asn Ser Gln  Lys Ile Leu
    2750                2755                2760

Arg Ser  Leu Glu Gly Ser Asp  Asp Ala Val Leu Leu  Gln Arg Arg
    2765                2770                2775
```

```
Leu Asp  Asn Met Asn Phe Lys  Trp Ser Glu Leu Arg  Lys Lys Ser
    2780                2785                2790

Leu Asn  Ile Arg Ser His Leu  Glu Ala Ser Ser Asp  Gln Trp Lys
    2795                2800                2805

Arg Leu  His Leu Ser Leu Gln  Glu Leu Leu Val Trp  Leu Gln Leu
    2810                2815                2820

Lys Asp  Asp Glu Leu Ser Arg  Gln Ala Pro Ile Gly  Gly Asp Phe
    2825                2830                2835

Pro Ala  Val Gln Lys Gln Asn  Asp Val His Arg Ala  Phe Lys Arg
    2840                2845                2850

Glu Leu  Lys Thr Lys Glu Pro  Val Ile Met Ser Thr  Leu Glu Thr
    2855                2860                2865

Val Arg  Ile Phe Leu Thr Glu  Gln Pro Leu Glu Gly  Leu Glu Lys
    2870                2875                2880

Leu Tyr  Gln Glu Pro Arg Glu  Leu Pro Pro Glu Glu  Arg Ala Gln
    2885                2890                2895

Asn Val  Thr Arg Leu Leu Arg  Lys Gln Ala Glu Glu  Val Asn Thr
    2900                2905                2910

Glu Trp  Glu Lys Leu Asn Leu  His Ser Ala Asp Trp  Gln Arg Lys
    2915                2920                2925

Ile Asp  Glu Thr Leu Glu Arg  Leu Arg Glu Leu Gln  Glu Ala Thr
    2930                2935                2940

Asp Glu  Leu Asp Leu Lys Leu  Arg Gln Ala Glu Val  Ile Lys Gly
    2945                2950                2955

Ser Trp  Gln Pro Val Gly Asp  Leu Leu Ile Asp Ser  Leu Gln Asp
    2960                2965                2970
```

```
His Leu  Glu Lys Val Lys Ala  Leu Arg Gly Glu Ile  Ala Pro Leu
    2975                2980                2985

Lys Glu  Asn Val Ser His Val  Asn Asp Leu Ala Arg  Gln Leu Thr
    2990                2995                3000

Thr Leu  Gly Ile Gln Leu Ser  Pro Tyr Asn Leu Ser  Thr Leu Glu
    3005                3010                3015

Asp Leu  Asn Thr Arg Trp Lys  Leu Leu Gln Val Ala  Val Glu Asp
    3020                3025                3030

Arg Val  Arg Gln Leu His Glu  Ala His Arg Asp Phe  Gly Pro Ala
    3035                3040                3045

Ser Gln  His Phe Leu Ser Thr  Ser Val Gln Gly Pro  Trp Glu Arg
    3050                3055                3060

Ala Ile  Ser Pro Asn Lys Val  Pro Tyr Tyr Ile Asn  His Glu Thr
    3065                3070                3075

Gln Thr  Thr Cys Trp Asp His  Pro Lys Met Thr Glu  Leu Tyr Gln
    3080                3085                3090

Ser Leu  Ala Asp Leu Asn Asn  Val Arg Phe Ser Ala  Tyr Arg Thr
    3095                3100                3105

Ala Met  Lys Leu Arg Arg Leu  Gln Lys Ala Leu Cys  Leu Asp Leu
    3110                3115                3120

Leu Ser  Leu Ser Ala Ala Cys  Asp Ala Leu Asp Gln  His Asn Leu
    3125                3130                3135

Lys Gln  Asn Asp Gln Pro Met  Asp Ile Leu Gln Ile  Ile Asn Cys
    3140                3145                3150

Leu Thr  Thr Ile Tyr Asp Arg  Leu Glu Gln Glu His  Asn Asn Leu
    3155                3160                3165

Val Asn  Val Pro Leu Cys Val  Asp Met Cys Leu Asn  Trp Leu Leu
    3170                3175                3180
```

```
Asn Val  Tyr Asp Thr Gly Arg  Thr Gly Arg Ile Arg  Val Leu Ser
    3185                3190                3195

Phe Lys  Thr Gly Ile Ile Ser  Leu Cys Lys Ala His  Leu Glu Asp
    3200                3205                3210

Lys Tyr  Arg Tyr Leu Phe Lys  Gln Val Ala Ser Ser  Thr Gly Phe
    3215                3220                3225

Cys Asp  Gln Arg Arg Leu Gly  Leu Leu Leu His Asp  Ser Ile Gln
    3230                3235                3240

Ile Pro  Arg Gln Leu Gly Glu  Val Ala Ser Phe Gly  Gly Ser Asn
    3245                3250                3255

Ile Glu  Pro Ser Val Arg Ser  Cys Phe Gln Phe Ala  Asn Asn Lys
    3260                3265                3270

Pro Glu  Ile Glu Ala Ala Leu  Phe Leu Asp Trp Met  Arg Leu Glu
    3275                3280                3285

Pro Gln  Ser Met Val Trp Leu  Pro Val Leu His Arg  Val Ala Ala
    3290                3295                3300

Ala Glu  Thr Ala Lys His Gln  Ala Lys Cys Asn Ile  Cys Lys Glu
    3305                3310                3315

Cys Pro  Ile Ile Gly Phe Arg  Tyr Arg Ser Leu Lys  His Phe Asn
    3320                3325                3330

Tyr Asp  Ile Cys Gln Ser Cys  Phe Phe Ser Gly Arg  Val Ala Lys
    3335                3340                3345

Gly His  Lys Met His Tyr Pro  Met Val Glu Tyr Cys  Thr Pro Thr
    3350                3355                3360

Thr Ser  Gly Glu Asp Val Arg  Asp Phe Ala Lys Val  Leu Lys Asn
    3365                3370                3375
```

```
Lys Phe  Arg Thr Lys Arg Tyr  Phe Ala Lys His Pro  Arg Met Gly
    3380                3385                3390

Tyr Leu  Pro Val Gln Thr Val  Leu Glu Gly Asp Asn  Met Glu Thr
    3395                3400                3405

Pro Ala  Ser Ser Pro Gln Leu  Ser His Asp Asp Thr  His Ser Arg
    3410                3415                3420

Ile Glu  His Tyr Ala Ser Arg  Leu Ala Glu Met Glu  Asn Ser Asn
    3425                3430                3435

Gly Ser  Tyr Leu Asn Asp Ser  Ile Ser Pro Asn Glu  Ser Ile Asp
    3440                3445                3450

Asp Glu  His Leu Leu Ile Gln  His Tyr Cys Gln Ser  Leu Asn Gln
    3455                3460                3465

Asp Ser  Pro Leu Ser Gln Pro  Arg Ser Pro Ala Gln  Ile Leu Ile
    3470                3475                3480

Ser Leu  Glu Ser Glu Glu Arg  Gly Glu Leu Glu Arg  Ile Leu Ala
    3485                3490                3495

Asp Leu  Glu Glu Glu Asn Arg  Asn Leu Gln Ala Glu  Tyr Asp Arg
    3500                3505                3510

Leu Lys  Gln Gln His Glu His  Lys Gly Leu Ser Pro  Leu Pro Ser
    3515                3520                3525

Pro Pro  Glu Met Met Pro Thr  Ser Pro Gln Ser Pro  Arg Asp Ala
    3530                3535                3540

Glu Leu  Ile Ala Glu Ala Lys  Leu Leu Arg Gln His  Lys Gly Arg
    3545                3550                3555

Leu Glu  Ala Arg Met Gln Ile  Leu Glu Asp His Asn  Lys Gln Leu
    3560                3565                3570

Glu Ser  Gln Leu His Arg Leu  Arg Gln Leu Leu Glu  Gln Pro Gln
    3575                3580                3585
```

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gacaggttaa atatataaac aaacaaacaa aaattgctca aaaaagagga gaaaagctca
12900

agaggaaaag ctaaggactg gtaggaaaaa gctttactct ttcatgccat tttatttctt
12960

tttgattttt aaatcattca ttcaatagat accaccgtgt gacctataat tttgcaaatc
13020

tgttacctct gacatcaagt gtaattagct tttggagagt gggctgacat caagtgtaat
13080

tagcttttgg agagtgggtt ttgtccatta ttaataatta attaattaac atcaaacacg
13140

gcttctcatg ctatttctac ctcactttgg ttttggggtg ttcctgataa ttgtgcacac
13200

ctgagttcac agcttcacca cttgtccatt gcgttatttt ctttttcctt tataattctt
13260

tctttttcct tcataatttt caaaagaaaa cccaaagctc taaggtaaca aattaccaaa
13320

ttacatgaag atttggtttt tgtcttgcat ttttttcctt tatgtgacgc tggacctttt
13380

ctttacccaa ggatttttaa aactcagatt taaaacaagg ggttacttta catcctacta
13440

agaagtttaa gtaagtaagt ttcattctaa aatcagaggt aaatagagtg cataaataat
13500

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13560

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13620

tatttcgtgt tgtgttcttt ataaccacca agtattaaac tgtaaatcat aatgtaactg
13680

aagcataaac atcacatggc atgttttgtc attgttttca ggtactgagt tcttacttga
13740

gtatcataat atattgtgtt ttaacaccaa cactgtaaca tttacgaatt atttttttaa
13800

acttcagttt tactgcattt tcacaacata tcagacttca ccaaatatat gccttactat
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13920

gta
13923

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<211> 3703
<212> PRT
<213> Homo sapiens

<400> 49
Met Leu Trp Trp Glu Glu Val Glu Asp Cys Tyr Glu Arg Glu Asp Val
1   5   10   15

Gln Lys Lys Thr Phe Thr Lys Trp Val Asn Ala Gln Phe Ser Lys Phe
            20   25   30

Gly Lys Gln His Ile Glu Asn Leu Phe Ser Asp Leu Gln Asp Gly Arg
        35   40   45

Arg Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Gln Lys Leu Pro Lys
    50   55   60

Glu Lys Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Lys Ala

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65                  70                  75                  80

Leu Arg Val Leu Gln Asn Asn Asn Val Asp Leu Val Asn Ile Gly Ser
                85                  90                  95

Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Ile Trp
            100                 105                 110

Asn Ile Ile Leu His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met
        115                 120                 125

Ala Gly Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
    130                 135                 140

Arg Gln Ser Thr Arg Asn Tyr Pro Gln Val Asn Val Ile Asn Phe Thr
145                 150                 155                 160

Thr Ser Trp Ser Asp Gly Leu Ala Leu Asn Ala Leu Ile His Ser His
                165                 170                 175

Arg Pro Asp Leu Phe Asp Trp Asn Ser Val Val Cys Gln Gln Ser Ala
            180                 185                 190

Thr Gln Arg Leu Glu His Ala Phe Asn Ile Ala Arg Tyr Gln Leu Gly
        195                 200                 205

Ile Glu Lys Leu Leu Asp Pro Glu Asp Val Asp Thr Thr Tyr Pro Asp
    210                 215                 220

Lys Lys Ser Ile Leu Met Tyr Ile Thr Ser Leu Phe Gln Val Leu Pro
225                 230                 235                 240

Gln Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg
                245                 250                 255

Pro Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met
            260                 265                 270

His Tyr Ser Gln Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg
        275                 280                 285
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Thr Ser Ser Pro Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala
    290                 295                 300

Ala Tyr Val Thr Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln
305                 310                 315                 320

His Leu Glu Ala Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu
                325                 330                 335

Ser Glu Val Asn Leu Asp Arg Tyr Gln Thr Ala Leu Glu Glu Val Leu
            340                 345                 350

Ser Trp Leu Leu Ser Ala Glu Asp Thr Leu Gln Ala Gln Gly Glu Ile
        355                 360                 365

Ser Asn Asp Val Glu Val Val Lys Asp Gln Phe His Thr His Glu Gly
    370                 375                 380

Tyr Met Met Asp Leu Thr Ala His Gln Gly Arg Val Gly Asn Ile Leu
385                 390                 395                 400

Gln Leu Gly Ser Lys Leu Ile Gly Thr Gly Lys Leu Ser Glu Asp Glu
                405                 410                 415

Glu Thr Glu Val Gln Glu Gln Met Asn Leu Leu Asn Ser Arg Trp Glu
            420                 425                 430

Cys Leu Arg Val Ala Ser Met Glu Lys Gln Ser Asn Leu His Arg Val
        435                 440                 445

Leu Met Asp Leu Gln Asn Gln Lys Leu Lys Glu Leu Asn Asp Trp Leu
    450                 455                 460

Thr Lys Thr Glu Glu Arg Thr Arg Lys Met Glu Glu Glu Pro Leu Gly
465                 470                 475                 480

Pro Asp Leu Glu Asp Leu Lys Arg Gln Val Gln Gln His Lys Val Leu
                485                 490                 495

Gln Glu Asp Leu Glu Gln Glu Gln Val Arg Val Asn Ser Leu Thr His
```

```
            500                 505                 510

Met Val Val Val Val Asp Glu Ser Ser Gly Asp His Ala Thr Ala Ala
        515                 520                 525

Leu Glu Glu Gln Leu Lys Val Leu Gly Asp Arg Trp Ala Asn Ile Cys
    530                 535                 540

Arg Trp Thr Glu Asp Arg Trp Val Leu Leu Gln Asp Ile Leu Leu Lys
545                 550                 555                 560

Trp Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ala Trp Leu Ser
                565                 570                 575

Glu Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp
            580                 585                 590

Gln Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala
        595                 600                 605

Asp Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys
    610                 615                 620

Gln Asp Leu Leu Ser Thr Leu Lys Asn Lys Ser Val Thr Gln Lys Thr
625                 630                 635                 640

Glu Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln
                645                 650                 655

Lys Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr
            660                 665                 670

Gln Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val
        675                 680                 685

Thr Thr Arg Glu Gln Ile Leu Val Lys His Ala Gln Glu Glu Leu Pro
    690                 695                 700

Pro Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile
705                 710                 715                 720
```

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Arg Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr
                725                 730                 735

Arg Ser Glu Ala Val Leu Gln Ser Pro Glu Phe Ala Ile Phe Arg Lys
            740                 745                 750

Glu Gly Asn Phe Ser Asp Leu Lys Glu Lys Val Asn Ala Ile Glu Arg
        755                 760                 765

Glu Lys Ala Glu Lys Phe Arg Lys Leu Gln Asp Ala Ser Arg Ser Ala
    770                 775                 780

Gln Ala Leu Val Glu Gln Met Val Asn Glu Gly Val Asn Ala Asp Ser
785                 790                 795                 800

Ile Lys Gln Ala Ser Glu Gln Leu Asn Ser Arg Trp Ile Glu Phe Cys
                805                 810                 815

Gln Leu Leu Ser Glu Arg Leu Asn Trp Leu Glu Tyr Gln Asn Asn Ile
            820                 825                 830

Ile Ala Phe Tyr Asn Gln Leu Gln Gln Leu Glu Gln Met Thr Thr Thr
        835                 840                 845

Ala Glu Asn Trp Leu Lys Ile Gln Pro Thr Thr Pro Ser Glu Pro Thr
    850                 855                 860

Ala Ile Lys Ser Gln Leu Lys Ile Cys Lys Asp Glu Val Asn Arg Leu
865                 870                 875                 880

Ser Asp Leu Gln Pro Gln Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala
                885                 890                 895

Leu Lys Glu Lys Gly Gln Gly Pro Met Phe Leu Asp Ala Asp Phe Val
            900                 905                 910

Ala Phe Thr Asn His Phe Lys Gln Val Phe Ser Asp Val Gln Ala Arg
        915                 920                 925

Glu Lys Glu Leu Gln Thr Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr
```

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    930                 935                 940

Gln Glu Thr Met Ser Ala Ile Arg Thr Trp Val Gln Gln Ser Glu Thr
945                 950                 955                 960

Lys Leu Ser Ile Pro Gln Leu Ser Val Thr Asp Tyr Glu Ile Met Glu
                965                 970                 975

Gln Arg Leu Gly Glu Leu Gln Ala Leu Gln Ser Ser Leu Gln Glu Gln
            980                 985                 990

Gln Ser Gly Leu Tyr Tyr Leu Ser  Thr Thr Val Lys Glu  Met Ser Lys
        995                 1000                1005

Lys Ala  Pro Ser Glu Ile Ser  Arg Lys Tyr Gln Ser  Glu Phe Glu
    1010                1015                1020

Glu Ile  Glu Gly Arg Trp Lys  Lys Leu Ser Ser Gln  Leu Val Glu
    1025                1030                1035

His Cys  Gln Lys Leu Glu Glu  Gln Met Asn Lys Leu  Arg Lys Ile
    1040                1045                1050

Gln Asn  His Ile Gln Thr Leu  Lys Lys Trp Met Ala  Glu Val Asp
    1055                1060                1065

Val Phe  Leu Lys Glu Glu Trp  Pro Ala Leu Gly Asp  Ser Glu Ile
    1070                1075                1080

Leu Lys  Lys Gln Leu Lys Gln  Cys Arg Leu Leu Val  Ser Asp Ile
    1085                1090                1095

Gln Thr  Ile Gln Pro Ser Leu  Asn Ser Val Asn Glu  Gly Gly Gln
    1100                1105                1110

Lys Ile  Lys Asn Glu Ala Glu  Pro Glu Phe Ala Ser  Arg Leu Glu
    1115                1120                1125

Thr Glu  Leu Lys Glu Leu Asn  Thr Gln Trp Asp His  Met Cys Gln
    1130                1135                1140
```

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Gln Val  Tyr Ala Arg Lys Glu  Ala Leu Lys Gly Gly  Leu Glu Lys
    1145                1150                1155

Thr Val  Ser Leu Gln Lys Asp  Leu Ser Glu Met His  Glu Trp Met
    1160                1165                1170

Thr Gln  Ala Glu Glu Glu Tyr  Leu Glu Arg Asp Phe  Glu Tyr Lys
    1175                1180                1185

Thr Pro  Asp Glu Leu Gln Lys  Ala Val Glu Glu Met  Lys Arg Ala
    1190                1195                1200

Lys Glu  Glu Ala Gln Gln Lys  Glu Ala Lys Val Lys  Leu Leu Thr
    1205                1210                1215

Glu Ser  Val Asn Ser Val Ile  Ala Gln Ala Pro Pro  Val Ala Gln
    1220                1225                1230

Glu Ala  Leu Lys Lys Glu Leu  Glu Thr Leu Thr Thr  Asn Tyr Gln
    1235                1240                1245

Trp Leu  Cys Thr Arg Leu Asn  Gly Lys Cys Lys Thr  Leu Glu Glu
    1250                1255                1260

Val Trp  Ala Cys Trp His Glu  Leu Leu Ser Tyr Leu  Glu Lys Ala
    1265                1270                1275

Asn Lys  Trp Leu Asn Glu Val  Glu Phe Lys Leu Lys  Thr Thr Glu
    1280                1285                1290

Asn Ile  Pro Gly Gly Ala Glu  Glu Ile Ser Glu Val  Leu Asp Ser
    1295                1300                1305

Leu Glu  Asn Leu Met Arg His  Ser Glu Asp Asn Pro  Asn Gln Ile
    1310                1315                1320

Arg Ile  Leu Ala Gln Thr Leu  Thr Asp Gly Gly Val  Met Asp Glu
    1325                1330                1335

Leu Ile  Asn Glu Glu Leu Glu  Thr Phe Asn Ser Arg  Trp Arg Glu
```

1340 1345 1350

Leu His Glu Glu Ala Val Arg Arg Gln Lys Leu Leu Glu Gln Ser
1355 1360 1365

Ile Gln Ser Ala Gln Glu Thr Glu Lys Ser Leu His Leu Ile Gln
1370 1375 1380

Glu Ser Leu Thr Phe Ile Asp Lys Gln Leu Ala Ala Tyr Ile Ala
1385 1390 1395

Asp Lys Val Asp Ala Ala Gln Met Pro Gln Glu Ala Gln Lys Ile
1400 1405 1410

Gln Ser Asp Leu Thr Ser His Glu Ile Ser Leu Glu Glu Met Lys
1415 1420 1425

Lys His Asn Gln Gly Lys Glu Ala Ala Gln Arg Val Leu Ser Gln
1430 1435 1440

Ile Asp Val Ala Gln Lys Lys Leu Gln Asp Val Ser Met Lys Phe
1445 1450 1455

Arg Leu Phe Gln Lys Pro Ala Asn Phe Glu Gln Arg Leu Gln Glu
1460 1465 1470

Ser Lys Met Ile Leu Asp Glu Val Lys Met His Leu Pro Ala Leu
1475 1480 1485

Glu Thr Lys Ser Val Glu Gln Glu Val Val Gln Ser Gln Leu Asn
1490 1495 1500

His Cys Val Asn Leu Tyr Lys Ser Leu Ser Glu Val Lys Ser Glu
1505 1510 1515

Val Glu Met Val Ile Lys Thr Gly Arg Gln Ile Val Gln Lys Lys
1520 1525 1530

Gln Thr Glu Asn Pro Lys Glu Leu Asp Glu Arg Val Thr Ala Leu
1535 1540 1545

Lys Leu His Tyr Asn Glu Leu Gly Ala Lys Val Thr Glu Arg Lys
1550 1555 1560

Gln Gln Leu Glu Lys Cys Leu Lys Leu Ser Arg Lys Met Arg Lys
1565 1570 1575

Glu Met Asn Val Leu Thr Glu Trp Leu Ala Ala Thr Asp Met Glu
1580 1585 1590

Leu Thr Lys Arg Ser Ala Val Glu Gly Met Pro Ser Asn Leu Asp
1595 1600 1605

Ser Glu Val Ala Trp Gly Lys Ala Thr Gln Lys Glu Ile Glu Lys
1610 1615 1620

Gln Lys Val His Leu Lys Ser Ile Thr Glu Val Gly Glu Ala Leu
1625 1630 1635

Lys Thr Val Leu Gly Lys Lys Glu Thr Leu Val Glu Asp Lys Leu
1640 1645 1650

Ser Leu Leu Asn Ser Asn Trp Ile Ala Val Thr Ser Arg Ala Glu
1655 1660 1665

Glu Trp Leu Asn Leu Leu Leu Glu Tyr Gln Lys His Met Glu Thr
1670 1675 1680

Phe Asp Gln Asn Val Asp His Ile Thr Lys Trp Ile Ile Gln Ala
1685 1690 1695

Asp Thr Leu Leu Asp Glu Ser Glu Lys Lys Lys Pro Gln Gln Lys
1700 1705 1710

Glu Asp Val Leu Lys Arg Leu Lys Ala Glu Leu Asn Asp Ile Arg
1715 1720 1725

Pro Lys Val Asp Ser Thr Arg Asp Gln Ala Ala Asn Leu Met Ala
1730 1735 1740

Asn Arg Gly Asp His Cys Arg Lys Leu Val Glu Pro Gln Ile Ser

1745 1750 1755

Glu Leu Asn His Arg Phe Ala Ala Ile Ser His Arg Ile Lys Thr
1760 1765 1770

Gly Lys Ala Ser Ile Pro Leu Lys Glu Leu Glu Gln Phe Asn Ser
1775 1780 1785

Asp Ile Gln Lys Leu Leu Glu Pro Leu Glu Ala Glu Ile Gln Gln
1790 1795 1800

Gly Val Asn Leu Lys Glu Glu Asp Phe Asn Lys Asp Met Asn Glu
1805 1810 1815

Asp Asn Glu Gly Thr Val Lys Glu Leu Leu Gln Arg Gly Asp Asn
1820 1825 1830

Leu Gln Gln Arg Ile Thr Asp Glu Arg Lys Arg Glu Glu Ile Lys
1835 1840 1845

Ile Lys Gln Gln Leu Leu Gln Thr Lys His Asn Ala Leu Lys Asp
1850 1855 1860

Leu Arg Ser Gln Arg Arg Lys Lys Ala Leu Glu Ile Ser His Gln
1865 1870 1875

Trp Tyr Gln Tyr Lys Arg Gln Ala Asp Asp Leu Leu Lys Cys Leu
1880 1885 1890

Asp Asp Ile Glu Lys Lys Leu Ala Ser Leu Pro Glu Pro Arg Asp
1895 1900 1905

Glu Arg Lys Ile Lys Glu Ile Asp Arg Glu Leu Gln Lys Lys Lys
1910 1915 1920

Glu Glu Leu Asn Ala Val Arg Arg Gln Ala Glu Gly Leu Ser Glu
1925 1930 1935

Asp Gly Ala Ala Met Ala Val Glu Pro Thr Gln Ile Gln Leu Ser
1940 1945 1950

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Lys Arg  Trp Arg Glu Ile Glu  Ser Lys Phe Ala Gln  Phe Arg Arg
    1955                1960                1965

Leu Asn  Phe Ala Gln Ile His  Thr Val Arg Glu Glu  Thr Met Met
    1970                1975                1980

Val Met  Thr Glu Asp Met Pro  Leu Glu Ile Ser Tyr  Val Pro Ser
    1985                1990                1995

Thr Tyr  Leu Thr Glu Ile Thr  His Val Ser Gln Ala  Leu Leu Glu
    2000                2005                2010

Val Glu  Gln Leu Leu Asn Ala  Pro Asp Leu Cys Ala  Lys Asp Phe
    2015                2020                2025

Glu Asp  Leu Phe Lys Gln Glu  Glu Ser Leu Lys Asn  Ile Lys Asp
    2030                2035                2040

Ser Leu  Gln Gln Ser Ser Gly  Arg Ile Asp Ile Ile  His Ser Lys
    2045                2050                2055

Lys Thr  Ala Ala Leu Gln Ser  Ala Thr Pro Val Glu  Arg Val Lys
    2060                2065                2070

Leu Gln  Glu Ala Leu Ser Gln  Leu Asp Phe Gln Trp  Glu Lys Val
    2075                2080                2085

Asn Lys  Met Tyr Lys Asp Arg  Gln Gly Arg Phe Asp  Arg Ser Val
    2090                2095                2100

Glu Lys  Trp Arg Arg Phe His  Tyr Asp Ile Lys Ile  Phe Asn Gln
    2105                2110                2115

Trp Leu  Thr Glu Ala Glu Gln  Phe Leu Arg Lys Thr  Gln Ile Pro
    2120                2125                2130

Glu Asn  Trp Glu His Ala Lys  Tyr Lys Trp Tyr Leu  Lys Glu Leu
    2135                2140                2145

Gln Asp  Gly Ile Gly Gln Arg  Gln Thr Val Val Arg  Thr Leu Asn
```

2150 2155 2160

Ala Thr Gly Glu Glu Ile Ile Gln Gln Ser Ser Lys Thr Asp Ala
2165 2170 2175

Ser Ile Leu Gln Glu Lys Leu Gly Ser Leu Asn Leu Arg Trp Gln
2180 2185 2190

Glu Val Cys Lys Gln Leu Ser Asp Arg Lys Lys Arg Leu Glu Glu
2195 2200 2205

Gln Lys Asn Ile Leu Ser Glu Phe Gln Arg Asp Leu Asn Glu Phe
2210 2215 2220

Val Leu Trp Leu Glu Glu Ala Asp Asn Ile Ala Ser Ile Pro Leu
2225 2230 2235

Glu Pro Gly Lys Glu Gln Gln Leu Lys Glu Lys Leu Glu Gln Val
2240 2245 2250

Lys Leu Leu Val Glu Glu Leu Pro Leu Arg Gln Gly Ile Leu Lys
2255 2260 2265

Gln Leu Asn Glu Thr Gly Gly Pro Val Leu Val Ser Ala Pro Ile
2270 2275 2280

Ser Pro Glu Glu Gln Asp Lys Leu Glu Asn Lys Leu Lys Gln Thr
2285 2290 2295

Asn Leu Gln Trp Ile Lys Val Ser Arg Ala Leu Pro Glu Lys Gln
2300 2305 2310

Gly Glu Ile Glu Ala Gln Ile Lys Asp Leu Gly Gln Leu Glu Lys
2315 2320 2325

Lys Leu Glu Asp Leu Glu Glu Gln Leu Asn His Leu Leu Leu Trp
2330 2335 2340

Leu Ser Pro Ile Arg Asn Gln Leu Glu Ile Tyr Asn Gln Pro Asn
2345 2350 2355

Gln Glu Gly Pro Phe Asp Val Lys Glu Thr Glu Ile Ala Val Gln
2360 2365 2370

Ala Lys Gln Pro Asp Val Glu Glu Ile Leu Ser Lys Gly Gln His
2375 2380 2385

Leu Tyr Lys Glu Lys Pro Ala Thr Gln Pro Val Lys Arg Lys Leu
2390 2395 2400

Glu Asp Leu Ser Ser Glu Trp Lys Ala Val Asn Arg Leu Leu Gln
2405 2410 2415

Glu Leu Arg Ala Lys Gln Pro Asp Leu Ala Pro Gly Leu Thr Thr
2420 2425 2430

Ile Gly Ala Ser Pro Thr Gln Thr Val Thr Leu Val Thr Gln Pro
2435 2440 2445

Val Val Thr Lys Glu Thr Ala Ile Ser Lys Leu Glu Met Pro Ser
2450 2455 2460

Ser Leu Met Leu Glu Val Pro Ala Leu Ala Asp Phe Asn Arg Ala
2465 2470 2475

Trp Thr Glu Leu Thr Asp Trp Leu Ser Leu Leu Asp Gln Val Ile
2480 2485 2490

Lys Ser Gln Arg Val Met Val Gly Asp Leu Glu Asp Ile Asn Glu
2495 2500 2505

Met Ile Ile Lys Gln Lys Ala Thr Met Gln Asp Leu Glu Gln Arg
2510 2515 2520

Arg Pro Gln Leu Glu Glu Leu Ile Thr Ala Ala Gln Asn Leu Lys
2525 2530 2535

Asn Lys Thr Ser Asn Gln Glu Ala Arg Thr Ile Ile Thr Asp Arg
2540 2545 2550

Ile Glu Arg Ile Gln Asn Gln Trp Asp Glu Val Gln Glu His Leu

2555 2560 2565

Gln Asn Arg Arg Gln Gln Leu Asn Glu Met Leu Lys Asp Ser Thr
2570 2575 2580

Gln Trp Leu Glu Ala Lys Glu Glu Ala Glu Gln Val Leu Gly Gln
2585 2590 2595

Ala Arg Ala Lys Leu Glu Ser Trp Lys Glu Gly Pro Tyr Thr Val
2600 2605 2610

Asp Ala Ile Gln Lys Lys Ile Thr Glu Thr Lys Gln Leu Ala Lys
2615 2620 2625

Asp Leu Arg Gln Trp Gln Thr Asn Val Asp Val Ala Asn Asp Leu
2630 2635 2640

Ala Leu Lys Leu Leu Arg Asp Tyr Ser Ala Asp Asp Thr Arg Lys
2645 2650 2655

Val His Met Ile Thr Glu Asn Ile Asn Ala Ser Trp Arg Ser Ile
2660 2665 2670

His Lys Arg Val Ser Glu Arg Glu Ala Ala Leu Glu Glu Thr His
2675 2680 2685

Arg Leu Leu Gln Gln Phe Pro Leu Asp Leu Glu Lys Phe Leu Ala
2690 2695 2700

Trp Leu Thr Glu Ala Glu Thr Thr Ala Asn Val Leu Gln Asp Ala
2705 2710 2715

Thr Arg Lys Glu Arg Leu Leu Glu Asp Ser Lys Gly Val Lys Glu
2720 2725 2730

Leu Met Lys Gln Trp Gln Asp Leu Gln Gly Glu Ile Glu Ala His
2735 2740 2745

Thr Asp Val Tyr His Asn Leu Asp Glu Asn Ser Gln Lys Ile Leu
2750 2755 2760

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Arg Ser  Leu Glu Gly Ser Asp  Asp Ala Val Leu Leu  Gln Arg Arg
    2765                2770                2775

Leu Asp  Asn Met Asn Phe Lys  Trp Ser Glu Leu Arg  Lys Lys Ser
    2780                2785                2790

Leu Asn  Ile Arg Ser His Leu  Glu Ala Ser Ser Asp  Gln Trp Lys
    2795                2800                2805

Arg Leu  His Leu Ser Leu Gln  Glu Leu Leu Val Trp  Leu Gln Leu
    2810                2815                2820

Lys Asp  Asp Glu Leu Ser Arg  Gln Ala Pro Ile Gly  Gly Asp Phe
    2825                2830                2835

Pro Ala  Val Gln Lys Gln Asn  Asp Val His Arg Ala  Phe Lys Arg
    2840                2845                2850

Glu Leu  Lys Thr Lys Glu Pro  Val Ile Met Ser Thr  Leu Glu Thr
    2855                2860                2865

Val Arg  Ile Phe Leu Thr Glu  Gln Pro Leu Glu Gly  Leu Glu Lys
    2870                2875                2880

Leu Tyr  Gln Glu Pro Arg Glu  Leu Pro Pro Glu Glu  Arg Ala Gln
    2885                2890                2895

Asn Val  Thr Arg Leu Leu Arg  Lys Gln Ala Glu Glu  Val Asn Thr
    2900                2905                2910

Glu Trp  Glu Lys Leu Asn Leu  His Ser Ala Asp Trp  Gln Arg Lys
    2915                2920                2925

Ile Asp  Glu Thr Leu Glu Arg  Leu Arg Glu Leu Gln  Glu Ala Thr
    2930                2935                2940

Asp Glu  Leu Asp Leu Lys Leu  Arg Gln Ala Glu Val  Ile Lys Gly
    2945                2950                2955

Ser Trp  Gln Pro Val Gly Asp  Leu Leu Ile Asp Ser  Leu Gln Asp
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    2960                2965                2970

His Leu  Glu Lys Val Lys Ala  Leu Arg Gly Glu Ile  Ala Pro Leu
    2975                2980                2985

Lys Glu  Asn Val Ser His Val  Asn Asp Leu Ala Arg  Gln Leu Thr
    2990                2995                3000

Thr Leu  Gly Ile Gln Leu Ser  Pro Tyr Asn Leu Ser  Thr Leu Glu
    3005                3010                3015

Asp Leu  Asn Thr Arg Trp Lys  Leu Leu Gln Val Ala  Val Glu Asp
    3020                3025                3030

Arg Val  Arg Gln Leu His Glu  Ala His Arg Asp Phe  Gly Pro Ala
    3035                3040                3045

Ser Gln  His Phe Leu Ser Thr  Ser Val Gln Gly Pro  Trp Glu Arg
    3050                3055                3060

Ala Ile  Ser Pro Asn Lys Val  Pro Tyr Tyr Ile Asn  His Glu Thr
    3065                3070                3075

Gln Thr  Thr Cys Trp Asp His  Pro Lys Met Thr Glu  Leu Tyr Gln
    3080                3085                3090

Ser Leu  Ala Asp Leu Asn Asn  Val Arg Phe Ser Ala  Tyr Arg Thr
    3095                3100                3105

Ala Met  Lys Leu Arg Arg Leu  Gln Lys Ala Leu Cys  Leu Asp Leu
    3110                3115                3120

Leu Ser  Leu Ser Ala Ala Cys  Asp Ala Leu Asp Gln  His Asn Leu
    3125                3130                3135

Lys Gln  Asn Asp Gln Pro Met  Asp Ile Leu Gln Ile  Ile Asn Cys
    3140                3145                3150

Leu Thr  Thr Ile Tyr Asp Arg  Leu Glu Gln Glu His  Asn Asn Leu
    3155                3160                3165
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Val Asn  Val Pro Leu Cys Val  Asp Met Cys Leu Asn  Trp Leu Leu
    3170                3175                3180

Asn Val  Tyr Asp Thr Gly Arg  Thr Gly Arg Ile Arg  Val Leu Ser
    3185                3190                3195

Phe Lys  Thr Gly Ile Ile Ser  Leu Cys Lys Ala His  Leu Glu Asp
    3200                3205                3210

Lys Tyr  Arg Tyr Leu Phe Lys  Gln Val Ala Ser Ser  Thr Gly Phe
    3215                3220                3225

Cys Asp  Gln Arg Arg Leu Gly  Leu Leu Leu His Asp  Ser Ile Gln
    3230                3235                3240

Ile Pro  Arg Gln Leu Gly Glu  Val Ala Ser Phe Gly  Gly Ser Asn
    3245                3250                3255

Ile Glu  Pro Ser Val Arg Ser  Cys Phe Gln Phe Ala  Asn Asn Lys
    3260                3265                3270

Pro Glu  Ile Glu Ala Ala Leu  Phe Leu Asp Trp Met  Arg Leu Glu
    3275                3280                3285

Pro Gln  Ser Met Val Trp Leu  Pro Val Leu His Arg  Val Ala Ala
    3290                3295                3300

Ala Glu  Thr Ala Lys His Gln  Ala Lys Cys Asn Ile  Cys Lys Glu
    3305                3310                3315

Cys Pro  Ile Ile Gly Phe Arg  Tyr Arg Ser Leu Lys  His Phe Asn
    3320                3325                3330

Tyr Asp  Ile Cys Gln Ser Cys  Phe Phe Ser Gly Arg  Val Ala Lys
    3335                3340                3345

Gly His  Lys Met His Tyr Pro  Met Val Glu Tyr Cys  Thr Pro Thr
    3350                3355                3360

Thr Ser  Gly Glu Asp Val Arg  Asp Phe Ala Lys Val  Leu Lys Asn
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3365 3370 3375

Lys Phe Arg Thr Lys Arg Tyr Phe Ala Lys His Pro Arg Met Gly
3380 3385 3390

Tyr Leu Pro Val Gln Thr Val Leu Glu Gly Asp Asn Met Glu Thr
3395 3400 3405

Pro Val Thr Leu Ile Asn Phe Trp Pro Val Asp Ser Ala Pro Ala
3410 3415 3420

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                85                  90                  95

Lys Asn Ile Lys Asp Ser Leu Gln Gln Ser Ser Gly Arg Ile Asp Ile
            100                 105                 110

Ile His Ser Lys Lys Thr Ala Ala Leu Gln Ser Ala Thr Pro Val Glu
        115                 120                 125

Arg Val Lys Leu Gln Glu Ala Leu Ser Gln Leu Asp Phe Gln Trp Glu
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Lys Val Asn Lys Met Tyr Lys Asp Arg Gln Gly Arg Phe Asp Arg Ser
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Val Glu Lys Trp Arg Arg Phe His Tyr Asp Ile Lys Ile Phe Asn Gln
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Trp Leu Thr Glu Ala Glu Gln Phe Leu Arg Lys Thr Gln Ile Pro Glu
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Asn Trp Glu His Ala Lys Tyr Lys Trp Tyr Leu Lys Glu Leu Gln Asp
        195                 200                 205

Gly Ile Gly Gln Arg Gln Thr Val Val Arg Thr Leu Asn Ala Thr Gly
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Glu Glu Ile Ile Gln Gln Ser Ser Lys Thr Asp Ala Ser Ile Leu Gln
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Glu Lys Leu Gly Ser Leu Asn Leu Arg Trp Gln Glu Val Cys Lys Gln
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Glu Phe Gln Arg Asp Leu Asn Glu Phe Val Leu Trp Leu Glu Glu Ala
        275                 280                 285

Asp Asn Ile Ala Ser Ile Pro Leu Glu Pro Gly Lys Glu Gln Gln Leu
    290                 295                 300

Lys Glu Lys Leu Glu Gln Val Lys Leu Leu Val Glu Glu Leu Pro Leu
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Arg Gln Gly Ile Leu Lys Gln Leu Asn Glu Thr Gly Gly Pro Val Leu
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Val Ser Ala Pro Ile Ser Pro Glu Glu Gln Asp Lys Leu Glu Asn Lys
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Leu Lys Gln Thr Asn Leu Gln Trp Ile Lys Val Ser Arg Ala Leu Pro
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Glu Lys Gln Gly Glu Ile Glu Ala Gln Ile Lys Asp Leu Gly Gln Leu
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Glu Lys Lys Leu Glu Asp Leu Glu Glu Gln Leu Asn His Leu Leu Leu
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Trp Leu Ser Pro Ile Arg Asn Gln Leu Glu Ile Tyr Asn Gln Pro Asn
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Gln Glu Gly Pro Phe Asp Val Lys Glu Thr Glu Ile Ala Val Gln Ala
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Lys Gln Pro Asp Val Glu Glu Ile Leu Ser Lys Gly Gln His Leu Tyr
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Lys Glu Lys Pro Ala Thr Gln Pro Val Lys Arg Lys Leu Glu Asp Leu
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Ser Ser Glu Trp Lys Ala Val Asn Arg Leu Leu Gln Glu Leu Arg Ala
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Thr Gln Thr Val Thr Leu Val Thr Gln Pro Val Val Thr Lys Glu Thr
            500                 505                 510

Ala Ile Ser Lys Leu Glu Met Pro Ser Ser Leu Met Leu Glu Val Pro
        515                 520                 525

Ala Leu Ala Asp Phe Asn Arg Ala Trp Thr Glu Leu Thr Asp Trp Leu
    530                 535                 540

Ser Leu Leu Asp Gln Val Ile Lys Ser Gln Arg Val Met Val Gly Asp
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Leu Glu Asp Ile Asn Glu Met Ile Ile Lys Gln Lys Ala Thr Met Gln
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Asp Leu Glu Gln Arg Arg Pro Gln Leu Glu Glu Leu Ile Thr Ala Ala
            580                 585                 590

Gln Asn Leu Lys Asn Lys Thr Ser Asn Gln Glu Ala Arg Thr Ile Ile
        595                 600                 605

Thr Asp Arg Ile Glu Arg Ile Gln Asn Gln Trp Asp Glu Val Gln Glu
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His Leu Gln Asn Arg Arg Gln Gln Leu Asn Glu Met Leu Lys Asp Ser
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Thr Gln Trp Leu Glu Ala Lys Glu Glu Ala Glu Gln Val Leu Gly Gln
                645                 650                 655

Ala Arg Ala Lys Leu Glu Ser Trp Lys Glu Gly Pro Tyr Thr Val Asp
            660                 665                 670

Ala Ile Gln Lys Lys Ile Thr Glu Thr Lys Gln Leu Ala Lys Asp Leu
        675                 680                 685
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    690                 695                 700

Leu Leu Arg Asp Tyr Ser Ala Asp Asp Thr Arg Lys Val His Met Ile
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Thr Glu Asn Ile Asn Ala Ser Trp Arg Ser Ile His Lys Arg Val Ser
                725                 730                 735

Glu Arg Glu Ala Ala Leu Glu Glu Thr His Arg Leu Leu Gln Gln Phe
            740                 745                 750

Pro Leu Asp Leu Glu Lys Phe Leu Ala Trp Leu Thr Glu Ala Glu Thr
        755                 760                 765

Thr Ala Asn Val Leu Gln Asp Ala Thr Arg Lys Glu Arg Leu Leu Glu
    770                 775                 780

Asp Ser Lys Gly Val Lys Glu Leu Met Lys Gln Trp Gln Asp Leu Gln
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Gly Glu Ile Glu Ala His Thr Asp Val Tyr His Asn Leu Asp Glu Asn
                805                 810                 815

Ser Gln Lys Ile Leu Arg Ser Leu Glu Gly Ser Asp Asp Ala Val Leu
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Leu Gln Arg Arg Leu Asp Asn Met Asn Phe Lys Trp Ser Glu Leu Arg
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Lys Lys Ser Leu Asn Ile Arg Ser His Leu Glu Ala Ser Ser Asp Gln
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Trp Lys Arg Leu His Leu Ser Leu Gln Glu Leu Leu Val Trp Leu Gln
865                 870                 875                 880

Leu Lys Asp Asp Glu Leu Ser Arg Gln Ala Pro Ile Gly Gly Asp Phe
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Pro Ala Val Gln Lys Gln Asn Asp Val His Arg Ala Phe Lys Arg Glu
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Leu Leu Arg Lys Gln Ala Glu Glu Val Asn Thr Glu Trp Glu Lys Leu
                965                 970                 975

Asn Leu His Ser Ala Asp Trp Gln Arg Lys Ile Asp Glu Thr Leu Glu
            980                 985                 990

Arg Leu Arg Glu Leu Gln Glu Ala  Thr Asp Glu Leu Asp  Leu Lys Leu
        995                 1000                1005

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Leu Leu  Ile Asp Ser Leu Gln  Asp His Leu Glu Lys  Val Lys Ala
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Leu Arg  Gly Glu Ile Ala Pro  Leu Lys Glu Asn Val  Ser His Val
    1040                1045                1050

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Arg Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Gln Lys Leu Pro Lys
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Glu Lys Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Lys Ala
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Leu Arg Val Leu Gln Asn Asn Asn Val Asp Leu Val Asn Ile Gly Ser
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Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Ile Trp
100 105 110

Asn Ile Ile Leu His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met
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Ala Gly Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
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Arg Gln Ser Thr Arg Asn Tyr Pro Gln Val Asn Val Ile Asn Phe Thr
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Thr Ser Trp Ser Asp Gly Leu Ala Leu Asn Ala Leu Ile His Ser His
                165                 170                 175

Arg Pro Asp Leu Phe Asp Trp Asn Ser Val Val Cys Gln Gln Ser Ala
            180                 185                 190

Thr Gln Arg Leu Glu His Ala Phe Asn Ile Ala Arg Tyr Gln Leu Gly
        195                 200                 205

Ile Glu Lys Leu Leu Asp Pro Glu Asp Val Asp Thr Thr Tyr Pro Asp
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Lys Lys Ser Ile Leu Met Tyr Ile Thr Ser Leu Phe Gln Val Leu Pro
225                 230                 235                 240

Gln Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg
                245                 250                 255

Pro Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met
            260                 265                 270

His Tyr Ser Gln Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg
        275                 280                 285

Thr Ser Ser Pro Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala
    290                 295                 300

Ala Tyr Val Thr Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln
305                 310                 315                 320

His Leu Glu Ala Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu
                325                 330                 335

Ser Glu Val Asn Leu Asp Arg Tyr Gln Thr Ala Leu Glu Glu Val Leu
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```

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Ser Trp Leu Leu Ser Ala Glu Asp Thr Leu Gln Ala Gln Gly Glu Ile
        355                 360                 365

Ser Asn Asp Val Glu Val Val Lys Asp Gln Phe His Thr His Glu Gly
    370                 375                 380

Tyr Met Met Asp Leu Thr Ala His Gln Gly Arg Val Gly Asn Ile Leu
385                 390                 395                 400

Gln Leu Gly Ser Lys Leu Ile Gly Thr Gly Lys Leu Ser Glu Asp Glu
                405                 410                 415

Glu Thr Glu Val Gln Glu Gln Met Asn Leu Leu Asn Ser Arg Trp Glu
            420                 425                 430

Cys Leu Arg Val Ala Ser Met Glu Lys Gln Ser Asn Leu His Arg Val
        435                 440                 445

Leu Met Asp Leu Gln Asn Gln Lys Leu Lys Glu Leu Asn Asp Trp Leu
    450                 455                 460

Thr Lys Thr Glu Glu Arg Thr Arg Lys Met Glu Glu Glu Pro Leu Gly
465                 470                 475                 480

Pro Asp Leu Glu Asp Leu Lys Arg Gln Val Gln Gln His Lys Val Leu
                485                 490                 495

Gln Glu Asp Leu Glu Gln Glu Gln Val Arg Val Asn Ser Leu Thr His
            500                 505                 510

Met Val Val Val Val Asp Glu Ser Ser Gly Asp His Ala Thr Ala Ala
        515                 520                 525

Leu Glu Glu Gln Leu Lys Val Leu Gly Asp Arg Trp Ala Asn Ile Cys
    530                 535                 540

Arg Trp Thr Glu Asp Arg Trp Val Leu Leu Gln Asp Ile Leu Leu Lys
545                 550                 555                 560
```

```
Trp Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ala Trp Leu Ser
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Glu Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp
            580                 585                 590

Gln Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala
        595                 600                 605

Asp Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys
    610                 615                 620

Gln Asp Leu Leu Ser Thr Leu Lys Asn Lys Ser Val Thr Gln Lys Thr
625                 630                 635                 640

Glu Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln
                645                 650                 655

Lys Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr
            660                 665                 670

Gln Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val
        675                 680                 685

Thr Thr Arg Glu Gln Ile Leu Val Lys His Ala Gln Glu Glu Leu Pro
    690                 695                 700

Pro Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile
705                 710                 715                 720

Arg Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr
                725                 730                 735

Arg Ser Glu Ala Val Leu Gln Ser Pro Glu Phe Ala Ile Phe Arg Lys
            740                 745                 750

Glu Gly Asn Phe Ser Asp Leu Lys Glu Lys Val Asn Ala Ile Glu Arg
        755                 760                 765

Glu Lys Ala Glu Lys Phe Arg Lys Leu Gln Asp Ala Ser Arg Ser Ala
    770                 775                 780
```

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Gln Ala Leu Val Glu Gln Met Val Asn Glu Gly Val Asn Ala Asp Ser
785                 790                 795                 800

Ile Lys Gln Ala Ser Glu Gln Leu Asn Ser Arg Trp Ile Glu Phe Cys
                805                 810                 815

Gln Leu Leu Ser Glu Arg Leu Asn Trp Leu Glu Tyr Gln Asn Asn Ile
            820                 825                 830

Ile Ala Phe Tyr Asn Gln Leu Gln Gln Leu Glu Gln Met Thr Thr Thr
        835                 840                 845

Ala Glu Asn Trp Leu Lys Ile Gln Pro Thr Thr Pro Ser Glu Pro Thr
    850                 855                 860

Ala Ile Lys Ser Gln Leu Lys Ile Cys Lys Asp Glu Val Asn Arg Leu
865                 870                 875                 880

Ser Asp Leu Gln Pro Gln Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala
                885                 890                 895

Leu Lys Glu Lys Gly Gln Gly Pro Met Phe Leu Asp Ala Asp Phe Val
            900                 905                 910

Ala Phe Thr Asn His Phe Lys Gln Val Phe Ser Asp Val Gln Ala Arg
        915                 920                 925

Glu Lys Glu Leu Gln Thr Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr
    930                 935                 940

Gln Glu Thr Met Ser Ala Ile Arg Thr Trp Val Gln Gln Ser Glu Thr
945                 950                 955                 960

Lys Leu Ser Ile Pro Gln Leu Ser Val Thr Asp Tyr Glu Ile Met Glu
                965                 970                 975

Gln Arg Leu Gly Glu Leu Gln Ala Leu Gln Ser Ser Leu Gln Glu Gln
            980                 985                 990
```

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Gln Ser Gly Leu Tyr Tyr Leu Ser  Thr Thr Val Lys Glu  Met Ser Lys
       995                1000                1005

Lys Ala  Pro Ser Glu Ile Ser  Arg Lys Tyr Gln Ser  Glu Phe Glu
    1010                1015                1020

Glu Ile  Glu Gly Arg Trp Lys  Lys Leu Ser Ser Gln  Leu Val Glu
    1025                1030                1035

His Cys  Gln Lys Leu Glu Glu  Gln Met Asn Lys Leu  Arg Lys Ile
    1040                1045                1050

Gln Asn  His Ile Gln Thr Leu  Lys Lys Trp Met Ala  Glu Val Asp
    1055                1060                1065

Val Phe  Leu Lys Glu Glu Trp  Pro Ala Leu Gly Asp  Ser Glu Ile
    1070                1075                1080

Leu Lys  Lys Gln Leu Lys Gln  Cys Arg Leu Leu Val  Ser Asp Ile
    1085                1090                1095

Gln Thr  Ile Gln Pro Ser Leu  Asn Ser Val Asn Glu  Gly Gly Gln
    1100                1105                1110

Lys Ile  Lys Asn Glu Ala Glu  Pro Glu Phe Ala Ser  Arg Leu Glu
    1115                1120                1125

Thr Glu  Leu Lys Glu Leu Asn  Thr Gln Trp Asp His  Met Cys Gln
    1130                1135                1140

Gln Val  Tyr Ala Arg Lys Glu  Ala Leu Lys Gly Gly  Leu Glu Lys
    1145                1150                1155

Thr Val  Ser Leu Gln Lys Asp  Leu Ser Glu Met His  Glu Trp Met
    1160                1165                1170

Thr Gln  Ala Glu Glu Glu Tyr  Leu Glu Arg Asp Phe  Glu Tyr Lys
    1175                1180                1185

Thr Pro  Asp Glu Leu Gln Lys  Ala Val Glu Glu Met  Lys Arg Ala
    1190                1195                1200
```

```
Lys Glu  Glu Ala Gln Gln Lys  Glu Ala Lys Val Lys  Leu Leu Thr
    1205                 1210                 1215

Glu Ser  Val Asn Ser Val Ile  Ala Gln Ala Pro Pro  Val Ala Gln
    1220                 1225                 1230

Glu Ala  Leu Lys Lys Glu Leu  Glu Thr Leu Thr Thr  Asn Tyr Gln
    1235                 1240                 1245

Trp Leu  Cys Thr Arg Leu Asn  Gly Lys Cys Lys Thr  Leu Glu Glu
    1250                 1255                 1260

Val Trp  Ala Cys Trp His Glu  Leu Leu Ser Tyr Leu  Glu Lys Ala
    1265                 1270                 1275

Asn Lys  Trp Leu Asn Glu Val  Glu Phe Lys Leu Lys  Thr Thr Glu
    1280                 1285                 1290

Asn Ile  Pro Gly Gly Ala Glu  Glu Ile Ser Glu Val  Leu Asp Ser
    1295                 1300                 1305

Leu Glu  Asn Leu Met Arg His  Ser Glu Asp Asn Pro  Asn Gln Ile
    1310                 1315                 1320

Arg Ile  Leu Ala Gln Thr Leu  Thr Asp Gly Gly Val  Met Asp Glu
    1325                 1330                 1335

Leu Ile  Asn Glu Glu Leu Glu  Thr Phe Asn Ser Arg  Trp Arg Glu
    1340                 1345                 1350

Leu His  Glu Glu Ala Val Arg  Arg Gln Lys Leu Leu  Glu Gln Ser
    1355                 1360                 1365

Ile Gln  Ser Ala Gln Glu Thr  Glu Lys Ser Leu His  Leu Ile Gln
    1370                 1375                 1380

Glu Ser  Leu Thr Phe Ile Asp  Lys Gln Leu Ala Ala  Tyr Ile Ala
    1385                 1390                 1395
```

```
Asp Lys  Val Asp Ala Ala Gln  Met Pro Gln Glu Ala  Gln Lys Ile
    1400                 1405                 1410

Gln Ser  Asp Leu Thr Ser His  Glu Ile Ser Leu Glu  Glu Met Lys
    1415                 1420                 1425

Lys His  Asn Gln Gly Lys Glu  Ala Ala Gln Arg Val  Leu Ser Gln
    1430                 1435                 1440

Ile Asp  Val Ala Gln Lys Lys  Leu Gln Asp Val Ser  Met Lys Phe
    1445                 1450                 1455

Arg Leu  Phe Gln Lys Pro Ala  Asn Phe Glu Gln Arg  Leu Gln Glu
    1460                 1465                 1470

Ser Lys  Met Ile Leu Asp Glu  Val Lys Met His Leu  Pro Ala Leu
    1475                 1480                 1485

Glu Thr  Lys Ser Val Glu Gln  Glu Val Val Gln Ser  Gln Leu Asn
    1490                 1495                 1500

His Cys  Val Asn Leu Tyr Lys  Ser Leu Ser Glu Val  Lys Ser Glu
    1505                 1510                 1515

Val Glu  Met Val Ile Lys Thr  Gly Arg Gln Ile Val  Gln Lys Lys
    1520                 1525                 1530

Gln Thr  Glu Asn Pro Lys Glu  Leu Asp Glu Arg Val  Thr Ala Leu
    1535                 1540                 1545

Lys Leu  His Tyr Asn Glu Leu  Gly Ala Lys Val Thr  Glu Arg Lys
    1550                 1555                 1560

Gln Gln  Leu Glu Lys Cys Leu  Lys Leu Ser Arg Lys  Met Arg Lys
    1565                 1570                 1575

Glu Met  Asn Val Leu Thr Glu  Trp Leu Ala Ala Thr  Asp Met Glu
    1580                 1585                 1590

Leu Thr  Lys Arg Ser Ala Val  Glu Gly Met Pro Ser  Asn Leu Asp
    1595                 1600                 1605
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Ser Glu Val Ala Trp Gly Lys Ala Thr Gln Lys Glu Ile Glu Lys
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Gln Lys Val His Leu Lys Ser Ile Thr Glu Val Gly Glu Ala Leu
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Lys Thr Val Leu Gly Lys Lys Glu Thr Leu Val Glu Asp Lys Leu
1640 1645 1650

Ser Leu Leu Asn Ser Asn Trp Ile Ala Val Thr Ser Arg Ala Glu
1655 1660 1665

Glu Trp Leu Asn Leu Leu Leu Glu Tyr Gln Lys His Met Glu Thr
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Phe Asp Gln Asn Val Asp His Ile Thr Lys Trp Ile Ile Gln Ala
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Asp Thr Leu Leu Asp Glu Ser Glu Lys Lys Lys Pro Gln Gln Lys
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Glu Asp Val Leu Lys Arg Leu Lys Ala Glu Leu Asn Asp Ile Arg
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Pro Lys Val Asp Ser Thr Arg Asp Gln Ala Ala Asn Leu Met Ala
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Asn Arg Gly Asp His Cys Arg Lys Leu Val Glu Pro Gln Ile Ser
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Glu Leu Asn His Arg Phe Ala Ala Ile Ser His Arg Ile Lys Thr
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Gly Lys Ala Ser Ile Pro Leu Lys Glu Leu Glu Gln Phe Asn Ser
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Asp Ile Gln Lys Leu Leu Glu Pro Leu Glu Ala Glu Ile Gln Gln
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```
Gly Val  Asn Leu Lys Glu Glu  Asp Phe Asn Lys Asp  Met Asn Glu
    1805                1810                1815

Asp Asn  Glu Gly Thr Val Lys  Glu Leu Leu Gln Arg  Gly Asp Asn
    1820                1825                1830

Leu Gln  Gln Arg Ile Thr Asp  Glu Arg Lys Arg Glu  Glu Ile Lys
    1835                1840                1845

Ile Lys  Gln Gln Leu Leu Gln  Thr Lys His Asn Ala  Leu Lys Asp
    1850                1855                1860

Leu Arg  Ser Gln Arg Arg Lys  Lys Ala Leu Glu Ile  Ser His Gln
    1865                1870                1875

Trp Tyr  Gln Tyr Lys Arg Gln  Ala Asp Asp Leu Leu  Lys Cys Leu
    1880                1885                1890

Asp Asp  Ile Glu Lys Lys Leu  Ala Ser Leu Pro Glu  Pro Arg Asp
    1895                1900                1905

Glu Arg  Lys Ile Lys Glu Ile  Asp Arg Glu Leu Gln  Lys Lys Lys
    1910                1915                1920

Glu Glu  Leu Asn Ala Val Arg  Arg Gln Ala Glu Gly  Leu Ser Glu
    1925                1930                1935

Asp Gly  Ala Ala Met Ala Val  Glu Pro Thr Gln Ile  Gln Leu Ser
    1940                1945                1950

Lys Arg  Trp Arg Glu Ile Glu  Ser Lys Phe Ala Gln  Phe Arg Arg
    1955                1960                1965

Leu Asn  Phe Ala Gln Ile His  Thr Val Arg Glu Glu  Thr Met Met
    1970                1975                1980

Val Met  Thr Glu Asp Met Pro  Leu Glu Ile Ser Tyr  Val Pro Ser
    1985                1990                1995

Thr Tyr  Leu Thr Glu Ile Thr  His Val Ser Gln Ala  Leu Leu Glu
    2000                2005                2010
```

```
Val Glu  Gln Leu Leu Asn Ala  Pro Asp Leu Cys Ala  Lys Asp Phe
    2015                2020                2025

Glu Asp  Leu Phe Lys Gln Glu  Glu Ser Leu Lys Asn  Ile Lys Asp
    2030                2035                2040

Ser Leu  Gln Gln Ser Ser Gly  Arg Ile Asp Ile Ile  His Ser Lys
    2045                2050                2055

Lys Thr  Ala Ala Leu Gln Ser  Ala Thr Pro Val Glu  Arg Val Lys
    2060                2065                2070

Leu Gln  Glu Ala Leu Ser Gln  Leu Asp Phe Gln Trp  Glu Lys Val
    2075                2080                2085

Asn Lys  Met Tyr Lys Asp Arg  Gln Gly Arg Phe Asp  Arg Ser Val
    2090                2095                2100

Glu Lys  Trp Arg Arg Phe His  Tyr Asp Ile Lys Ile  Phe Asn Gln
    2105                2110                2115

Trp Leu  Thr Glu Ala Glu Gln  Phe Leu Arg Lys Thr  Gln Ile Pro
    2120                2125                2130

Glu Asn  Trp Glu His Ala Lys  Tyr Lys Trp Tyr Leu  Lys Glu Leu
    2135                2140                2145

Gln Asp  Gly Ile Gly Gln Arg  Gln Thr Val Val Arg  Thr Leu Asn
    2150                2155                2160

Ala Thr  Gly Glu Glu Ile Ile  Gln Gln Ser Ser Lys  Thr Asp Ala
    2165                2170                2175

Ser Ile  Leu Gln Glu Lys Leu  Gly Ser Leu Asn Leu  Arg Trp Gln
    2180                2185                2190

Glu Val  Cys Lys Gln Leu Ser  Asp Arg Lys Lys Arg  Leu Glu Glu
    2195                2200                2205
```

```
Gln Lys  Asn Ile Leu Ser Glu  Phe Gln Arg Asp Leu  Asn Glu Phe
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Val Leu  Trp Leu Glu Glu Ala  Asp Asn Ile Ala Ser  Ile Pro Leu
    2225                 2230                 2235

Glu Pro  Gly Lys Glu Gln Gln  Leu Lys Glu Lys Leu  Glu Gln Val
    2240                 2245                 2250

Lys Leu  Leu Val Glu Glu Leu  Pro Leu Arg Gln Gly  Ile Leu Lys
    2255                 2260                 2265

Gln Leu  Asn Glu Thr Gly Gly  Pro Val Leu Val Ser  Ala Pro Ile
    2270                 2275                 2280

Ser Pro  Glu Glu Gln Asp Lys  Leu Glu Asn Lys Leu  Lys Gln Thr
    2285                 2290                 2295

Asn Leu  Gln Trp Ile Lys Val  Ser Arg Ala Leu Pro  Glu Lys Gln
    2300                 2305                 2310

Gly Glu  Ile Glu Ala Gln Ile  Lys Asp Leu Gly Gln  Leu Glu Lys
    2315                 2320                 2325

Lys Leu  Glu Asp Leu Glu Glu  Gln Leu Asn His Leu  Leu Leu Trp
    2330                 2335                 2340

Leu Ser  Pro Ile Arg Asn Gln  Leu Glu Ile Tyr Asn  Gln Pro Asn
    2345                 2350                 2355

Gln Glu  Gly Pro Phe Asp Val  Lys Glu Thr Glu Ile  Ala Val Gln
    2360                 2365                 2370

Ala Lys  Gln Pro Asp Val Glu  Glu Ile Leu Ser Lys  Gly Gln His
    2375                 2380                 2385

Leu Tyr  Lys Glu Lys Pro Ala  Thr Gln Pro Val Lys  Arg Lys Leu
    2390                 2395                 2400

Glu Asp  Leu Ser Ser Glu Trp  Lys Ala Val Asn Arg  Leu Leu Gln
    2405                 2410                 2415
```

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Glu Leu  Arg Ala Lys Gln Pro  Asp Leu Ala Pro Gly  Leu Thr Thr
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Ile Gly  Ala Ser Pro Thr Gln  Thr Val Thr Leu Val  Thr Gln Pro
    2435                2440                2445

Val Val  Thr Lys Glu Thr Ala  Ile Ser Lys Leu Glu  Met Pro Ser
    2450                2455                2460

Ser Leu  Met Leu Glu Val Pro  Ala Leu Ala Asp Phe  Asn Arg Ala
    2465                2470                2475

Trp Thr  Glu Leu Thr Asp Trp  Leu Ser Leu Leu Asp  Gln Val Ile
    2480                2485                2490

Lys Ser  Gln Arg Val Met Val  Gly Asp Leu Glu Asp  Ile Asn Glu
    2495                2500                2505

Met Ile  Ile Lys Gln Lys Ala  Thr Met Gln Asp Leu  Glu Gln Arg
    2510                2515                2520

Arg Pro  Gln Leu Glu Glu Leu  Ile Thr Ala Ala Gln  Asn Leu Lys
    2525                2530                2535

Asn Lys  Thr Ser Asn Gln Glu  Ala Arg Thr Ile Ile  Thr Asp Arg
    2540                2545                2550

Ile Glu  Arg Ile Gln Asn Gln  Trp Asp Glu Val Gln  Glu His Leu
    2555                2560                2565

Gln Asn  Arg Arg Gln Gln Leu  Asn Glu Met Leu Lys  Asp Ser Thr
    2570                2575                2580

Gln Trp  Leu Glu Ala Lys Glu  Glu Ala Glu Gln Val  Leu Gly Gln
    2585                2590                2595

Ala Arg  Ala Lys Leu Glu Ser  Trp Lys Glu Gly Pro  Tyr Thr Val
    2600                2605                2610
```

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Asp Ala  Ile Gln Lys Lys Ile  Thr Glu Thr Lys Gln  Leu Ala Lys
    2615                 2620                 2625

Asp Leu  Arg Gln Trp Gln Thr  Asn Val Asp Val Ala  Asn Asp Leu
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        35 40 45

Arg Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Gln Lys Leu Pro Lys
    50 55 60

Glu Lys Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Lys Ala

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65                  70                  75                  80

Leu Arg Val Leu Gln Asn Asn Asn Val Asp Leu Val Asn Ile Gly Ser
                85                  90                  95

Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Ile Trp
            100                 105                 110

Asn Ile Ile Leu His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met
        115                 120                 125

Ala Gly Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
    130                 135                 140

Arg Gln Ser Thr Arg Asn Tyr Pro Gln Val Asn Val Ile Asn Phe Thr
145                 150                 155                 160

Thr Ser Trp Ser Asp Gly Leu Ala Leu Asn Ala Leu Ile His Ser His
                165                 170                 175

Arg Pro Asp Leu Phe Asp Trp Asn Ser Val Val Cys Gln Gln Ser Ala
            180                 185                 190

Thr Gln Arg Leu Glu His Ala Phe Asn Ile Ala Arg Tyr Gln Leu Gly
        195                 200                 205

Ile Glu Lys Leu Leu Asp Pro Glu Asp Val Asp Thr Thr Tyr Pro Asp
    210                 215                 220

Lys Lys Ser Ile Leu Met Tyr Ile Thr Ser Leu Phe Gln Val Leu Pro
225                 230                 235                 240

Gln Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg
                245                 250                 255

Pro Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met
            260                 265                 270

His Tyr Ser Gln Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg
        275                 280                 285
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Thr Ser Ser Pro Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala
    290                 295                 300

Ala Tyr Val Thr Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln
305                 310                 315                 320

His Leu Glu Ala Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu
                325                 330                 335

Ser Glu Val Asn Leu Asp Arg Tyr Gln Thr Ala Leu Glu Glu Val Leu
            340                 345                 350

Ser Trp Leu Leu Ser Ala Glu Asp Thr Leu Gln Ala Gln Gly Glu Ile
        355                 360                 365

Ser Asn Asp Val Glu Val Val Lys Asp Gln Phe His Thr His Glu Gly
    370                 375                 380

Tyr Met Met Asp Leu Thr Ala His Gln Gly Arg Val Gly Asn Ile Leu
385                 390                 395                 400

Gln Leu Gly Ser Lys Leu Ile Gly Thr Gly Lys Leu Ser Glu Asp Glu
                405                 410                 415

Glu Thr Glu Val Gln Glu Gln Met Asn Leu Leu Asn Ser Arg Trp Glu
            420                 425                 430

Cys Leu Arg Val Ala Ser Met Glu Lys Gln Ser Asn Leu His Arg Val
        435                 440                 445

Leu Met Asp Leu Gln Asn Gln Lys Leu Lys Glu Leu Asn Asp Trp Leu
    450                 455                 460

Thr Lys Thr Glu Glu Arg Thr Arg Lys Met Glu Glu Glu Pro Leu Gly
465                 470                 475                 480

Pro Asp Leu Glu Asp Leu Lys Arg Gln Val Gln Gln His Lys Val Leu
                485                 490                 495

Gln Glu Asp Leu Glu Gln Glu Gln Val Arg Val Asn Ser Leu Thr His
```

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            500                 505                 510

Met Val Val Val Val Asp Glu Ser Ser Gly Asp His Ala Thr Ala Ala
        515                 520                 525

Leu Glu Glu Gln Leu Lys Val Leu Gly Asp Arg Trp Ala Asn Ile Cys
    530                 535                 540

Arg Trp Thr Glu Asp Arg Trp Val Leu Leu Gln Asp Ile Leu Leu Lys
545                 550                 555                 560

Trp Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ala Trp Leu Ser
                565                 570                 575

Glu Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp
            580                 585                 590

Gln Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala
        595                 600                 605

Asp Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys
    610                 615                 620

Gln Asp Leu Leu Ser Thr Leu Lys Asn Lys Ser Val Thr Gln Lys Thr
625                 630                 635                 640

Glu Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln
                645                 650                 655

Lys Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr
            660                 665                 670

Gln Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val
        675                 680                 685

Thr Thr Arg Glu Gln Ile Leu Val Lys His Ala Gln Glu Glu Leu Pro
    690                 695                 700

Pro Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile
705                 710                 715                 720
```

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Arg Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr
                725                 730                 735

Arg Ser Glu Ala Val Leu Gln Ser Pro Glu Phe Ala Ile Phe Arg Lys
            740                 745                 750

Glu Gly Asn Phe Ser Asp Leu Lys Glu Lys Val Asn Ala Ile Glu Arg
        755                 760                 765

Glu Lys Ala Glu Lys Phe Arg Lys Leu Gln Asp Ala Ser Arg Ser Ala
    770                 775                 780

Gln Ala Leu Val Glu Gln Met Val Asn Glu Gly Val Asn Ala Asp Ser
785                 790                 795                 800

Ile Lys Gln Ala Ser Glu Gln Leu Asn Ser Arg Trp Ile Glu Phe Cys
                805                 810                 815

Gln Leu Leu Ser Glu Arg Leu Asn Trp Leu Glu Tyr Gln Asn Asn Ile
            820                 825                 830

Ile Ala Phe Tyr Asn Gln Leu Gln Gln Leu Glu Gln Met Thr Thr Thr
        835                 840                 845

Ala Glu Asn Trp Leu Lys Ile Gln Pro Thr Thr Pro Ser Glu Pro Thr
    850                 855                 860

Ala Ile Lys Ser Gln Leu Lys Ile Cys Lys Asp Glu Val Asn Arg Leu
865                 870                 875                 880

Ser Asp Leu Gln Pro Gln Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala
                885                 890                 895

Leu Lys Glu Lys Gly Gln Gly Pro Met Phe Leu Asp Ala Asp Phe Val
            900                 905                 910

Ala Phe Thr Asn His Phe Lys Gln Val Phe Ser Asp Val Gln Ala Arg
        915                 920                 925

Glu Lys Glu Leu Gln Thr Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr
```

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    930                 935                 940

Gln Glu Thr Met Ser Ala Ile Arg Thr Trp Val Gln Gln Ser Glu Thr
945                 950                 955                 960

Lys Leu Ser Ile Pro Gln Leu Ser Val Thr Asp Tyr Glu Ile Met Glu
                965                 970                 975

Gln Arg Leu Gly Glu Leu Gln Ala Leu Gln Ser Ser Leu Gln Glu Gln
            980                 985                 990

Gln Ser Gly Leu Tyr Tyr Leu Ser  Thr Thr Val Lys Glu  Met Ser Lys
        995                 1000                1005

Lys Ala  Pro Ser Glu Ile Ser  Arg Lys Tyr Gln Ser  Glu Phe Glu
    1010                1015                1020

Glu Ile  Glu Gly Arg Trp Lys  Lys Leu Ser Ser Gln  Leu Val Glu
    1025                1030                1035

His Cys  Gln Lys Leu Glu Glu  Gln Met Asn Lys Leu  Arg Lys Ile
    1040                1045                1050

Gln Asn  His Ile Gln Thr Leu  Lys Lys Trp Met Ala  Glu Val Asp
    1055                1060                1065

Val Phe  Leu Lys Glu Glu Trp  Pro Ala Leu Gly Asp  Ser Glu Ile
    1070                1075                1080

Leu Lys  Lys Gln Leu Lys Gln  Cys Arg Leu Leu Val  Ser Asp Ile
    1085                1090                1095

Gln Thr  Ile Gln Pro Ser Leu  Asn Ser Val Asn Glu  Gly Gly Gln
    1100                1105                1110

Lys Ile  Lys Asn Glu Ala Glu  Pro Glu Phe Ala Ser  Arg Leu Glu
    1115                1120                1125

Thr Glu  Leu Lys Glu Leu Asn  Thr Gln Trp Asp His  Met Cys Gln
    1130                1135                1140
```

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Gln Val  Tyr Ala Arg Lys Glu  Ala Leu Lys Gly Gly  Leu Glu Lys
    1145                1150                1155

Thr Val  Ser Leu Gln Lys Asp  Leu Ser Glu Met His  Glu Trp Met
    1160                1165                1170

Thr Gln  Ala Glu Glu Glu Tyr  Leu Glu Arg Asp Phe  Glu Tyr Lys
    1175                1180                1185

Thr Pro  Asp Glu Leu Gln Lys  Ala Val Glu Glu Met  Lys Arg Ala
    1190                1195                1200

Lys Glu  Glu Ala Gln Gln Lys  Glu Ala Lys Val Lys  Leu Leu Thr
    1205                1210                1215

Glu Ser  Val Asn Ser Val Ile  Ala Gln Ala Pro Pro  Val Ala Gln
    1220                1225                1230

Glu Ala  Leu Lys Lys Glu Leu  Glu Thr Leu Thr Thr  Asn Tyr Gln
    1235                1240                1245

Trp Leu  Cys Thr Arg Leu Asn  Gly Lys Cys Lys Thr  Leu Glu Glu
    1250                1255                1260

Val Trp  Ala Cys Trp His Glu  Leu Leu Ser Tyr Leu  Glu Lys Ala
    1265                1270                1275

Asn Lys  Trp Leu Asn Glu Val  Glu Phe Lys Leu Lys  Thr Thr Glu
    1280                1285                1290

Asn Ile  Pro Gly Gly Ala Glu  Glu Ile Ser Glu Val  Leu Asp Ser
    1295                1300                1305

Leu Glu  Asn Leu Met Arg His  Ser Glu Asp Asn Pro  Asn Gln Ile
    1310                1315                1320

Arg Ile  Leu Ala Gln Thr Leu  Thr Asp Gly Gly Val  Met Asp Glu
    1325                1330                1335

Leu Ile  Asn Glu Glu Leu Glu  Thr Phe Asn Ser Arg  Trp Arg Glu
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Leu His Glu Glu Ala Val Arg Arg Gln Lys Leu Leu Glu Gln Ser
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Ile Gln Ser Ala Gln Glu Thr Glu Lys Ser Leu His Leu Ile Gln
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Glu Ser Leu Thr Phe Ile Asp Lys Gln Leu Ala Ala Tyr Ile Ala
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Asp Lys Val Asp Ala Ala Gln Met Pro Gln Glu Ala Gln Lys Ile
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Gln Ser Asp Leu Thr Ser His Glu Ile Ser Leu Glu Glu Met Lys
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Lys His Asn Gln Gly Lys Glu Ala Ala Gln Arg Val Leu Ser Gln
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Ile Asp Val Ala Gln Lys Lys Leu Gln Asp Val Ser Met Lys Phe
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Arg Leu Phe Gln Lys Pro Ala Asn Phe Glu Gln Arg Leu Gln Glu
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Ser Lys Met Ile Leu Asp Glu Val Lys Met His Leu Pro Ala Leu
1475 1480 1485

Glu Thr Lys Ser Val Glu Gln Glu Val Val Gln Ser Gln Leu Asn
1490 1495 1500

His Cys Val Asn Leu Tyr Lys Ser Leu Ser Glu Val Lys Ser Glu
1505 1510 1515

Val Glu Met Val Ile Lys Thr Gly Arg Gln Ile Val Gln Lys Lys
1520 1525 1530

Gln Thr Glu Asn Pro Lys Glu Leu Asp Glu Arg Val Thr Ala Leu
1535 1540 1545

Lys Leu His Tyr Asn Glu Leu Gly Ala Lys Val Thr Glu Arg Lys
1550 1555 1560

Gln Gln Leu Glu Lys Cys Leu Lys Leu Ser Arg Lys Met Arg Lys
1565 1570 1575

Glu Met Asn Val Leu Thr Glu Trp Leu Ala Ala Thr Asp Met Glu
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Leu Thr Lys Arg Ser Ala Val Glu Gly Met Pro Ser Asn Leu Asp
1595 1600 1605

Ser Glu Val Ala Trp Gly Lys Ala Thr Gln Lys Glu Ile Glu Lys
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Gln Lys Val His Leu Lys Ser Ile Thr Glu Val Gly Glu Ala Leu
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Lys Thr Val Leu Gly Lys Lys Glu Thr Leu Val Glu Asp Lys Leu
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Ser Leu Leu Asn Ser Asn Trp Ile Ala Val Thr Ser Arg Ala Glu
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Glu Trp Leu Asn Leu Leu Leu Glu Tyr Gln Lys His Met Glu Thr
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Phe Asp Gln Asn Val Asp His Ile Thr Lys Trp Ile Ile Gln Ala
1685 1690 1695

Asp Thr Leu Leu Asp Glu Ser Glu Lys Lys Lys Pro Gln Gln Lys
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Glu Asp Val Leu Lys Arg Leu Lys Ala Glu Leu Asn Asp Ile Arg
1715 1720 1725

Pro Lys Val Asp Ser Thr Arg Asp Gln Ala Ala Asn Leu Met Ala
1730 1735 1740

Asn Arg Gly Asp His Cys Arg Lys Leu Val Glu Pro Gln Ile Ser

1745 1750 1755

Glu Leu Asn His Arg Phe Ala Ala Ile Ser His Arg Ile Lys Thr
1760 1765 1770

Gly Lys Ala Ser Ile Pro Leu Lys Glu Leu Glu Gln Phe Asn Ser
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Asp Ile Gln Lys Leu Leu Glu Pro Leu Glu Ala Glu Ile Gln Gln
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Gly Val Asn Leu Lys Glu Glu Asp Phe Asn Lys Asp Met Asn Glu
1805 1810 1815

Asp Asn Glu Gly Thr Val Lys Glu Leu Leu Gln Arg Gly Asp Asn
1820 1825 1830

Leu Gln Gln Arg Ile Thr Asp Glu Arg Lys Arg Glu Glu Ile Lys
1835 1840 1845

Ile Lys Gln Gln Leu Leu Gln Thr Lys His Asn Ala Leu Lys Asp
1850 1855 1860

Leu Arg Ser Gln Arg Arg Lys Lys Ala Leu Glu Ile Ser His Gln
1865 1870 1875

Trp Tyr Gln Tyr Lys Arg Gln Ala Asp Asp Leu Leu Lys Cys Leu
1880 1885 1890

Asp Asp Ile Glu Lys Lys Leu Ala Ser Leu Pro Glu Pro Arg Asp
1895 1900 1905

Glu Arg Lys Ile Lys Glu Ile Asp Arg Glu Leu Gln Lys Lys Lys
1910 1915 1920

Glu Glu Leu Asn Ala Val Arg Arg Gln Ala Glu Gly Leu Ser Glu
1925 1930 1935

Asp Gly Ala Ala Met Ala Val Glu Pro Thr Gln Ile Gln Leu Ser
1940 1945 1950

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Lys Arg  Trp Arg Glu Ile Glu  Ser Lys Phe Ala Gln  Phe Arg Arg
    1955                1960                1965

Leu Asn  Phe Ala Gln Ile His  Thr Val Arg Glu Glu  Thr Met Met
    1970                1975                1980

Val Met  Thr Glu Asp Met Pro  Leu Glu Ile Ser Tyr  Val Pro Ser
    1985                1990                1995

Thr Tyr  Leu Thr Glu Ile Thr  His Val Ser Gln Ala  Leu Leu Glu
    2000                2005                2010

Val Glu  Gln Leu Leu Asn Ala  Pro Asp Leu Cys Ala  Lys Asp Phe
    2015                2020                2025

Glu Asp  Leu Phe Lys Gln Glu  Glu Ser Leu Lys Asn  Ile Lys Asp
    2030                2035                2040

Ser Leu  Gln Gln Ser Ser Gly  Arg Ile Asp Ile Ile  His Ser Lys
    2045                2050                2055

Lys Thr  Ala Ala Leu Gln Ser  Ala Thr Pro Val Glu  Arg Val Lys
    2060                2065                2070

Leu Gln  Glu Ala Leu Ser Gln  Leu Asp Phe Gln Trp  Glu Lys Val
    2075                2080                2085

Asn Lys  Met Tyr Lys Asp Arg  Gln Gly Arg Phe Asp  Arg Ser Val
    2090                2095                2100

Glu Lys  Trp Arg Arg Phe His  Tyr Asp Ile Lys Ile  Phe Asn Gln
    2105                2110                2115

Trp Leu  Thr Glu Ala Glu Gln  Phe Leu Arg Lys Thr  Gln Ile Pro
    2120                2125                2130

Glu Asn  Trp Glu His Ala Lys  Tyr Lys Trp Tyr Leu  Lys Glu Leu
    2135                2140                2145

Gln Asp  Gly Ile Gly Gln Arg  Gln Thr Val Val Arg  Thr Leu Asn
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Ala Thr  Gly Glu Glu Ile Ile  Gln Gln Ser Ser Lys  Thr Asp Ala
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Ser Ile  Leu Gln Glu Lys Leu  Gly Ser Leu Asn Leu  Arg Trp Gln
    2180                2185                2190

Glu Val  Cys Lys Gln Leu Ser  Asp Arg Lys Lys Arg  Leu Glu Glu
    2195                2200                2205

Gln Lys  Asn Ile Leu Ser Glu  Phe Gln Arg Asp Leu  Asn Glu Phe
    2210                2215                2220

Val Leu  Trp Leu Glu Glu Ala  Asp Asn Ile Ala Ser  Ile Pro Leu
    2225                2230                2235

Glu Pro  Gly Lys Glu Gln Gln  Leu Lys Glu Lys Leu  Glu Gln Val
    2240                2245                2250

Lys Leu  Leu Val Glu Glu Leu  Pro Leu Arg Gln Gly  Ile Leu Lys
    2255                2260                2265

Gln Leu  Asn Glu Thr Gly Gly  Pro Val Leu Val Ser  Ala Pro Ile
    2270                2275                2280

Ser Pro  Glu Glu Gln Asp Lys  Leu Glu Asn Lys Leu  Lys Gln Thr
    2285                2290                2295

Asn Leu  Gln Trp Ile Lys Val  Ser Arg Ala Leu Pro  Glu Lys Gln
    2300                2305                2310

Gly Glu  Ile Glu Ala Gln Ile  Lys Asp Leu Gly Gln  Leu Glu Lys
    2315                2320                2325

Lys Leu  Glu Asp Leu Glu Glu  Gln Leu Asn His Leu  Leu Leu Trp
    2330                2335                2340

Leu Ser  Pro Ile Arg Asn Gln  Leu Glu Ile Tyr Asn  Gln Pro Asn
    2345                2350                2355
```

Gln Glu Gly Pro Phe Asp Val Lys Glu Thr Glu Ile Ala Val Gln
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Ala Lys Gln Pro Asp Val Glu Glu Ile Leu Ser Lys Gly Gln His
2375 2380 2385

Leu Tyr Lys Glu Lys Pro Ala Thr Gln Pro Val Lys Arg Lys Leu
2390 2395 2400

Glu Asp Leu Ser Ser Glu Trp Lys Ala Val Asn Arg Leu Leu Gln
2405 2410 2415

Glu Leu Arg Ala Lys Gln Pro Asp Leu Ala Pro Gly Leu Thr Thr
2420 2425 2430

Ile Gly Ala Ser Pro Thr Gln Thr Val Thr Leu Val Thr Gln Pro
2435 2440 2445

Val Val Thr Lys Glu Thr Ala Ile Ser Lys Leu Glu Met Pro Ser
2450 2455 2460

Ser Leu Met Leu Glu Val Pro Ala Leu Ala Asp Phe Asn Arg Ala
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Trp Thr Glu Leu Thr Asp Trp Leu Ser Leu Leu Asp Gln Val Ile
2480 2485 2490

Lys Ser Gln Arg Val Met Val Gly Asp Leu Glu Asp Ile Asn Glu
2495 2500 2505

Met Ile Ile Lys Gln Lys Ala Thr Met Gln Asp Leu Glu Gln Arg
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Arg Pro Gln Leu Glu Glu Leu Ile Thr Ala Ala Gln Asn Leu Lys
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Asn Lys Thr Ser Asn Gln Glu Ala Arg Thr Ile Ile Thr Asp Arg
2540 2545 2550

Ile Glu Arg Ile Gln Asn Gln Trp Asp Glu Val Gln Glu His Leu

2555 2560 2565

Gln Asn Arg Arg Gln Gln Leu Asn Glu Met Leu Lys Asp Ser Thr
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Gly Lys Gln His Ile Glu Asn Leu Phe Ser Asp Leu Gln Asp Gly Arg
        35                  40                  45

Arg Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Gln Lys Leu Pro Lys
    50                  55                  60

Glu Lys Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Lys Ala
65                  70                  75                  80

Leu Arg Val Leu Gln Asn Asn Asn Val Asp Leu Val Asn Ile Gly Ser
                85                  90                  95

Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Ile Trp
            100                 105                 110

Asn Ile Ile Leu His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met
        115                 120                 125

Ala Gly Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
    130                 135                 140

Arg Gln Ser Thr Arg Asn Tyr Pro Gln Val Asn Val Ile Asn Phe Thr
145                 150                 155                 160

Thr Ser Trp Ser Asp Gly Leu Ala Leu Asn Ala Leu Ile His Ser His
                165                 170                 175

Arg Pro Asp Leu Phe Asp Trp Asn Ser Val Val Cys Gln Gln Ser Ala
            180                 185                 190

Thr Gln Arg Leu Glu His Ala Phe Asn Ile Ala Arg Tyr Gln Leu Gly
        195                 200                 205
```

```
Ile Glu Lys Leu Leu Asp Pro Glu Asp Val Asp Thr Thr Tyr Pro Asp
    210                 215                 220

Lys Lys Ser Ile Leu Met Tyr Ile Thr Ser Leu Phe Gln Val Leu Pro
225                 230                 235                 240

Gln Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg
                245                 250                 255

Pro Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met
            260                 265                 270

His Tyr Ser Gln Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg
        275                 280                 285

Thr Ser Ser Pro Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala
    290                 295                 300

Ala Tyr Val Thr Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln
305                 310                 315                 320

His Leu Glu Ala Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu
                325                 330                 335

Ser Glu Val Asn Leu Asp Arg Tyr Gln Thr Ala Leu Glu Glu Val Leu
            340                 345                 350

Ser Trp Leu Leu Ser Ala Glu Asp Thr Leu Gln Ala Gln Gly Glu Ile
        355                 360                 365

Ser Asn Asp Val Glu Val Val Lys Asp Gln Phe His Thr His Glu Gly
    370                 375                 380

Tyr Met Met Asp Leu Thr Ala His Gln Gly Arg Val Gly Asn Ile Leu
385                 390                 395                 400

Gln Leu Gly Ser Lys Leu Ile Gly Thr Gly Lys Leu Ser Glu Asp Glu
                405                 410                 415
```

```
Glu Thr Glu Val Gln Glu Gln Met Asn Leu Leu Asn Ser Arg Trp Glu
            420                 425                 430

Cys Leu Arg Val Ala Ser Met Glu Lys Gln Ser Asn Leu His Arg Val
        435                 440                 445

Leu Met Asp Leu Gln Asn Gln Lys Leu Lys Glu Leu Asn Asp Trp Leu
    450                 455                 460

Thr Lys Thr Glu Glu Arg Thr Arg Lys Met Glu Glu Glu Pro Leu Gly
465                 470                 475                 480

Pro Asp Leu Glu Asp Leu Lys Arg Gln Val Gln Gln His Lys Val Leu
                485                 490                 495

Gln Glu Asp Leu Glu Gln Glu Gln Val Arg Val Asn Ser Leu Thr His
            500                 505                 510

Met Val Val Val Val Asp Glu Ser Ser Gly Asp His Ala Thr Ala Ala
        515                 520                 525

Leu Glu Glu Gln Leu Lys Val Leu Gly Asp Arg Trp Ala Asn Ile Cys
    530                 535                 540

Arg Trp Thr Glu Asp Arg Trp Val Leu Leu Gln Asp Ile Leu Leu Lys
545                 550                 555                 560

Trp Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ala Trp Leu Ser
                565                 570                 575

Glu Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp
            580                 585                 590

Gln Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala
        595                 600                 605

Asp Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys
    610                 615                 620

Gln Asp Leu Leu Ser Thr Leu Lys Asn Lys Ser Val Thr Gln Lys Thr
625                 630                 635                 640
```

```
Glu Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln
               645                 650                 655

Lys Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr
           660                 665                 670

Gln Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val
       675                 680                 685

Thr Thr Arg Glu Gln Ile Leu Val Lys His Ala Gln Glu Glu Leu Pro
   690                 695                 700

Pro Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile
705                 710                 715                 720

Arg Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr
               725                 730                 735

Arg Ser Glu Ala Val Leu Gln Ser Pro Glu Phe Ala Ile Phe Arg Lys
           740                 745                 750

Glu Gly Asn Phe Ser Asp Leu Lys Glu Lys Val Asn Ala Ile Glu Arg
       755                 760                 765

Glu Lys Ala Glu Lys Phe Arg Lys Leu Gln Asp Ala Ser Arg Ser Ala
   770                 775                 780

Gln Ala Leu Val Glu Gln Met Val Asn Glu Gly Val Asn Ala Asp Ser
785                 790                 795                 800

Ile Lys Gln Ala Ser Glu Gln Leu Asn Ser Arg Trp Ile Glu Phe Cys
               805                 810                 815

Gln Leu Leu Ser Glu Arg Leu Asn Trp Leu Glu Tyr Gln Asn Asn Ile
           820                 825                 830

Ile Ala Phe Tyr Asn Gln Leu Gln Gln Leu Glu Gln Met Thr Thr Thr
       835                 840                 845
```

```
Ala Glu Asn Trp Leu Lys Ile Gln Pro Thr Thr Pro Ser Glu Pro Thr
    850                 855                 860

Ala Ile Lys Ser Gln Leu Lys Ile Cys Lys Asp Glu Val Asn Arg Leu
865                 870                 875                 880

Ser Asp Leu Gln Pro Gln Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala
                885                 890                 895

Leu Lys Glu Lys Gly Gln Gly Pro Met Phe Leu Asp Ala Asp Phe Val
            900                 905                 910

Ala Phe Thr Asn His Phe Lys Gln Val Phe Ser Asp Val Gln Ala Arg
        915                 920                 925

Glu Lys Glu Leu Gln Thr Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr
    930                 935                 940

Gln Glu Thr Met Ser Ala Ile Arg Thr Trp Val Gln Gln Ser Glu Thr
945                 950                 955                 960

Lys Leu Ser Ile Pro Gln Leu Ser Val Thr Asp Tyr Glu Ile Met Glu
                965                 970                 975

Gln Arg Leu Gly Glu Leu Gln Ala Leu Gln Ser Ser Leu Gln Glu Gln
            980                 985                 990

Gln Ser Gly Leu Tyr Tyr Leu Ser  Thr Thr Val Lys Glu  Met Ser Lys
        995                 1000                1005

Lys Ala  Pro Ser Glu Ile Ser  Arg Lys Tyr Gln Ser  Glu Phe Glu
    1010                1015                1020

Glu Ile  Glu Gly Arg Trp Lys  Lys Leu Ser Ser Gln  Leu Val Glu
    1025                1030                1035

His Cys  Gln Lys Leu Glu Glu  Gln Met Asn Lys Leu  Arg Lys Ile
    1040                1045                1050

Gln Asn  His Ile Gln Thr Leu  Lys Lys Trp Met Ala  Glu Val Asp
    1055                1060                1065
```

```
Val Phe  Leu Lys Glu Glu Trp  Pro Ala Leu Gly Asp  Ser Glu Ile
    1070                1075                1080

Leu Lys  Lys Gln Leu Lys Gln  Cys Arg Leu Leu Val  Ser Asp Ile
    1085                1090                1095

Gln Thr  Ile Gln Pro Ser Leu  Asn Ser Val Asn Glu  Gly Gly Gln
    1100                1105                1110

Lys Ile  Lys Asn Glu Ala Glu  Pro Glu Phe Ala Ser  Arg Leu Glu
    1115                1120                1125

Thr Glu  Leu Lys Glu Leu Asn  Thr Gln Trp Asp His  Met Cys Gln
    1130                1135                1140

Gln Val  Tyr Ala Arg Lys Glu  Ala Leu Lys Gly Gly  Leu Glu Lys
    1145                1150                1155

Thr Val  Ser Leu Gln Lys Asp  Leu Ser Glu Met His  Glu Trp Met
    1160                1165                1170

Thr Gln  Ala Glu Glu Glu Tyr  Leu Glu Arg Asp Phe  Glu Tyr Lys
    1175                1180                1185

Thr Pro  Asp Glu Leu Gln Lys  Ala Val Glu Glu Met  Lys Arg Ala
    1190                1195                1200

Lys Glu  Glu Ala Gln Gln Lys  Glu Ala Lys Val Lys  Leu Leu Thr
    1205                1210                1215

Glu Ser  Val Asn Ser Val Ile  Ala Gln Ala Pro Pro  Val Ala Gln
    1220                1225                1230

Glu Ala  Leu Lys Lys Glu Leu  Glu Thr Leu Thr Thr  Asn Tyr Gln
    1235                1240                1245

Trp Leu  Cys Thr Arg Leu Asn  Gly Lys Cys Lys Thr  Leu Glu Glu
    1250                1255                1260
```

```
Val Trp  Ala Cys Trp His Glu  Leu Leu Ser Tyr Leu  Glu Lys Ala
    1265                1270                1275

Asn Lys  Trp Leu Asn Glu Val  Glu Phe Lys Leu Lys  Thr Thr Glu
    1280                1285                1290

Asn Ile  Pro Gly Gly Ala Glu  Glu Ile Ser Glu Val  Leu Asp Ser
    1295                1300                1305

Leu Glu  Asn Leu Met Arg His  Ser Glu Asp Asn Pro  Asn Gln Ile
    1310                1315                1320

Arg Ile  Leu Ala Gln Thr Leu  Thr Asp Gly Gly Val  Met Asp Glu
    1325                1330                1335

Leu Ile  Asn Glu Glu Leu Glu  Thr Phe Asn Ser Arg  Trp Arg Glu
    1340                1345                1350

Leu His  Glu Glu Ala Val Arg  Arg Gln Lys Leu Leu  Glu Gln Ser
    1355                1360                1365

Ile Gln  Ser Ala Gln Glu Thr  Glu Lys Ser Leu His  Leu Ile Gln
    1370                1375                1380

Glu Ser  Leu Thr Phe Ile Asp  Lys Gln Leu Ala Ala  Tyr Ile Ala
    1385                1390                1395

Asp Lys  Val Asp Ala Ala Gln  Met Pro Gln Glu Ala  Gln Lys Ile
    1400                1405                1410

Gln Ser  Asp Leu Thr Ser His  Glu Ile Ser Leu Glu  Glu Met Lys
    1415                1420                1425

Lys His  Asn Gln Gly Lys Glu  Ala Ala Gln Arg Val  Leu Ser Gln
    1430                1435                1440

Ile Asp  Val Ala Gln Lys Lys  Leu Gln Asp Val Ser  Met Lys Phe
    1445                1450                1455

Arg Leu  Phe Gln Lys Pro Ala  Asn Phe Glu Gln Arg  Leu Gln Glu
    1460                1465                1470
```

```
Ser Lys  Met Ile Leu Asp Glu  Val Lys Met His Leu  Pro Ala Leu
    1475                1480                1485

Glu Thr  Lys Ser Val Glu Gln  Glu Val Val Gln Ser  Gln Leu Asn
    1490                1495                1500

His Cys  Val Asn Leu Tyr Lys  Ser Leu Ser Glu Val  Lys Ser Glu
    1505                1510                1515

Val Glu  Met Val Ile Lys Thr  Gly Arg Gln Ile Val  Gln Lys Lys
    1520                1525                1530

Gln Thr  Glu Asn Pro Lys Glu  Leu Asp Glu Arg Val  Thr Ala Leu
    1535                1540                1545

Lys Leu  His Tyr Asn Glu Leu  Gly Ala Lys Val Thr  Glu Arg Lys
    1550                1555                1560

Gln Gln  Leu Glu Lys Cys Leu  Lys Leu Ser Arg Lys  Met Arg Lys
    1565                1570                1575

Glu Met  Asn Val Leu Thr Glu  Trp Leu Ala Ala Thr  Asp Met Glu
    1580                1585                1590

Leu Thr  Lys Arg Ser Ala Val  Glu Gly Met Pro Ser  Asn Leu Asp
    1595                1600                1605

Ser Glu  Val Ala Trp Gly Lys  Ala Thr Gln Lys Glu  Ile Glu Lys
    1610                1615                1620

Gln Lys  Val His Leu Lys Ser  Ile Thr Glu Val Gly  Glu Ala Leu
    1625                1630                1635

Lys Thr  Val Leu Gly Lys Lys  Glu Thr Leu Val Glu  Asp Lys Leu
    1640                1645                1650

Ser Leu  Leu Asn Ser Asn Trp  Ile Ala Val Thr Ser  Arg Ala Glu
    1655                1660                1665
```

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Glu Trp  Leu Asn Leu Leu Leu  Glu Tyr Gln Lys His  Met Glu Thr
    1670                1675                1680

Phe Asp  Gln Asn Val Asp His  Ile Thr Lys Trp Ile  Ile Gln Ala
    1685                1690                1695

Asp Thr  Leu Leu Asp Glu Ser  Glu Lys Lys Lys Pro  Gln Gln Lys
    1700                1705                1710

Glu Asp  Val Leu Lys Arg Leu  Lys Ala Glu Leu Asn  Asp Ile Arg
    1715                1720                1725

Pro Lys  Val Asp Ser Thr Arg  Asp Gln Ala Ala Asn  Leu Met Ala
    1730                1735                1740

Asn Arg  Gly Asp His Cys Arg  Lys Leu Val Glu Pro  Gln Ile Ser
    1745                1750                1755

Glu Leu  Asn His Arg Phe Ala  Ala Ile Ser His Arg  Ile Lys Thr
    1760                1765                1770

Gly Lys  Ala Ser Ile Pro Leu  Lys Glu Leu Glu Gln  Phe Asn Ser
    1775                1780                1785

Asp Ile  Gln Lys Leu Leu Glu  Pro Leu Glu Ala Glu  Ile Gln Gln
    1790                1795                1800

Gly Val  Asn Leu Lys Glu Glu  Asp Phe Asn Lys Asp  Met Asn Glu
    1805                1810                1815

Asp Asn  Glu Gly Thr Val Lys  Glu Leu Leu Gln Arg  Gly Asp Asn
    1820                1825                1830

Leu Gln  Gln Arg Ile Thr Asp  Glu Arg Lys Arg Glu  Glu Ile Lys
    1835                1840                1845

Ile Lys  Gln Gln Leu Leu Gln  Thr Lys His Asn Ala  Leu Lys Asp
    1850                1855                1860

Leu Arg  Ser Gln Arg Arg Lys  Lys Ala Leu Glu Ile  Ser His Gln
    1865                1870                1875
```

```
Trp Tyr  Gln Tyr Lys Arg Gln  Ala Asp Asp Leu Leu  Lys Cys Leu
    1880                1885                1890

Asp Asp  Ile Glu Lys Lys Leu  Ala Ser Leu Pro Glu  Pro Arg Asp
    1895                1900                1905

Glu Arg  Lys Ile Lys Glu Ile  Asp Arg Glu Leu Gln  Lys Lys Lys
    1910                1915                1920

Glu Glu  Leu Asn Ala Val Arg  Arg Gln Ala Glu Gly  Leu Ser Glu
    1925                1930                1935

Asp Gly  Ala Ala Met Ala Val  Glu Pro Thr Gln Ile  Gln Leu Ser
    1940                1945                1950

Lys Arg  Trp Arg Glu Ile Glu  Ser Lys Phe Ala Gln  Phe Arg Arg
    1955                1960                1965

Leu Asn  Phe Ala Gln Ile His  Thr Val Arg Glu Glu  Thr Met Met
    1970                1975                1980

Val Met  Thr Glu Asp Met Pro  Leu Glu Ile Ser Tyr  Val Pro Ser
    1985                1990                1995

Thr Tyr  Leu Thr Glu Ile Thr  His Val Ser Gln Ala  Leu Leu Glu
    2000                2005                2010

Val Glu  Gln Leu Leu Asn Ala  Pro Asp Leu Cys Ala  Lys Asp Phe
    2015                2020                2025

Glu Asp  Leu Phe Lys Gln Glu  Glu Ser Leu Lys Asn  Ile Lys Asp
    2030                2035                2040

Ser Leu  Gln Gln Ser Ser Gly  Arg Ile Asp Ile Ile  His Ser Lys
    2045                2050                2055

Lys Thr  Ala Ala Leu Gln Ser  Ala Thr Pro Val Glu  Arg Val Lys
    2060                2065                2070
```

```
Leu Gln  Glu Ala Leu Ser Gln  Leu Asp Phe Gln Trp  Glu Lys Val
    2075                2080                2085

Asn Lys  Met Tyr Lys Asp Arg  Gln Gly Arg Phe Asp  Arg Ser Val
    2090                2095                2100

Glu Lys  Trp Arg Arg Phe His  Tyr Asp Ile Lys Ile  Phe Asn Gln
    2105                2110                2115

Trp Leu  Thr Glu Ala Glu Gln  Phe Leu Arg Lys Thr  Gln Ile Pro
    2120                2125                2130

Glu Asn  Trp Glu His Ala Lys  Tyr Lys Trp Tyr Leu  Lys Glu Leu
    2135                2140                2145

Gln Asp  Gly Ile Gly Gln Arg  Gln Thr Val Val Arg  Thr Leu Asn
    2150                2155                2160

Ala Thr  Gly Glu Glu Ile Ile  Gln Gln Ser Ser Lys  Thr Asp Ala
    2165                2170                2175

Ser Ile  Leu Gln Glu Lys Leu  Gly Ser Leu Asn Leu  Arg Trp Gln
    2180                2185                2190

Glu Val  Cys Lys Gln Leu Ser  Asp Arg Lys Lys Arg  Leu Glu Glu
    2195                2200                2205

Gln Lys  Asn Ile Leu Ser Glu  Phe Gln Arg Asp Leu  Asn Glu Phe
    2210                2215                2220

Val Leu  Trp Leu Glu Glu Ala  Asp Asn Ile Ala Ser  Ile Pro Leu
    2225                2230                2235

Glu Pro  Gly Lys Glu Gln Gln  Leu Lys Glu Lys Leu  Glu Gln Val
    2240                2245                2250

Lys Leu  Leu Val Glu Glu Leu  Pro Leu Arg Gln Gly  Ile Leu Lys
    2255                2260                2265

Gln Leu  Asn Glu Thr Gly Gly  Pro Val Leu Val Ser  Ala Pro Ile
    2270                2275                2280
```

Ser Pro Glu Glu Gln Asp Lys Leu Glu Asn Lys Leu Lys Gln Thr
2285 2290 2295

Asn Leu Gln Trp Ile Lys Val Ser Arg Ala Leu Pro Glu Lys Gln
2300 2305 2310

Gly Glu Ile Glu Ala Gln Ile Lys Asp Leu Gly Gln Leu Glu Lys
2315 2320 2325

Lys Leu Glu Asp Leu Glu Glu Gln Leu Asn His Leu Leu Leu Trp
2330 2335 2340

Leu Ser Pro Ile Arg Asn Gln Leu Glu Ile Tyr Asn Gln Pro Asn
2345 2350 2355

Gln Glu Gly Pro Phe Asp Val Lys Glu Thr Glu Ile Ala Val Gln
2360 2365 2370

Ala Lys Gln Pro Asp Val Glu Glu Ile Leu Ser Lys Gly Gln His
2375 2380 2385

Leu Tyr Lys Glu Lys Pro Ala Thr Gln Pro Val Lys Arg Lys Leu
2390 2395 2400

Glu Asp Leu Ser Ser Glu Trp Lys Ala Val Asn Arg Leu Leu Gln
2405 2410 2415

Glu Leu Arg Ala Lys Gln Pro Asp Leu Ala Pro Gly Leu Thr Thr
2420 2425 2430

Ile Gly Ala Ser Pro Thr Gln Thr Val Thr Leu Val Thr Gln Pro
2435 2440 2445

Val Val Thr Lys Glu Thr Ala Ile Ser Lys Leu Glu Met Pro Ser
2450 2455 2460

Ser Leu Met Leu Glu Val Pro Ala Leu Ala Asp Phe Asn Arg Ala
2465 2470 2475

```
Trp Thr  Glu Leu Thr Asp Trp  Leu Ser Leu Leu Asp  Gln Val Ile
    2480                2485                2490

Lys Ser  Gln Arg Val Met Val  Gly Asp Leu Glu Asp  Ile Asn Glu
    2495                2500                2505

Met Ile  Ile Lys Gln Lys Ala  Thr Met Gln Asp Leu  Glu Gln Arg
    2510                2515                2520

Arg Pro  Gln Leu Glu Glu Leu  Ile Thr Ala Ala Gln  Asn Leu Lys
    2525                2530                2535

Asn Lys  Thr Ser Asn Gln Glu  Ala Arg Thr Ile Ile  Thr Asp Arg
    2540                2545                2550

Ile Glu  Arg Ile Gln Asn Gln  Trp Asp Glu Val Gln  Glu His Leu
    2555                2560                2565

Gln Asn  Arg Arg Gln Gln Leu  Asn Glu Met Leu Lys  Asp Ser Thr
    2570                2575                2580

Gln Trp  Leu Glu Ala Lys Glu  Glu Ala Glu Gln Val  Leu Gly Gln
    2585                2590                2595

Ala Arg  Ala Lys Leu Glu Ser  Trp Lys Glu Gly Pro  Tyr Thr Val
    2600                2605                2610

Asp Ala  Ile Gln Lys Lys Ile  Thr Glu Thr Lys Gln  Leu Ala Lys
    2615                2620                2625

Asp Leu  Arg Gln Trp Gln Thr  Asn Val Asp Val Ala  Asn Asp Leu
    2630                2635                2640

Ala Leu  Lys Leu Leu Arg Asp  Tyr Ser Ala Asp Asp  Thr Arg Lys
    2645                2650                2655

Val His  Met Ile Thr Glu Asn  Ile Asn Ala Ser Trp  Arg Ser Ile
    2660                2665                2670

His Lys  Arg Val Ser Glu Arg  Glu Ala Ala Leu Glu  Glu Thr His
    2675                2680                2685
```

```
Arg Leu  Leu Gln Gln Phe Pro  Leu Asp Leu Glu Lys  Phe Leu Ala
    2690                2695                2700

Trp Leu  Thr Glu Ala Glu Thr  Thr Ala Asn Val Leu  Gln Asp Ala
    2705                2710                2715

Thr Arg  Lys Glu Arg Leu Leu  Glu Asp Ser Lys Gly  Val Lys Glu
    2720                2725                2730

Leu Met  Lys Gln Trp Gln Asp  Leu Gln Gly Glu Ile  Glu Ala His
    2735                2740                2745

Thr Asp  Val Tyr His Asn Leu  Asp Glu Asn Ser Gln  Lys Ile Leu
    2750                2755                2760

Arg Ser  Leu Glu Gly Ser Asp  Asp Ala Val Leu Leu  Gln Arg Arg
    2765                2770                2775

Leu Asp  Asn Met Asn Phe Lys  Trp Ser Glu Leu Arg  Lys Lys Ser
    2780                2785                2790

Leu Asn  Ile Arg Ser His Leu  Glu Ala Ser Ser Asp  Gln Trp Lys
    2795                2800                2805

Arg Leu  His Leu Ser Leu Gln  Glu Leu Leu Val Trp  Leu Gln Leu
    2810                2815                2820

Lys Asp  Asp Glu Leu Ser Arg  Gln Ala Pro Ile Gly  Gly Asp Phe
    2825                2830                2835

Pro Ala  Val Gln Lys Gln Asn  Asp Val His Arg Ala  Phe Lys Arg
    2840                2845                2850

Glu Leu  Lys Thr Lys Glu Pro  Val Ile Met Ser Thr  Leu Glu Thr
    2855                2860                2865

Val Arg  Ile Phe Leu Thr Glu  Gln Pro Leu Glu Gly  Leu Glu Lys
    2870                2875                2880
```

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Leu Tyr  Gln Glu Pro Arg Glu  Leu Pro Pro Glu Glu  Arg Ala Gln
    2885                 2890                 2895

Asn Val  Thr Arg Leu Leu Arg  Lys Gln Ala Glu Glu  Val Asn Thr
    2900                 2905                 2910

Glu Trp  Glu Lys Leu Asn Leu  His Ser Ala Asp Trp  Gln Arg Lys
    2915                 2920                 2925

Ile Asp  Glu Thr Leu Glu Arg  Leu Arg Glu Leu Gln  Glu Ala Thr
    2930                 2935                 2940

Asp Glu  Leu Asp Leu Lys Leu  Arg Gln Ala Glu Val  Ile Lys Gly
    2945                 2950                 2955

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Ser Trp Leu Leu Ser Ala Glu Asp Thr Leu Gln Ala Gln Gly Glu Ile
        355                 360                 365
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Ser Asn Asp Val Glu Val Val Lys Asp Gln Phe His Thr His Glu Gly
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Tyr Met Met Asp Leu Thr Ala His Gln Gly Arg Val Gly Asn Ile Leu
385                 390                 395                 400

Gln Leu Gly Ser Lys Leu Ile Gly Thr Gly Lys Leu Ser Glu Asp Glu
                405                 410                 415

Glu Thr Glu Val Gln Glu Gln Met Asn Leu Leu Asn Ser Arg Trp Glu
            420                 425                 430

Cys Leu Arg Val Ala Ser Met Glu Lys Gln Ser Asn Leu His Arg Val
        435                 440                 445

Leu Met Asp Leu Gln Asn Gln Lys Leu Lys Glu Leu Asn Asp Trp Leu
    450                 455                 460

Thr Lys Thr Glu Glu Arg Thr Arg Lys Met Glu Glu Glu Pro Leu Gly
465                 470                 475                 480

Pro Asp Leu Glu Asp Leu Lys Arg Gln Val Gln Gln His Lys Val Leu
                485                 490                 495

Gln Glu Asp Leu Glu Gln Glu Gln Val Arg Val Asn Ser Leu Thr His
            500                 505                 510

Met Val Val Val Val Asp Glu Ser Ser Gly Asp His Ala Thr Ala Ala
        515                 520                 525

Leu Glu Glu Gln Leu Lys Val Leu Gly Asp Arg Trp Ala Asn Ile Cys
    530                 535                 540

Arg Trp Thr Glu Asp Arg Trp Val Leu Leu Gln Asp Ile Leu Leu Lys
545                 550                 555                 560

Trp Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ala Trp Leu Ser
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Glu Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp
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Gln Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala
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Asp Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys
    610                 615                 620

Gln Asp Leu Leu Ser Thr Leu Lys Asn Lys Ser Val Thr Gln Lys Thr
625                 630                 635                 640

Glu Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln
                645                 650                 655

Lys Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr
            660                 665                 670

Gln Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val
        675                 680                 685

Thr Thr Arg Glu Gln Ile Leu Val Lys His Ala Gln Glu Glu Leu Pro
    690                 695                 700

Pro Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile
705                 710                 715                 720

Arg Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr
                725                 730                 735

Arg Ser Glu Ala Val Leu Gln Ser Pro Glu Phe Ala Ile Phe Arg Lys
            740                 745                 750

Glu Gly Asn Phe Ser Asp Leu Lys Glu Lys Val Asn Ala Ile Glu Arg
        755                 760                 765

Glu Lys Ala Glu Lys Phe Arg Lys Leu Gln Asp Ala Ser Arg Ser Ala
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Gln Ala Leu Val Glu Gln Met Val Asn Glu Gly Val Asn Ala Asp Ser
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Gln Leu Leu Ser Glu Arg Leu Asn Trp Leu Glu Tyr Gln Asn Asn Ile
            820                 825                 830

Ile Ala Phe Tyr Asn Gln Leu Gln Gln Leu Glu Gln Met Thr Thr Thr
        835                 840                 845

Ala Glu Asn Trp Leu Lys Ile Gln Pro Thr Thr Pro Ser Glu Pro Thr
    850                 855                 860

Ala Ile Lys Ser Gln Leu Lys Ile Cys Lys Asp Glu Val Asn Arg Leu
865                 870                 875                 880

Ser Asp Leu Gln Pro Gln Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala
                885                 890                 895

Leu Lys Glu Lys Gly Gln Gly Pro Met Phe Leu Asp Ala Asp Phe Val
            900                 905                 910

Ala Phe Thr Asn His Phe Lys Gln Val Phe Ser Asp Val Gln Ala Arg
        915                 920                 925

Glu Lys Glu Leu Gln Thr Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr
    930                 935                 940

Gln Glu Thr Met Ser Ala Ile Arg Thr Trp Val Gln Gln Ser Glu Thr
945                 950                 955                 960

Lys Leu Ser Ile Pro Gln Leu Ser Val Thr Asp Tyr Glu Ile Met Glu
                965                 970                 975

Gln Arg Leu Gly Glu Leu Gln Ala Leu Gln Ser Ser Leu Gln Glu Gln
            980                 985                 990

Gln Ser Gly Leu Tyr Tyr Leu Ser  Thr Thr Val Lys Glu  Met Ser Lys
        995                 1000                1005

Lys Ala  Pro Ser Glu Ile Ser  Arg Lys Tyr Gln Ser  Glu Phe Glu
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His Cys Gln Lys Leu Glu Glu Gln Met Asn Lys Leu Arg Lys Ile
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Gln Asn His Ile Gln Thr Leu Lys Lys Trp Met Ala Glu Val Asp
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Val Phe Leu Lys Glu Glu Trp Pro Ala Leu Gly Asp Ser Glu Ile
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Leu Lys Lys Gln Leu Lys Gln Cys Arg Leu Leu Val Ser Asp Ile
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Gln Thr Ile Gln Pro Ser Leu Asn Ser Val Asn Glu Gly Gly Gln
1100 1105 1110

Lys Ile Lys Asn Glu Ala Glu Pro Glu Phe Ala Ser Arg Leu Glu
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Thr Glu Leu Lys Glu Leu Asn Thr Gln Trp Asp His Met Cys Gln
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Gln Val Tyr Ala Arg Lys Glu Ala Leu Lys Gly Gly Leu Glu Lys
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Thr Gln Ala Glu Glu Glu Tyr Leu Glu Arg Asp Phe Glu Tyr Lys
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Lys Glu Glu Ala Gln Gln Lys Glu Ala Lys Val Lys Leu Leu Thr
1205 1210 1215

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Glu Ala  Leu Lys Lys Glu Leu  Glu Thr Leu Thr Thr  Asn Tyr Gln
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Trp Leu  Cys Thr Arg Leu Asn  Gly Lys Cys Lys Thr  Leu Glu Glu
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Val Trp  Ala Cys Trp His Glu  Leu Leu Ser Tyr Leu  Glu Lys Ala
    1265                1270                1275

Asn Lys  Trp Leu Asn Glu Val  Glu Phe Lys Leu Lys  Thr Thr Glu
    1280                1285                1290

Asn Ile  Pro Gly Gly Ala Glu  Glu Ile Ser Glu Val  Leu Asp Ser
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Leu Glu  Asn Leu Met Arg His  Ser Glu Asp Asn Pro  Asn Gln Ile
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Arg Ile  Leu Ala Gln Thr Leu  Thr Asp Gly Gly Val  Met Asp Glu
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Leu Ile  Asn Glu Glu Leu Glu  Thr Phe Asn Ser Arg  Trp Arg Glu
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Leu His  Glu Glu Ala Val Arg  Arg Gln Lys Leu Leu  Glu Gln Ser
    1355                1360                1365

Ile Gln  Ser Ala Gln Glu Thr  Glu Lys Ser Leu His  Leu Ile Gln
    1370                1375                1380

Glu Ser  Leu Thr Phe Ile Asp  Lys Gln Leu Ala Ala  Tyr Ile Ala
    1385                1390                1395

Asp Lys  Val Asp Ala Ala Gln  Met Pro Gln Glu Ala  Gln Lys Ile
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Gln Ser  Asp Leu Thr Ser His  Glu Ile Ser Leu Glu  Glu Met Lys
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Lys His Asn Gln Gly Lys Glu Ala Ala Gln Arg Val Leu Ser Gln
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Ile Asp Val Ala Gln Lys Lys Leu Gln Asp Val Ser Met Lys Phe
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Arg Leu Phe Gln Lys Pro Ala Asn Phe Glu Gln Arg Leu Gln Glu
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Ser Lys Met Ile Leu Asp Glu Val Lys Met His Leu Pro Ala Leu
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Glu Thr Lys Ser Val Glu Gln Glu Val Val Gln Ser Gln Leu Asn
1490 1495 1500

His Cys Val Asn Leu Tyr Lys Ser Leu Ser Glu Val Lys Ser Glu
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Val Glu Met Val Ile Lys Thr Gly Arg Gln Ile Val Gln Lys Lys
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Gln Thr Glu Asn Pro Lys Glu Leu Asp Glu Arg Val Thr Ala Leu
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Lys Leu His Tyr Asn Glu Leu Gly Ala Lys Val Thr Glu Arg Lys
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Gln Gln Leu Glu Lys Cys Leu Lys Leu Ser Arg Lys Met Arg Lys
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Glu Met Asn Val Leu Thr Glu Trp Leu Ala Ala Thr Asp Met Glu
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Leu Thr Lys Arg Ser Ala Val Glu Gly Met Pro Ser Asn Leu Asp
1595 1600 1605

Ser Glu Val Ala Trp Gly Lys Ala Thr Gln Lys Glu Ile Glu Lys
1610 1615 1620

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Lys Thr  Val Leu Gly Lys Lys  Glu Thr Leu Val Glu  Asp Lys Leu
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Ser Leu  Leu Asn Ser Asn Trp  Ile Ala Val Thr Ser  Arg Ala Glu
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Glu Trp  Leu Asn Leu Leu Leu  Glu Tyr Gln Lys His  Met Glu Thr
    1670                1675                1680

Phe Asp  Gln Asn Val Asp His  Ile Thr Lys Trp Ile  Ile Gln Ala
    1685                1690                1695

Asp Thr  Leu Leu Asp Glu Ser  Glu Lys Lys Lys Pro  Gln Gln Lys
    1700                1705                1710

Glu Asp  Val Leu Lys Arg Leu  Lys Ala Glu Leu Asn  Asp Ile Arg
    1715                1720                1725

Pro Lys  Val Asp Ser Thr Arg  Asp Gln Ala Ala Asn  Leu Met Ala
    1730                1735                1740

Asn Arg  Gly Asp His Cys Arg  Lys Leu Val Glu Pro  Gln Ile Ser
    1745                1750                1755

Glu Leu  Asn His Arg Phe Ala  Ala Ile Ser His Arg  Ile Lys Thr
    1760                1765                1770

Gly Lys  Ala Ser Ile Pro Leu  Lys Glu Leu Glu Gln  Phe Asn Ser
    1775                1780                1785

Asp Ile  Gln Lys Leu Leu Glu  Pro Leu Glu Ala Glu  Ile Gln Gln
    1790                1795                1800

Gly Val  Asn Leu Lys Glu Glu  Asp Phe Asn Lys Asp  Met Asn Glu
    1805                1810                1815

Asp Asn  Glu Gly Thr Val Lys  Glu Leu Leu Gln Arg  Gly Asp Asn
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    1820                1825                1830

Leu Gln  Gln Arg Ile Thr Asp  Glu Arg Lys Arg Glu  Glu Ile Lys
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Ile Lys  Gln Gln Leu Leu Gln  Thr Lys His Asn Ala  Leu Lys Asp
    1850                1855                1860

Leu Arg  Ser Gln Arg Arg Lys  Lys Ala Leu Glu Ile  Ser His Gln
    1865                1870                1875

Trp Tyr  Gln Tyr Lys Arg Gln  Ala Asp Asp Leu Leu  Lys Cys Leu
    1880                1885                1890

Asp Asp  Ile Glu Lys Lys Leu  Ala Ser Leu Pro Glu  Pro Arg Asp
    1895                1900                1905

Glu Arg  Lys Ile Lys Glu Ile  Asp Arg Glu Leu Gln  Lys Lys Lys
    1910                1915                1920

Glu Glu  Leu Asn Ala Val Arg  Arg Gln Ala Glu Gly  Leu Ser Glu
    1925                1930                1935

Asp Gly  Ala Ala Met Ala Val  Glu Pro Thr Gln Ile  Gln Leu Ser
    1940                1945                1950

Lys Arg  Trp Arg Glu Ile Glu  Ser Lys Phe Ala Gln  Phe Arg Arg
    1955                1960                1965

Leu Asn  Phe Ala Gln Ile His  Thr Val Arg Glu Glu  Thr Met Met
    1970                1975                1980

Val Met  Thr Glu Asp Met Pro  Leu Glu Ile Ser Tyr  Val Pro Ser
    1985                1990                1995

Thr Tyr  Leu Thr Glu Ile Thr  His Val Ser Gln Ala  Leu Leu Glu
    2000                2005                2010

Val Glu  Gln Leu Leu Asn Ala  Pro Asp Leu Cys Ala  Lys Asp Phe
    2015                2020                2025
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Glu Asp Leu Phe Lys Gln Glu Glu Ser Leu Lys Asn Ile Lys Asp
2030 2035 2040

Ser Leu Gln Gln Ser Ser Gly Arg Ile Asp Ile Ile His Ser Lys
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Lys Thr Ala Ala Leu Gln Ser Ala Thr Pro Val Glu Arg Val Lys
2060 2065 2070

Leu Gln Glu Ala Leu Ser Gln Leu Asp Phe Gln Trp Glu Lys Val
2075 2080 2085

Asn Lys Met Tyr Lys Asp Arg Gln Gly Arg Phe Asp Arg Ser Val
2090 2095 2100

Glu Lys Trp Arg Arg Phe His Tyr Asp Ile Lys Ile Phe Asn Gln
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Trp Leu Thr Glu Ala Glu Gln Phe Leu Arg Lys Thr Gln Ile Pro
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sintético"

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sintético"

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sintético"

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sintético”

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sintético"

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sintético"

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sintético”

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sintético"

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sintético"

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sintético"

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<210> 420
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sintético"

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sintético"

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<400> 658
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sintético"

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sintético”

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<400> 667
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<210> 668
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sintético"

<400> 669
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sintético"

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sintético"

<400> 671
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<210> 672
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sintético"

<400> 672

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24

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<210> 675
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24

<210> 676
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
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<400> 676
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24

<210> 677
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 677
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24

<210> 678
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 678
gcagccucuc gcucacucac ccug
24

<210> 679
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
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<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 679
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24

<210> 680
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 680
cugcaacagu ucccccugga ccug
24

<210> 681
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<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 681
ugcaacaguu cccccuggac cugg
24

<210> 682
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 682
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24

<210> 683
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido

sintético”

<400> 683
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24

<210> 684
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<213> Secuencia artificial

<220>
<221> fuente
<223> /nota=“Descripción de la secuencia artificial: Oligonucleótido sintético”

<400> 684
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24

<210> 685
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<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota=“Descripción de la secuencia artificial: Oligonucleótido sintético”

<400> 685
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24

<210> 686
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<213> Secuencia artificial

<220>
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<223> /nota=“Descripción de la secuencia artificial: Oligonucleótido sintético”

<400> 686
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24

<210> 687
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<212> ARN
<213> Secuencia artificial

<220>
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<223> /nota="Descripción de la secuencia artificial: Oligonucleótido
sintético"

<400> 687
cuccaaggga guaaaagagc ugau
24

<210> 688
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<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido
sintético"

<400> 688
uggauccaca agagugcuaa agcg
24

<210> 689
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido
sintético"

<400> 689
guucaauugg auccacaaga gugc
24

<210> 690
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<213> Secuencia artificial

<220>
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sintético"

<400> 690

uacuuguaac ugacaagcca ggga
24

<210> 691
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<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 691
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24

<210> 692
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<213> Secuencia artificial

<220>
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<400> 692
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24

<210> 693
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<220>
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<400> 693
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<210> 694
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<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido
sintético"

<400> 694
ucccuggcuu gucaguuaca agua
24

<210> 695
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<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido
sintético"

<400> 695
cagaguaaca gucugaguag gagc
24

<210> 696
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
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sintético"

<400> 696
uacuuuguuu agcaauacau ggua
24

<210> 697
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<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido
sintético"

<400> 697
uggcucaaau uguuacucuu caau
24

<210> 698
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 698
cuuucaaaga acuuugcaga gccu
24

<210> 699
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 699
guugaagcca uuuuguugcu cuuu
24

<210> 700
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 700
guugaagcca uuuuauugcu cuuu
24

<210> 701
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido

sintético”

<400> 701
uuuugaggcu cugcaaaguu cuuu
24

<210> 702
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota=“Descripción de la secuencia artificial: Oligonucleótido sintético”

<400> 702
aguuauuaau gcauagauau ucag
24

<210> 703
<211> 24
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<213> Secuencia artificial

<220>
<221> fuente
<223> /nota=“Descripción de la secuencia artificial: Oligonucleótido sintético”

<400> 703
uauaauaugc ccuguaauau aaua
24

<210> 704
<211> 24
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota=“Descripción de la secuencia artificial: Oligonucleótido sintético”

<400> 704
uaaaggccaa accucggcuu accu
24

<210> 705
<211> 24

<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido
sintético"

<400> 705
ucaauaucuu ugaaggacuc uggg
24

<210> 706
<211> 19
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<213> Mus musculus

<400> 706
agagtaacag tctgactgg
19

<210> 707
<211> 19
<212> ADN
<213> Mus musculus

<400> 707
gaaatgatca tcaaacaga
19

<210> 708
<211> 20
<212> ADN
<213> Mus musculus

<400> 708
cactagagta acagtctgac
20

<210> 709
<211> 19
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido
sintético"

<400> 709

ccagucagac uguuacucu
19

<210> 710
<211> 19
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 710
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19

<210> 711
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<213> Secuencia artificial

<220>
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<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 711
gucagacugu uacucuagug
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<210> 712
<211> 19
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<213> Homo sapiens

<400> 712
agagtaacag tctgagtag
19

<210> 713
<211> 19
<212> ADN
<213> Homo sapiens

<400> 713
gagatgatca tcaagcaga
19

<210> 714
<211> 20
<212> ADN
<213> Homo sapiens

<400> 714
caccagagta acagtctgag
20

<210> 715
<211> 19
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 715
cuacucagac uguuacucu
19

<210> 716
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<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 716
ucugcuugau gaucaucuc
19

<210> 717
<211> 20
<212> ARN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 717
cucagacugu uacucuggug
20

<210> 718
<211> 20
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<213> Homo sapiens

<400> 718
caccagagta acagtctgag
20

<210> 719
<211> 20
<212> ADN
<213> Homo sapiens

<400> 719
tattttgggt ttttgcaaaa
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<210> 720
<211> 20
<212> ADN
<213> Homo sapiens

<400> 720
agtaggagct aaaatatttt
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<210> 721
<211> 20
<212> ADN
<213> Homo sapiens

<400> 721
gagtaggagc taaaatattt
20

<210> 722
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<212> ADN
<213> Homo sapiens

<400> 722
accagagtaa cagtctgagt
20

<210> 723
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<212> ADN

<213> Homo sapiens

<400> 723
tcctactcag actgttactc
20

<210> 724
<211> 20
<212> ADN
<213> Homo sapiens

<400> 724
tactctggtg acacaacctg
20

<210> 725
<211> 20
<212> ADN
<213> Homo sapiens

<400> 725
gcagtttcct tagtaaccac
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<210> 726
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<400> 726
gacacaacct gtggttacta
20

<210> 727
<211> 20
<212> ADN
<213> Homo sapiens

<400> 727
tgtcaccaga gtaacagtct
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<210> 728
<211> 20
<212> ADN
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<400> 728

aggttgtgtc accagagtaa
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<210> 729
<211> 20
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<213> Homo sapiens

<400> 729
aaccacaggt tgtgtcacca
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<210> 730
<211> 20
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<400> 730
gtaaccacag gttgtgtcac
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<210> 731
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<400> 731
atttatttt ccttttattc
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<210> 732
<211> 20
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<400> 732
tttcctttta ttctagttga
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<210> 733
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<400> 733
tgattctgaa ttctttcaac
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<210> 734
<211> 20
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<400> 734
aattctttca actagaataa
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<210> 735
<211> 20
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<400> 735
ttattctagt tgaaagaatt
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<210> 736
<211> 20
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<400> 736
tagttgaaag aattcagaat
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<210> 737
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<400> 737
aattcagaat cagtgggatg
20

<210> 738
<211> 20
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<400> 738
attctttcaa ctagaataaa
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<210> 739
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<400> 739
ttgaaagaat tcagaatcag
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<210> 740
<211> 20
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<400> 740
tgaaagaatt cagaatcagt
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<210> 741
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<400> 741
actgttgcct ccggttctga
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<210> 742
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<400> 742
cagatctgtc aaatcgcctg
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<210> 743
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<400> 743
aaaacgccgc catttctcaa
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<400> 745
tatggatcaa gaaaaataga
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<210> 746
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cgcctgcagg taaaagcata
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<210> 747
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<400> 747
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<210> 748
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<210> 749
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acagatctgt tgagaaatgg
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<210> 750
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<212> ADN
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<210> 751
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ggcgttttca ttatgatata
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<210> 752
<211> 20
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atgatataaa gatatttaat
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<210> 753
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gatatttaat cagtggctaa
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agaaactgtt cagcttctgt
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gttttaaaat ttttatatta
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ttttatatta cagaatataa
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atattacaga atataaaaga
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gttcctgtaa gataccaaaa
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<210> 760
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<210> 762
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<210> 767
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<210> 769
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<210> 774
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sintético"

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sintético"

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cucagacugu uacucuggug
20

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sintético"

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20

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sintético"

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20

<210> 794
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<220>
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sintético"

<400> 794
aaauauuuua gcuccuacuc
20

<210> 795
<211> 20
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<220>
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sintético"

<400> 795
acucagacug uuacucuggu
20

<210> 796
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<400> 796
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sintético"

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<220>
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<210> 848
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<400> 848
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<210> 849
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<400> 849
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<210> 850
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<210> 852
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<210> 853
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sintético"

<400> 862
uugaacaucu ucucuuucau
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<210> 863
<211> 20
<212> ADN
<213> Canis lupis

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<210> 864
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sintético"

<400> 864
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<210> 865
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<213> Homo sapiens

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120

aagcctactg gagcaataaa gtttgaagaa cttttaccag gtttttttta tcgctgcctt
180

gatatacact tttcaaaatg ctttggtggg aagaagtaga ggactgttat gaaagagaag
240

atgttcaaaa gaaaacattc acaaaatggg taaatgcaca attttctaag tttgggaagc
300

agcatattga gaacctcttc agtgacctac aggatgggag gcgcctccta gacctcctcg
360

aaggcctgac agggcaaaaa ctgccaaaag aaaaaggatc cacaagagtt catgccctga
420

acaatgtcaa caaggcactg cgggttttgc agaacaataa tgttgattta gtgaatattg
480

gaagtactga catcgtagat ggaaatcata aactgactct tggtttgatt tggaatataa
540

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600

acagtgaaaa gattctcctg agctgggtcc gacaatcaac tcgtaattat ccacaggtta
660

atgtaatcaa cttcaccacc agctggtctg atggcctggc tttgaatgct ctcatccata
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780

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1080

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1260

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1380

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1440

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1560

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1740

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1860

aagacatcct tctcaaatgg caacgtctta ctgaagaaca gtgccttttt agtgcatggc
1920

tttcagaaaa agaagatgca gtgaacaaga ttcacacaac tggctttaaa gatcaaaatg
1980

aaatgttatc aagtcttcaa aaactggccg ttttaaaagc ggatctagaa aagaaaaagc
2040

aatccatggg caaactgtat tcactcaaac aagatcttct ttcaacactg aagaataagt
2100

cagtgaccca gaagacggaa gcatggctgg ataactttgc ccggtgttgg gataatttag
2160

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2460

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<400> 866
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Gly Lys Gln His Ile Glu Asn Leu Phe Ser Asp Leu Gln Asp Gly Arg
35 40 45

Arg Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Gln Lys Leu Pro Lys
50 55 60

Glu Lys Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Lys Ala

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65                  70                  75                  80

Leu Arg Val Leu Gln Asn Asn Asn Val Asp Leu Val Asn Ile Gly Ser
                85                  90                  95

Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Ile Trp
            100                 105                 110

Asn Ile Ile Leu His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met
        115                 120                 125

Ala Gly Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
    130                 135                 140

Arg Gln Ser Thr Arg Asn Tyr Pro Gln Val Asn Val Ile Asn Phe Thr
145                 150                 155                 160

Thr Ser Trp Ser Asp Gly Leu Ala Leu Asn Ala Leu Ile His Ser His
                165                 170                 175

Arg Pro Asp Leu Phe Asp Trp Asn Ser Val Val Cys Gln Gln Ser Ala
            180                 185                 190

Thr Gln Arg Leu Glu His Ala Phe Asn Ile Ala Arg Tyr Gln Leu Gly
        195                 200                 205

Ile Glu Lys Leu Leu Asp Pro Glu Asp Val Asp Thr Thr Tyr Pro Asp
    210                 215                 220

Lys Lys Ser Ile Leu Met Tyr Ile Thr Ser Leu Phe Gln Val Leu Pro
225                 230                 235                 240

Gln Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg
                245                 250                 255

Pro Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met
            260                 265                 270

His Tyr Ser Gln Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg
        275                 280                 285
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Thr Ser Ser Pro Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala
    290                 295                 300

Ala Tyr Val Thr Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln
305                 310                 315                 320

His Leu Glu Ala Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu
                325                 330                 335

Ser Glu Val Asn Leu Asp Arg Tyr Gln Thr Ala Leu Glu Glu Val Leu
            340                 345                 350

Ser Trp Leu Leu Ser Ala Glu Asp Thr Leu Gln Ala Gln Gly Glu Ile
        355                 360                 365

Ser Asn Asp Val Glu Val Val Lys Asp Gln Phe His Thr His Glu Gly
    370                 375                 380

Tyr Met Met Asp Leu Thr Ala His Gln Gly Arg Val Gly Asn Ile Leu
385                 390                 395                 400

Gln Leu Gly Ser Lys Leu Ile Gly Thr Gly Lys Leu Ser Glu Asp Glu
                405                 410                 415

Glu Thr Glu Val Gln Glu Gln Met Asn Leu Leu Asn Ser Arg Trp Glu
            420                 425                 430

Cys Leu Arg Val Ala Ser Met Glu Lys Gln Ser Asn Leu His Arg Val
        435                 440                 445

Leu Met Asp Leu Gln Asn Gln Lys Leu Lys Glu Leu Asn Asp Trp Leu
    450                 455                 460

Thr Lys Thr Glu Glu Arg Thr Arg Lys Met Glu Glu Glu Pro Leu Gly
465                 470                 475                 480

Pro Asp Leu Glu Asp Leu Lys Arg Gln Val Gln Gln His Lys Val Leu
                485                 490                 495

Gln Glu Asp Leu Glu Gln Glu Gln Val Arg Val Asn Ser Leu Thr His
```

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Met Val Val Val Val Asp Glu Ser Ser Gly Asp His Ala Thr Ala Ala
        515                 520                 525

Leu Glu Glu Gln Leu Lys Val Leu Gly Asp Arg Trp Ala Asn Ile Cys
    530                 535                 540

Arg Trp Thr Glu Asp Arg Trp Val Leu Leu Gln Asp Ile Leu Leu Lys
545                 550                 555                 560

Trp Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ala Trp Leu Ser
                565                 570                 575

Glu Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp
            580                 585                 590

Gln Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala
        595                 600                 605

Asp Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys
    610                 615                 620

Gln Asp Leu Leu Ser Thr Leu Lys Asn Lys Ser Val Thr Gln Lys Thr
625                 630                 635                 640

Glu Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln
                645                 650                 655

Lys Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr
            660                 665                 670

Gln Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val
        675                 680                 685

Thr Thr Arg Glu Gln Ile Leu Val Lys His Ala Gln Glu Glu Leu Pro
    690                 695                 700

Pro Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile
705                 710                 715                 720
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Arg Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr
                725                 730                 735

Arg Ser Glu Ala Val Leu Gln Ser Pro Glu Phe Ala Ile Phe Arg Lys
            740                 745                 750

Glu Gly Asn Phe Ser Asp Leu Lys Glu Lys Val Asn Ala Ile Glu Arg
        755                 760                 765

Glu Lys Ala Glu Lys Phe Arg Lys Leu Gln Asp Ala Ser Arg Ser Ala
    770                 775                 780

Gln Ala Leu Val Glu Gln Met Val Asn Glu Gly Val Asn Ala Asp Ser
785                 790                 795                 800

Ile Lys Gln Ala Ser Glu Gln Leu Asn Ser Arg Trp Ile Glu Phe Cys
                805                 810                 815

Gln Leu Leu Ser Glu Arg Leu Asn Trp Leu Glu Tyr Gln Asn Asn Ile
            820                 825                 830

Ile Ala Phe Tyr Asn Gln Leu Gln Gln Leu Glu Gln Met Thr Thr Thr
        835                 840                 845

Ala Glu Asn Trp Leu Lys Ile Gln Pro Thr Thr Pro Ser Glu Pro Thr
    850                 855                 860

Ala Ile Lys Ser Gln Leu Lys Ile Cys Lys Asp Glu Val Asn Arg Leu
865                 870                 875                 880

Ser Asp Leu Gln Pro Gln Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala
                885                 890                 895

Leu Lys Glu Lys Gly Gln Gly Pro Met Phe Leu Asp Ala Asp Phe Val
            900                 905                 910

Ala Phe Thr Asn His Phe Lys Gln Val Phe Ser Asp Val Gln Ala Arg
        915                 920                 925

Glu Lys Glu Leu Gln Thr Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr
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    930                 935                 940

Gln Glu Thr Met Ser Ala Ile Arg Thr Trp Val Gln Gln Ser Glu Thr
945                 950                 955                 960

Lys Leu Ser Ile Pro Gln Leu Ser Val Thr Asp Tyr Glu Ile Met Glu
                965                 970                 975

Gln Arg Leu Gly Glu Leu Gln Ala Leu Gln Ser Ser Leu Gln Glu Gln
            980                 985                 990

Gln Ser Gly Leu Tyr Tyr Leu Ser  Thr Thr Val Lys Glu  Met Ser Lys
        995                 1000                1005

Lys Ala  Pro Ser Glu Ile Ser  Arg Lys Tyr Gln Ser  Glu Phe Glu
    1010                1015                1020

Glu Ile  Glu Gly Arg Trp Lys  Lys Leu Ser Ser Gln  Leu Val Glu
    1025                1030                1035

His Cys  Gln Lys Leu Glu Glu  Gln Met Asn Lys Leu  Arg Lys Ile
    1040                1045                1050

Gln Asn  His Ile Gln Thr Leu  Lys Lys Trp Met Ala  Glu Val Asp
    1055                1060                1065

Val Phe  Leu Lys Glu Glu Trp  Pro Ala Leu Gly Asp  Ser Glu Ile
    1070                1075                1080

Leu Lys  Lys Gln Leu Lys Gln  Cys Arg Leu Leu Val  Ser Asp Ile
    1085                1090                1095

Gln Thr  Ile Gln Pro Ser Leu  Asn Ser Val Asn Glu  Gly Gly Gln
    1100                1105                1110

Lys Ile  Lys Asn Glu Ala Glu  Pro Glu Phe Ala Ser  Arg Leu Glu
    1115                1120                1125

Thr Glu  Leu Lys Glu Leu Asn  Thr Gln Trp Asp His  Met Cys Gln
    1130                1135                1140
```

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Gln Val  Tyr Ala Arg Lys Glu  Ala Leu Lys Gly Gly  Leu Glu Lys
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Thr Val  Ser Leu Gln Lys Asp  Leu Ser Glu Met His  Glu Trp Met
    1160                1165                1170

Thr Gln  Ala Glu Glu Glu Tyr  Leu Glu Arg Asp Phe  Glu Tyr Lys
    1175                1180                1185

Thr Pro  Asp Glu Leu Gln Lys  Ala Val Glu Glu Met  Lys Arg Ala
    1190                1195                1200

Lys Glu  Glu Ala Gln Gln Lys  Glu Ala Lys Val Lys  Leu Leu Thr
    1205                1210                1215

Glu Ser  Val Asn Ser Val Ile  Ala Gln Ala Pro Pro  Val Ala Gln
    1220                1225                1230

Glu Ala  Leu Lys Lys Glu Leu  Glu Thr Leu Thr Thr  Asn Tyr Gln
    1235                1240                1245

Trp Leu  Cys Thr Arg Leu Asn  Gly Lys Cys Lys Thr  Leu Glu Glu
    1250                1255                1260

Val Trp  Ala Cys Trp His Glu  Leu Leu Ser Tyr Leu  Glu Lys Ala
    1265                1270                1275

Asn Lys  Trp Leu Asn Glu Val  Glu Phe Lys Leu Lys  Thr Thr Glu
    1280                1285                1290

Asn Ile  Pro Gly Gly Ala Glu  Glu Ile Ser Glu Val  Leu Asp Ser
    1295                1300                1305

Leu Glu  Asn Leu Met Arg His  Ser Glu Asp Asn Pro  Asn Gln Ile
    1310                1315                1320

Arg Ile  Leu Ala Gln Thr Leu  Thr Asp Gly Gly Val  Met Asp Glu
    1325                1330                1335

Leu Ile  Asn Glu Glu Leu Glu  Thr Phe Asn Ser Arg  Trp Arg Glu
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Leu His Glu Glu Ala Val Arg Arg Gln Lys Leu Leu Glu Gln Ser
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Ile Gln Ser Ala Gln Glu Thr Glu Lys Ser Leu His Leu Ile Gln
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Glu Ser Leu Thr Phe Ile Asp Lys Gln Leu Ala Ala Tyr Ile Ala
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Asp Lys Val Asp Ala Ala Gln Met Pro Gln Glu Ala Gln Lys Ile
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Lys His Asn Gln Gly Lys Glu Ala Ala Gln Arg Val Leu Ser Gln
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Ile Asp Val Ala Gln Lys Lys Leu Gln Asp Val Ser Met Lys Phe
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Arg Leu Phe Gln Lys Pro Ala Asn Phe Glu Gln Arg Leu Gln Glu
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Ser Lys Met Ile Leu Asp Glu Val Lys Met His Leu Pro Ala Leu
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Glu Thr Lys Ser Val Glu Gln Glu Val Val Gln Ser Gln Leu Asn
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His Cys Val Asn Leu Tyr Lys Ser Leu Ser Glu Val Lys Ser Glu
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Gln Thr Glu Asn Pro Lys Glu Leu Asp Glu Arg Val Thr Ala Leu
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Lys Leu His Tyr Asn Glu Leu Gly Ala Lys Val Thr Glu Arg Lys
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Gln Gln Leu Glu Lys Cys Leu Lys Leu Ser Arg Lys Met Arg Lys
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Glu Met Asn Val Leu Thr Glu Trp Leu Ala Ala Thr Asp Met Glu
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Glu Trp Leu Asn Leu Leu Leu Glu Tyr Gln Lys His Met Glu Thr
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Asp Thr Leu Leu Asp Glu Ser Glu Lys Lys Lys Pro Gln Gln Lys
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Glu Asp Val Leu Lys Arg Leu Lys Ala Glu Leu Asn Asp Ile Arg
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Pro Lys Val Asp Ser Thr Arg Asp Gln Ala Ala Asn Leu Met Ala
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Asp Asn Glu Gly Thr Val Lys Glu Leu Leu Gln Arg Gly Asp Asn
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Leu Gln Gln Arg Ile Thr Asp Glu Arg Lys Arg Glu Glu Ile Lys
1835 1840 1845

Ile Lys Gln Gln Leu Leu Gln Thr Lys His Asn Ala Leu Lys Asp
1850 1855 1860

Leu Arg Ser Gln Arg Arg Lys Lys Ala Leu Glu Ile Ser His Gln
1865 1870 1875

Trp Tyr Gln Tyr Lys Arg Gln Ala Asp Asp Leu Leu Lys Cys Leu
1880 1885 1890

Asp Asp Ile Glu Lys Lys Leu Ala Ser Leu Pro Glu Pro Arg Asp
1895 1900 1905

Glu Arg Lys Ile Lys Glu Ile Asp Arg Glu Leu Gln Lys Lys Lys
1910 1915 1920

Glu Glu Leu Asn Ala Val Arg Arg Gln Ala Glu Gly Leu Ser Glu
1925 1930 1935

Asp Gly Ala Ala Met Ala Val Glu Pro Thr Gln Ile Gln Leu Ser
1940 1945 1950

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Lys Arg  Trp Arg Glu Ile Glu  Ser Lys Phe Ala Gln  Phe Arg Arg
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Leu Asn  Phe Ala Gln Ile His  Thr Val Arg Glu Glu  Thr Met Met
    1970                1975                1980

Val Met  Thr Glu Asp Met Pro  Leu Glu Ile Ser Tyr  Val Pro Ser
    1985                1990                1995

Thr Tyr  Leu Thr Glu Ile Thr  His Val Ser Gln Ala  Leu Leu Glu
    2000                2005                2010

Val Glu  Gln Leu Leu Asn Ala  Pro Asp Leu Cys Ala  Lys Asp Phe
    2015                2020                2025

Glu Asp  Leu Phe Lys Gln Glu  Glu Ser Leu Lys Asn  Ile Lys Asp
    2030                2035                2040

Ser Leu  Gln Gln Ser Ser Gly  Arg Ile Asp Ile Ile  His Ser Lys
    2045                2050                2055

Lys Thr  Ala Ala Leu Gln Ser  Ala Thr Pro Val Glu  Arg Val Lys
    2060                2065                2070

Leu Gln  Glu Ala Leu Ser Gln  Leu Asp Phe Gln Trp  Glu Lys Val
    2075                2080                2085

Asn Lys  Met Tyr Lys Asp Arg  Gln Gly Arg Phe Asp  Arg Ser Val
    2090                2095                2100

Glu Lys  Trp Arg Arg Phe His  Tyr Asp Ile Lys Ile  Phe Asn Gln
    2105                2110                2115

Trp Leu  Thr Glu Ala Glu Gln  Phe Leu Arg Lys Thr  Gln Ile Pro
    2120                2125                2130

Glu Asn  Trp Glu His Ala Lys  Tyr Lys Trp Tyr Leu  Lys Ile Ser
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Gly Lys Gln His Ile Glu Asn Leu Phe Ser Asp Leu Gln Asp Gly Arg
        35                  40                  45

Arg Leu Leu Asp Leu Leu Glu Gly Leu Thr Gly Gln Lys Leu Pro Lys
    50                  55                  60

Glu Lys Gly Ser Thr Arg Val His Ala Leu Asn Asn Val Asn Lys Ala
65                  70                  75                  80

Leu Arg Val Leu Gln Asn Asn Asn Val Asp Leu Val Asn Ile Gly Ser
                85                  90                  95

Thr Asp Ile Val Asp Gly Asn His Lys Leu Thr Leu Gly Leu Ile Trp
            100                 105                 110

Asn Ile Ile Leu His Trp Gln Val Lys Asn Val Met Lys Asn Ile Met
        115                 120                 125

Ala Gly Leu Gln Gln Thr Asn Ser Glu Lys Ile Leu Leu Ser Trp Val
    130                 135                 140

Arg Gln Ser Thr Arg Asn Tyr Pro Gln Val Asn Val Ile Asn Phe Thr
145                 150                 155                 160

Thr Ser Trp Ser Asp Gly Leu Ala Leu Asn Ala Leu Ile His Ser His
                165                 170                 175

Arg Pro Asp Leu Phe Asp Trp Asn Ser Val Val Cys Gln Gln Ser Ala
            180                 185                 190

Thr Gln Arg Leu Glu His Ala Phe Asn Ile Ala Arg Tyr Gln Leu Gly
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        195                 200                 205

Ile Glu Lys Leu Leu Asp Pro Glu Asp Val Asp Thr Thr Tyr Pro Asp
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Lys Lys Ser Ile Leu Met Tyr Ile Thr Ser Leu Phe Gln Val Leu Pro
225                 230                 235                 240

Gln Gln Val Ser Ile Glu Ala Ile Gln Glu Val Glu Met Leu Pro Arg
                245                 250                 255

Pro Pro Lys Val Thr Lys Glu Glu His Phe Gln Leu His His Gln Met
            260                 265                 270

His Tyr Ser Gln Gln Ile Thr Val Ser Leu Ala Gln Gly Tyr Glu Arg
        275                 280                 285

Thr Ser Ser Pro Lys Pro Arg Phe Lys Ser Tyr Ala Tyr Thr Gln Ala
    290                 295                 300

Ala Tyr Val Thr Thr Ser Asp Pro Thr Arg Ser Pro Phe Pro Ser Gln
305                 310                 315                 320

His Leu Glu Ala Pro Glu Asp Lys Ser Phe Gly Ser Ser Leu Met Glu
                325                 330                 335

Ser Glu Val Asn Leu Asp Arg Tyr Gln Thr Ala Leu Glu Glu Val Leu
            340                 345                 350

Ser Trp Leu Leu Ser Ala Glu Asp Thr Leu Gln Ala Gln Gly Glu Ile
        355                 360                 365

Ser Asn Asp Val Glu Val Val Lys Asp Gln Phe His Thr His Glu Gly
    370                 375                 380

Tyr Met Met Asp Leu Thr Ala His Gln Gly Arg Val Gly Asn Ile Leu
385                 390                 395                 400

Gln Leu Gly Ser Lys Leu Ile Gly Thr Gly Lys Leu Ser Glu Asp Glu
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```
Glu Thr Glu Val Gln Glu Gln Met Asn Leu Leu Asn Ser Arg Trp Glu
            420                 425                 430

Cys Leu Arg Val Ala Ser Met Glu Lys Gln Ser Asn Leu His Arg Val
        435                 440                 445

Leu Met Asp Leu Gln Asn Gln Lys Leu Lys Glu Leu Asn Asp Trp Leu
    450                 455                 460

Thr Lys Thr Glu Glu Arg Thr Arg Lys Met Glu Glu Glu Pro Leu Gly
465                 470                 475                 480

Pro Asp Leu Glu Asp Leu Lys Arg Gln Val Gln Gln His Lys Val Leu
                485                 490                 495

Gln Glu Asp Leu Glu Gln Glu Gln Val Arg Val Asn Ser Leu Thr His
            500                 505                 510

Met Val Val Val Val Asp Glu Ser Ser Gly Asp His Ala Thr Ala Ala
        515                 520                 525

Leu Glu Glu Gln Leu Lys Val Leu Gly Asp Arg Trp Ala Asn Ile Cys
    530                 535                 540

Arg Trp Thr Glu Asp Arg Trp Val Leu Leu Gln Asp Ile Leu Leu Lys
545                 550                 555                 560

Trp Gln Arg Leu Thr Glu Glu Gln Cys Leu Phe Ser Ala Trp Leu Ser
                565                 570                 575

Glu Lys Glu Asp Ala Val Asn Lys Ile His Thr Thr Gly Phe Lys Asp
            580                 585                 590

Gln Asn Glu Met Leu Ser Ser Leu Gln Lys Leu Ala Val Leu Lys Ala
        595                 600                 605

Asp Leu Glu Lys Lys Lys Gln Ser Met Gly Lys Leu Tyr Ser Leu Lys
    610                 615                 620

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

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Glu Ala Trp Leu Asp Asn Phe Ala Arg Cys Trp Asp Asn Leu Val Gln
645 650 655

Lys Leu Glu Lys Ser Thr Ala Gln Ile Ser Gln Ala Val Thr Thr Thr
660 665 670

Gln Pro Ser Leu Thr Gln Thr Thr Val Met Glu Thr Val Thr Thr Val
675 680 685

Thr Thr Arg Glu Gln Ile Leu Val Lys His Ala Gln Glu Glu Leu Pro
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Pro Pro Pro Pro Gln Lys Lys Arg Gln Ile Thr Val Asp Ser Glu Ile
705 710 715 720

Arg Lys Arg Leu Asp Val Asp Ile Thr Glu Leu His Ser Trp Ile Thr
725 730 735

Arg Ser Glu Ala Val Leu Gln Ser Pro Glu Phe Ala Ile Phe Arg Lys
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Glu Gly Asn Phe Ser Asp Leu Lys Glu Lys Val Asn Ala Ile Glu Arg
755 760 765

Glu Lys Ala Glu Lys Phe Arg Lys Leu Gln Asp Ala Ser Arg Ser Ala
770 775 780

Gln Ala Leu Val Glu Gln Met Val Asn Glu Gly Val Asn Ala Asp Ser
785 790 795 800

Ile Lys Gln Ala Ser Glu Gln Leu Asn Ser Arg Trp Ile Glu Phe Cys
805 810 815

Gln Leu Leu Ser Glu Arg Leu Asn Trp Leu Glu Tyr Gln Asn Asn Ile
820 825 830

Ile Ala Phe Tyr Asn Gln Leu Gln Gln Leu Glu Gln Met Thr Thr Thr
835 840 845

```
Ala Glu Asn Trp Leu Lys Ile Gln Pro Thr Thr Pro Ser Glu Pro Thr
    850                 855                 860

Ala Ile Lys Ser Gln Leu Lys Ile Cys Lys Asp Glu Val Asn Arg Leu
865                 870                 875                 880

Ser Asp Leu Gln Pro Gln Ile Glu Arg Leu Lys Ile Gln Ser Ile Ala
                885                 890                 895

Leu Lys Glu Lys Gly Gln Gly Pro Met Phe Leu Asp Ala Asp Phe Val
            900                 905                 910

Ala Phe Thr Asn His Phe Lys Gln Val Phe Ser Asp Val Gln Ala Arg
        915                 920                 925

Glu Lys Glu Leu Gln Thr Ile Phe Asp Thr Leu Pro Pro Met Arg Tyr
    930                 935                 940

Gln Glu Thr Met Ser Ala Ile Arg Thr Trp Val Gln Gln Ser Glu Thr
945                 950                 955                 960

Lys Leu Ser Ile Pro Gln Leu Ser Val Thr Asp Tyr Glu Ile Met Glu
                965                 970                 975

Gln Arg Leu Gly Glu Leu Gln Ala Leu Gln Ser Ser Leu Gln Glu Gln
            980                 985                 990

Gln Ser Gly Leu Tyr Tyr Leu Ser  Thr Thr Val Lys Glu  Met Ser Lys
        995                 1000                1005

Lys Ala  Pro Ser Glu Ile Ser  Arg Lys Tyr Gln Ser  Glu Phe Glu
    1010                1015                1020

Glu Ile  Glu Gly Arg Trp Lys  Lys Leu Ser Ser Gln  Leu Val Glu
    1025                1030                1035

His Cys  Gln Lys Leu Glu Glu  Gln Met Asn Lys Leu  Arg Lys Ile
    1040                1045                1050

Gln Asn  His Ile Gln Thr Leu  Lys Lys Trp Met Ala  Glu Val Asp
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Val Phe  Leu Lys Glu Glu Trp  Pro Ala Leu Gly Asp  Ser Glu Ile
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Leu Lys  Lys Gln Leu Lys Gln  Cys Arg Leu Leu Val  Ser Asp Ile
    1085                1090                1095

Gln Thr  Ile Gln Pro Ser Leu  Asn Ser Val Asn Glu  Gly Gly Gln
    1100                1105                1110

Lys Ile  Lys Asn Glu Ala Glu  Pro Glu Phe Ala Ser  Arg Leu Glu
    1115                1120                1125

Thr Glu  Leu Lys Glu Leu Asn  Thr Gln Trp Asp His  Met Cys Gln
    1130                1135                1140

Gln Val  Tyr Ala Arg Lys Glu  Ala Leu Lys Gly Gly  Leu Glu Lys
    1145                1150                1155

Thr Val  Ser Leu Gln Lys Asp  Leu Ser Glu Met His  Glu Trp Met
    1160                1165                1170

Thr Gln  Ala Glu Glu Glu Tyr  Leu Glu Arg Asp Phe  Glu Tyr Lys
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Thr Pro  Asp Glu Leu Gln Lys  Ala Val Glu Glu Met  Lys Arg Ala
    1190                1195                1200

Lys Glu  Glu Ala Gln Gln Lys  Glu Ala Lys Val Lys  Leu Leu Thr
    1205                1210                1215

Glu Ser  Val Asn Ser Val Ile  Ala Gln Ala Pro Pro  Val Ala Gln
    1220                1225                1230

Glu Ala  Leu Lys Lys Glu Leu  Glu Thr Leu Thr Thr  Asn Tyr Gln
    1235                1240                1245

Trp Leu  Cys Thr Arg Leu Asn  Gly Lys Cys Lys Thr  Leu Glu Glu
    1250                1255                1260
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Val Trp  Ala Cys Trp His Glu  Leu Leu Ser Tyr Leu  Glu Lys Ala
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Asn Lys  Trp Leu Asn Glu Val  Glu Phe Lys Leu Lys  Thr Thr Glu
    1280                1285                1290

Asn Ile  Pro Gly Gly Ala Glu  Glu Ile Ser Glu Val  Leu Asp Ser
    1295                1300                1305

Leu Glu  Asn Leu Met Arg His  Ser Glu Asp Asn Pro  Asn Gln Ile
    1310                1315                1320

Arg Ile  Leu Ala Gln Thr Leu  Thr Asp Gly Gly Val  Met Asp Glu
    1325                1330                1335

Leu Ile  Asn Glu Glu Leu Glu  Thr Phe Asn Ser Arg  Trp Arg Glu
    1340                1345                1350

Leu His  Glu Glu Ala Val Arg  Arg Gln Lys Leu Leu  Glu Gln Ser
    1355                1360                1365

Ile Gln  Ser Ala Gln Glu Thr  Glu Lys Ser Leu His  Leu Ile Gln
    1370                1375                1380

Glu Ser  Leu Thr Phe Ile Asp  Lys Gln Leu Ala Ala  Tyr Ile Ala
    1385                1390                1395

Asp Lys  Val Asp Ala Ala Gln  Met Pro Gln Glu Ala  Gln Lys Ile
    1400                1405                1410

Gln Ser  Asp Leu Thr Ser His  Glu Ile Ser Leu Glu  Glu Met Lys
    1415                1420                1425

Lys His  Asn Gln Gly Lys Glu  Ala Ala Gln Arg Val  Leu Ser Gln
    1430                1435                1440

Ile Asp  Val Ala Gln Lys Lys  Leu Gln Asp Val Ser  Met Lys Phe
    1445                1450                1455

Arg Leu  Phe Gln Lys Pro Ala  Asn Phe Glu Gln Arg  Leu Gln Glu
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Ser Lys Met Ile Leu Asp Glu Val Lys Met His Leu Pro Ala Leu
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Glu Thr Lys Ser Val Glu Gln Glu Val Val Gln Ser Gln Leu Asn
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His Cys Val Asn Leu Tyr Lys Ser Leu Ser Glu Val Lys Ser Glu
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Val Glu Met Val Ile Lys Thr Gly Arg Gln Ile Val Gln Lys Lys
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1535 1540 1545

Lys Leu His Tyr Asn Glu Leu Gly Ala Lys Val Thr Glu Arg Lys
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Gln Gln Leu Glu Lys Cys Leu Lys Leu Ser Arg Lys Met Arg Lys
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Glu Met Asn Val Leu Thr Glu Trp Leu Ala Ala Thr Asp Met Glu
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Leu Thr Lys Arg Ser Ala Val Glu Gly Met Pro Ser Asn Leu Asp
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Ser Leu Leu Asn Ser Asn Trp Ile Ala Val Thr Ser Arg Ala Glu
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Phe Asp  Gln Asn Val Asp His  Ile Thr Lys Trp Ile  Ile Gln Ala
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Asp Thr  Leu Leu Asp Glu Ser  Glu Lys Lys Lys Pro  Gln Gln Lys
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Glu Asp  Val Leu Lys Arg Leu  Lys Ala Glu Leu Asn  Asp Ile Arg
    1715                1720                1725

Pro Lys  Val Asp Ser Thr Arg  Asp Gln Ala Ala Asn  Leu Met Ala
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Asn Arg  Gly Asp His Cys Arg  Lys Leu Val Glu Pro  Gln Ile Ser
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Glu Leu  Asn His Arg Phe Ala  Ala Ile Ser His Arg  Ile Lys Thr
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Gly Lys  Ala Ser Ile Pro Leu  Lys Glu Leu Glu Gln  Phe Asn Ser
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Asp Ile  Gln Lys Leu Leu Glu  Pro Leu Glu Ala Glu  Ile Gln Gln
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Gly Val  Asn Leu Lys Glu Glu  Asp Phe Asn Lys Asp  Met Asn Glu
    1805                1810                1815

Asp Asn  Glu Gly Thr Val Lys  Glu Leu Leu Gln Arg  Gly Asp Asn
    1820                1825                1830

Leu Gln  Gln Arg Ile Thr Asp  Glu Arg Lys Arg Glu  Glu Ile Lys
    1835                1840                1845

Ile Lys  Gln Gln Leu Leu Gln  Thr Lys His Asn Ala  Leu Lys Asp
    1850                1855                1860

Leu Arg  Ser Gln Arg Arg Lys  Lys Ala Leu Glu Ile  Ser His Gln
```

1865 1870 1875

Trp Tyr Gln Tyr Lys Arg Gln Ala Asp Asp Leu Leu Lys Cys Leu
1880 1885 1890

Asp Asp Ile Glu Lys Lys Leu Ala Ser Leu Pro Glu Pro Arg Asp
1895 1900 1905

Glu Arg Lys Ile Lys Met Asn
1910 1915

<210> 869
<211> 2158
<212> PRT
<213> Mus musculus

<400> 869
Met Trp Trp Val Asp Cys Tyr Arg Asp Val Lys Lys Thr Thr Lys Trp
1 5 10 15

Asn Ala Ser Lys Gly Lys His Asp Asn Ser Asp Asp Gly Lys Arg Asp
20 25 30

Gly Thr Gly Lys Lys Lys Gly Ser Thr Arg Val His Ala Asn Asn Val
35 40 45

Asn Lys Ala Arg Val Lys Asn Asn Val Asp Val Asn Gly Ser Thr Asp
50 55 60

Val Asp Gly Asn His Lys Thr Gly Trp Asn His Trp Val Lys Asn Val
65 70 75 80

Met Lys Thr Met Ala Gly Thr Asn Ser Lys Ser Trp Val Arg Ser Thr
85 90 95

Arg Asn Tyr Val Asn Val Asn Thr Ser Ser Trp Ser Asp Gly Ala Asn
100 105 110

Ala His Ser His Arg Asp Asp Trp Asn Ser Val Val Ser His Ser Ala
115 120 125

Thr Arg His Ala Asn Ala Lys Cys Gly Lys Asp Asp Val Ala Thr Thr

```
    130                 135                 140

Tyr Asp Lys Lys Ser Met Tyr Thr Ser Val Val Ser Ala Val Met Arg
145                 150                 155                 160

Thr Ser Ser Lys Val Thr Arg His His His Met His Tyr Ser Thr Val
                165                 170                 175

Ser Ala Gly Tyr Thr Ser Ser Ser Lys Arg Lys Ser Tyr Ala Thr Ala
            180                 185                 190

Ala Tyr Val Ala Thr Ser Asp Ser Thr Ser Tyr Ser His Ala Arg Asp
        195                 200                 205

Lys Ser Asp Ser Ser Met Thr Val Asn Asp Ser Tyr Thr Ala Val Ser
    210                 215                 220

Trp Ser Ala Asp Thr Arg Ala Gly Ser Asn Asp Val Val Lys His Ala
225                 230                 235                 240

His Gly Met Met Asp Thr Ser His Gly Val Gly Asn Val Gly Ser Val
                245                 250                 255

Gly Lys Gly Lys Ser Asp Ala Val Met Asn Asn Ser Arg Trp Cys Arg
            260                 265                 270

Val Ala Ser Met Lys Ser Lys His Lys Val Met Asp Asn Lys Lys Asp
        275                 280                 285

Asp Trp Thr Lys Thr Arg Thr Lys Lys Met Gly Asp Asp Lys Cys Val
    290                 295                 300

His Lys Val Asp Val Arg Val Asn Ser Thr His Met Val Val Val Val
305                 310                 315                 320

Asp Ser Ser Gly Asp His Ala Thr Ala Ala Lys Val Gly Asp Arg Trp
                325                 330                 335

Ala Asn Cys Arg Trp Thr Asp Arg Trp Val Asp Lys Trp His Thr Cys
            340                 345                 350
```

```
Ser Thr Trp Ser Lys Asp Ala Met Lys Asn Thr Ser Gly Lys Asp Asn
        355                 360                 365

Met Met Ser Ser His Lys Ser Thr Lys Asp Lys Lys Lys Thr Met Lys
    370                 375                 380

Ser Ser Asn Asp Ser Ala Lys Asn Lys Ser Val Thr Lys Met Trp Met
385                 390                 395                 400

Asn Ala Arg Trp Asp Asn Thr Lys Lys Ser Ser Ala Ser Ala Val Thr
                405                 410                 415

Thr Thr Ser Thr Thr Thr Val Met Thr Val Thr Met Val Thr Thr Arg
            420                 425                 430

Met Val Lys His Ala Lys Lys Arg Thr Val Asp Ser Arg Lys Arg Asp
        435                 440                 445

Val Asp Thr His Ser Trp Thr Arg Ser Ala Val Ser Ser Ala Val Tyr
    450                 455                 460

Arg Lys Gly Asn Ser Asp Lys Val Asn Ala Ala Arg Lys Ala Lys Arg
465                 470                 475                 480

Lys Asp Ala Ser Arg Ser Ala Ala Val Met Ala Asn Gly Val Asn Ala
                485                 490                 495

Ser Arg Ala Ser Asn Ser Arg Trp Thr Cys Ser Arg Val Asn Trp Tyr
            500                 505                 510

Thr Asn Thr Tyr Asn Met Thr Thr Thr Ala Asn Lys Thr Ser Thr Thr
        515                 520                 525

Ser Thr Ala Lys Ser Lys Cys Lys Asp Val Asn Arg Ser Ala Lys Ser
    530                 535                 540

Lys Lys Gly Gly Met Asp Ala Asp Val Ala Thr Asn His Asn His Asp
545                 550                 555                 560

Gly Val Arg Ala Lys Lys Thr Asp Thr Met Arg Tyr Thr Met Ser Ser
```

```
                565                 570                 575

Arg Thr Trp Ser Ser Lys Ser Val Tyr Ser Val Thr Tyr Met Arg Gly
            580                 585                 590

Lys Ala Ser Ser Lys Asn Gly Asn Tyr Ser Asp Thr Val Lys Met Ala
        595                 600                 605

Lys Lys Ala Ser Cys Lys Tyr Ser Gly His Trp Lys Lys Ser Ser Val
    610                 615                 620

Ser Cys Lys His Met Asn Lys Arg Lys Asn His Lys Thr Lys Trp Met
625                 630                 635                 640

Ala Val Asp Val Lys Trp Ala Gly Asp Ala Lys Lys Lys Cys Arg Val
                645                 650                 655

Gly Asp Thr Ser Asn Ser Val Asn Gly Gly Lys Lys Ser Ala Ala Ser
            660                 665                 670

Arg Thr Arg Asn Thr Trp Asp His Cys Arg Val Tyr Thr Arg Lys Ala
        675                 680                 685

Lys Ala Gly Asp Lys Thr Val Ser Lys Asp Ser Met His Trp Met Thr
    690                 695                 700

Ala Tyr Arg Asp Tyr Lys Thr Asp Thr Ala Val Met Lys Arg Ala Lys
705                 710                 715                 720

Ala Lys Thr Lys Val Lys Thr Thr Val Asn Ser Val Ala His Ala Ser
                725                 730                 735

Ala Ala Lys Lys Thr Thr Thr Asn Tyr Trp Cys Thr Arg Asn Gly Lys
            740                 745                 750

Cys Lys Thr Val Trp Ala Cys Trp His Ser Tyr Lys Ala Asn Lys Trp
        755                 760                 765

Asn Val Lys Lys Thr Met Asn Val Ala Gly Thr Val Ser Asn Met His
    770                 775                 780
```

```
His Ser Asn Asn Arg Ala Thr Thr Asp Gly Gly Val Met Asp Asn Thr
785                 790                 795                 800

Asn Ser Arg Trp Arg His Ala Val Arg Lys Lys Ser Ser Ala Lys Ser
                805                 810                 815

His Ser Asp Lys Ala Ala Tyr Thr Asp Lys Val Asp Ala Ala Met Ala
            820                 825                 830

Lys Ser Asp Thr Ser His Ser Met Lys Lys His Asn Gly Lys Asp Ala
        835                 840                 845

Asn Arg Val Ser Asp Val Ala Lys Lys Asp Val Ser Met Lys Arg Lys
    850                 855                 860

Ala Asn Arg Ser Lys Met Asp Val Lys Met His Ala Thr Lys Ser Val
865                 870                 875                 880

Val Ser Ser His Cys Val Asn Tyr Lys Ser Ser Val Lys Ser Val Met
                885                 890                 895

Val Lys Thr Gly Arg Val Lys Lys Thr Asn Lys Asp Arg Val Thr Ala
            900                 905                 910

Lys His Tyr Asn Gly Ala Lys Val Thr Arg Lys Lys Cys Lys Ser Arg
        915                 920                 925

Lys Met Arg Lys Met Asn Val Thr Trp Ala Ala Thr Asp Thr Thr Lys
    930                 935                 940

Arg Ser Ala Val Gly Met Ser Asn Asp Ser Val Ala Trp Gly Lys Ala
945                 950                 955                 960

Thr Lys Lys Lys Ala His Lys Ser Val Thr Gly Ser Lys Met Val Gly
                965                 970                 975

Lys Lys Thr Val Asp Lys Ser Asn Ser Asn Trp Ala Val Thr Ser Arg
            980                 985                 990

Val Trp Asn Tyr Lys His Met Thr  Asp Asn Thr Lys Trp  His Ala Asp
```

995 1000 1005

Asp Ser Lys Lys Lys Lys Asp Lys Arg Lys Ala Met Asn Asp Met
1010 1015 1020

Arg Lys Val Asp Ser Thr Arg Asp Ala Ala Lys Met Ala Asn Arg
1025 1030 1035

Gly Asp His Cys Arg Lys Val Val Ser Asn Arg Arg Ala Ala Ser
1040 1045 1050

His Arg Lys Thr Gly Lys Ala Ser Lys Asn Ser Asp Lys Ala Gly
1055 1060 1065

Val Asn Lys Asp Asn Lys Asp Met Ser Asp Asn Gly Thr Val Asn
1070 1075 1080

Arg Gly Asp Asn Arg Thr Asp Arg Lys Arg Lys Lys Thr Lys His
1085 1090 1095

Asn Ala Lys Asp Arg Ser Arg Arg Lys Lys Ala Ser His Trp Tyr
1100 1105 1110

Tyr Lys Arg Ala Asp Asp Lys Cys Asp Lys Lys Ala Ser Arg Asp
1115 1120 1125

Arg Lys Lys Asp Arg Lys Lys Lys Asn Ala Val Arg Arg Ala Gly
1130 1135 1140

Ser Asn Gly Ala Ala Met Ala Val Thr Ser Lys Arg Trp Arg Ser
1145 1150 1155

Asn Ala Arg Arg Asn Ala His Thr His Thr Met Val Val Thr Thr
1160 1165 1170

Asp Met Asp Val Ser Tyr Val Ser Thr Tyr Thr Ser His Ala Ser
1175 1180 1185

Val Asp His Asn Thr Cys Ala Lys Asp Asp Lys Ser Lys Asn Lys
1190 1195 1200

```
Asp Asn  Ser Gly Arg Asp His  Lys Lys Lys Thr Ala  Ala Ser Ala
    1205                 1210                 1215

Thr Ser  Met Lys Val Lys Val  Ala Val Ala Met Asp  Gly Lys His
    1220                 1225                 1230

Arg Met  Tyr Lys Arg Gly Arg  Asp Arg Ser Val Lys  Trp Arg His
    1235                 1240                 1245

His Tyr  Asp Met Lys Val Asn  Trp Asn Val Lys Lys  Thr Asn Asn
    1250                 1255                 1260

Trp His  Ala Lys Tyr Lys Trp  Tyr Lys Asp Gly Gly  Arg Ala Val
    1265                 1270                 1275

Val Arg  Thr Asn Ala Thr Gly  Ser Ser Lys Thr Asp  Val Asn Lys
    1280                 1285                 1290

Gly Ser  Ser Arg Trp His Asp  Cys Lys Ala Arg Arg  Lys Arg Lys
    1295                 1300                 1305

Asn Val  Ser Arg Asp Asn Val  Trp Ala Asp Asn Ala  Thr Gly Asp
    1310                 1315                 1320

Lys Val  Lys Ala Arg Gly Lys  Asn Thr Gly Gly Ala  Val Val Ser
    1325                 1330                 1335

Ala Arg  Asp Lys Lys Lys Lys  Thr Asn Trp Lys Val  Ser Arg Ala
    1340                 1345                 1350

Lys Gly  Val His Lys Asp Arg  Asp His Trp Ser Arg  Asn Tyr Asn
    1355                 1360                 1365

Ser Ala  Gly Asp Lys Val Thr  Val His Gly Lys Ala  Asp Val Arg
    1370                 1375                 1380

Ser Lys  Gly His Tyr Lys Lys  Ser Thr Val Lys Arg  Lys Asp Arg
    1385                 1390                 1395

Ser Trp  Ala Val Asn His Arg  Arg Thr Lys Asp Arg  Ala Gly Ser
```

1400 1405 1410

Thr Thr Gly Ala Ser Ala Ser Thr Val Thr Val Thr Ser Val Val
1415 1420 1425

Thr Lys Thr Val Ser Lys Met Ser Ser Val Ala Ala Asp Asn Arg
1430 1435 1440

Ala Trp Thr Thr Asp Trp Ser Asp Arg Val Lys Ser Arg Val Met
1445 1450 1455

Val Gly Asp Asp Asn Met Lys Lys Ala Thr Asp Arg Arg Thr Ala
1460 1465 1470

Ala Asn Lys Asn Lys Thr Ser Asn Ala Arg Thr Thr Asp Arg Arg
1475 1480 1485

Trp Asp Val Asn Arg Arg Asn Met Lys Asp Ser Thr Trp Ala Lys
1490 1495 1500

Ala Val Gly Val Arg Gly Lys Asp Ser Trp Lys Gly His Thr Val
1505 1510 1515

Asp Ala Lys Lys Thr Thr Lys Ala Lys Asp Arg Arg Ser Val Asp
1520 1525 1530

Val Ala Asn Asp Ala Lys Arg Asp Tyr Ser Ala Asp Asp Thr Arg
1535 1540 1545

Lys Val His Met Thr Asn Asn Thr Ser Trp Gly Asn His Lys Arg
1550 1555 1560

Val Ser Ala Ala Thr His Arg Asp Lys Ser Trp Thr Ala Thr Thr
1565 1570 1575

Ala Asn Val Asp Ala Ser Arg Lys Lys Asp Ser Arg Gly Val Arg
1580 1585 1590

Met Lys Trp Asp Gly Thr His Thr Asp Tyr His Asn Asp Asn Gly
1595 1600 1605

```
Lys Arg  Ser Gly Ser Asp Ala  Arg Arg Asp Asn Met  Asn Lys Trp
    1610                1615                1620

Ser Lys  Lys Ser Asn Arg Ser  His Ala Ser Ser Asp  Trp Lys Arg
    1625                1630                1635

His Ser  Val Trp Lys Asp Asp  Ser Arg Ala Gly Gly  Asp Ala Val
    1640                1645                1650

Lys Asn  Asp His Arg Ala Lys  Arg Lys Thr Lys Val  Met Ser Thr
    1655                1660                1665

Thr Val  Arg Thr Gly Lys Tyr  Arg Arg Ala Asn Val  Thr Arg Arg
    1670                1675                1680

Lys Ala  Val Asn Ala Trp Asp  Lys Asn Arg Ser Ala  Asp Trp Arg
    1685                1690                1695

Lys Asp  Ala Arg Ala Ala Asp  Asp Lys Arg Ala Val  Lys Gly Ser
    1700                1705                1710

Trp Val  Gly Asp Asp Ser Asp  His Lys Val Lys Ala  Arg Gly Ala
    1715                1720                1725

Lys Asn  Val Asn Arg Val Asn  Asp Ala His Thr Thr  Gly Ser Tyr
    1730                1735                1740

Asn Ser  Thr Asp Asn Thr Arg  Trp Arg Val Ala Val  Asp Arg Val
    1745                1750                1755

Arg His  Ala His Arg Asp Gly  Ala Ser His Ser Thr  Ser Val Gly
    1760                1765                1770

Trp Arg  Ala Ser Asn Lys Val  Tyr Tyr Asn His Thr  Thr Thr Cys
    1775                1780                1785

Trp Asp  His Lys Met Thr Tyr  Ser Ala Asp Asn Asn  Val Arg Ser
    1790                1795                1800

Ala Tyr  Arg Thr Ala Met Lys  Arg Arg Lys Ala Cys  Asp Ser Ser
```

```
    1805                1810                1815

Ala Ala  Cys Asp Ala Asp His  Asn Lys Asn Asp Met  Asp Asn Cys
    1820                1825                1830

Thr Thr  Tyr Asp Arg His Asn  Asn Val Asn Val Cys  Val Asp Met
    1835                1840                1845

Cys Asn  Trp Asn Val Tyr Asp  Thr Gly Arg Thr Gly  Arg Arg Val
    1850                1855                1860

Ser Lys  Thr Gly Ser Cys Lys  Ala His Asp Lys Tyr  Arg Tyr Lys
    1865                1870                1875

Val Ala  Ser Ser Thr Gly Cys  Asp Arg Arg Gly His  Asp Ser Arg
    1880                1885                1890

Gly Val  Ala Ser Gly Gly Ser  Asn Ser Val Arg Ser  Cys Ala Asn
    1895                1900                1905

Asn Lys  Ala Ala Asp Trp Met  Arg Ser Met Val Trp  Val His Arg
    1910                1915                1920

Val Ala  Ala Ala Thr Ala Lys  His Ala Lys Cys Asn  Cys Lys Cys
    1925                1930                1935

Gly Arg  Tyr Arg Ser Lys His  Asn Tyr Asp Cys Ser  Cys Ser Gly
    1940                1945                1950

Arg Val  Ala Lys Gly His Lys  Met His Tyr Met Val  Tyr Cys Thr
    1955                1960                1965

Thr Thr  Ser Gly Asp Val Arg  Asp Ala Lys Val Lys  Asn Lys Arg
    1970                1975                1980

Thr Lys  Arg Tyr Ala Lys His  Arg Met Gly Tyr Val  Thr Val Gly
    1985                1990                1995

Asp Asn  Met Thr Val Thr Asn  Trp Val Asp Ser Ala  Ala Ser Ser
    2000                2005                2010
```

```
Ser His  Asp Asp Thr His Ser  Arg His Tyr Ala Ser  Arg Ala Met
    2015                2020                2025

Asn Ser  Asn Gly Ser Tyr Asn  Asp Ser Ser Asn Ser  Asp Asp His
    2030                2035                2040

His Tyr  Cys Ser Asn Asp Ser  Ser Arg Ser Ala Ser  Ser Arg Gly
    2045                2050                2055

Arg Ala  Asp Asn Arg Asn Ala  Tyr Asp Arg Lys His  His Lys Gly
    2060                2065                2070

Ser Ser  Met Met Thr Ser Ser  Arg Asp Ala Ala Ala  Lys Arg His
    2075                2080                2085

Lys Gly  Arg Ala Arg Met Asp  His Asn Lys Ser His  Arg Arg Ala
    2090                2095                2100

Ala Lys  Val Asn Gly Thr Thr  Val Ser Ser Ser Thr  Ser Arg Ser
    2105                2110                2115

Asp Ser  Ser Met Arg Val Val  Gly Ser Thr Ser Ser  Met Gly Asp
    2120                2125                2130

Ser Asp  Thr Ser Thr Gly Val  Met Asn Asn Ser Ser  Ser Arg Gly
    2135                2140                2145

Arg Asn  Ala Gly Lys Met Arg  Asp Thr Met
    2150                2155
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<211> 1307
<212> PRT
<213> Acidaminococcus sp.

<400> 870

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Met Thr Gln Phe Glu Gly Phe Thr Asn Leu Tyr Gln Val Ser Lys Thr
1               5                  10                  15

Leu Arg Phe Glu Leu Ile Pro Gln Gly Lys Thr Leu Lys His Ile Gln
            20                  25                  30
```

```
Glu Gln Gly Phe Ile Glu Glu Asp Lys Ala Arg Asn Asp His Tyr Lys
        35                  40                  45

Glu Leu Lys Pro Ile Ile Asp Arg Ile Tyr Lys Thr Tyr Ala Asp Gln
    50                  55                  60

Cys Leu Gln Leu Val Gln Leu Asp Trp Glu Asn Leu Ser Ala Ala Ile
65                  70                  75                  80

Asp Ser Tyr Arg Lys Glu Lys Thr Glu Glu Thr Arg Asn Ala Leu Ile
                85                  90                  95

Glu Glu Gln Ala Thr Tyr Arg Asn Ala Ile His Asp Tyr Phe Ile Gly
            100                 105                 110

Arg Thr Asp Asn Leu Thr Asp Ala Ile Asn Lys Arg His Ala Glu Ile
        115                 120                 125

Tyr Lys Gly Leu Phe Lys Ala Glu Leu Phe Asn Gly Lys Val Leu Lys
    130                 135                 140

Gln Leu Gly Thr Val Thr Thr Thr Glu His Glu Asn Ala Leu Leu Arg
145                 150                 155                 160

Ser Phe Asp Lys Phe Thr Thr Tyr Phe Ser Gly Phe Tyr Glu Asn Arg
                165                 170                 175

Lys Asn Val Phe Ser Ala Glu Asp Ile Ser Thr Ala Ile Pro His Arg
            180                 185                 190

Ile Val Gln Asp Asn Phe Pro Lys Phe Lys Glu Asn Cys His Ile Phe
        195                 200                 205

Thr Arg Leu Ile Thr Ala Val Pro Ser Leu Arg Glu His Phe Glu Asn
    210                 215                 220

Val Lys Lys Ala Ile Gly Ile Phe Val Ser Thr Ser Ile Glu Glu Val
225                 230                 235                 240

Phe Ser Phe Pro Phe Tyr Asn Gln Leu Leu Thr Gln Thr Gln Ile Asp
```

```
                245                 250                 255

Leu Tyr Asn Gln Leu Leu Gly Gly Ile Ser Arg Glu Ala Gly Thr Glu
            260                 265                 270

Lys Ile Lys Gly Leu Asn Glu Val Leu Asn Leu Ala Ile Gln Lys Asn
        275                 280                 285

Asp Glu Thr Ala His Ile Ile Ala Ser Leu Pro His Arg Phe Ile Pro
    290                 295                 300

Leu Phe Lys Gln Ile Leu Ser Asp Arg Asn Thr Leu Ser Phe Ile Leu
305                 310                 315                 320

Glu Glu Phe Lys Ser Asp Glu Glu Val Ile Gln Ser Phe Cys Lys Tyr
                325                 330                 335

Lys Thr Leu Leu Arg Asn Glu Asn Val Leu Glu Thr Ala Glu Ala Leu
            340                 345                 350

Phe Asn Glu Leu Asn Ser Ile Asp Leu Thr His Ile Phe Ile Ser His
        355                 360                 365

Lys Lys Leu Glu Thr Ile Ser Ser Ala Leu Cys Asp His Trp Asp Thr
    370                 375                 380

Leu Arg Asn Ala Leu Tyr Glu Arg Arg Ile Ser Glu Leu Thr Gly Lys
385                 390                 395                 400

Ile Thr Lys Ser Ala Lys Glu Lys Val Gln Arg Ser Leu Lys His Glu
                405                 410                 415

Asp Ile Asn Leu Gln Glu Ile Ile Ser Ala Ala Gly Lys Glu Leu Ser
            420                 425                 430

Glu Ala Phe Lys Gln Lys Thr Ser Glu Ile Leu Ser His Ala His Ala
        435                 440                 445

Ala Leu Asp Gln Pro Leu Pro Thr Thr Leu Lys Lys Gln Glu Glu Lys
    450                 455                 460
```

```
Glu Ile Leu Lys Ser Gln Leu Asp Ser Leu Leu Gly Leu Tyr His Leu
465                 470                 475                 480

Leu Asp Trp Phe Ala Val Asp Glu Ser Asn Glu Val Asp Pro Glu Phe
                485                 490                 495

Ser Ala Arg Leu Thr Gly Ile Lys Leu Glu Met Glu Pro Ser Leu Ser
            500                 505                 510

Phe Tyr Asn Lys Ala Arg Asn Tyr Ala Thr Lys Lys Pro Tyr Ser Val
        515                 520                 525

Glu Lys Phe Lys Leu Asn Phe Gln Met Pro Thr Leu Ala Ser Gly Trp
    530                 535                 540

Asp Val Asn Lys Glu Lys Asn Asn Gly Ala Ile Leu Phe Val Lys Asn
545                 550                 555                 560

Gly Leu Tyr Tyr Leu Gly Ile Met Pro Lys Gln Lys Gly Arg Tyr Lys
                565                 570                 575

Ala Leu Ser Phe Glu Pro Thr Glu Lys Thr Ser Glu Gly Phe Asp Lys
            580                 585                 590

Met Tyr Tyr Asp Tyr Phe Pro Asp Ala Ala Lys Met Ile Pro Lys Cys
        595                 600                 605

Ser Thr Gln Leu Lys Ala Val Thr Ala His Phe Gln Thr His Thr Thr
    610                 615                 620

Pro Ile Leu Leu Ser Asn Asn Phe Ile Glu Pro Leu Glu Ile Thr Lys
625                 630                 635                 640

Glu Ile Tyr Asp Leu Asn Asn Pro Glu Lys Glu Pro Lys Lys Phe Gln
                645                 650                 655

Thr Ala Tyr Ala Lys Lys Thr Gly Asp Gln Lys Gly Tyr Arg Glu Ala
            660                 665                 670

Leu Cys Lys Trp Ile Asp Phe Thr Arg Asp Phe Leu Ser Lys Tyr Thr
```

675 680 685

Lys Thr Thr Ser Ile Asp Leu Ser Ser Leu Arg Pro Ser Ser Gln Tyr
690 695 700

Lys Asp Leu Gly Glu Tyr Tyr Ala Glu Leu Asn Pro Leu Leu Tyr His
705 710 715 720

Ile Ser Phe Gln Arg Ile Ala Glu Lys Glu Ile Met Asp Ala Val Glu
725 730 735

Thr Gly Lys Leu Tyr Leu Phe Gln Ile Tyr Asn Lys Asp Phe Ala Lys
740 745 750

Gly His His Gly Lys Pro Asn Leu His Thr Leu Tyr Trp Thr Gly Leu
755 760 765

Phe Ser Pro Glu Asn Leu Ala Lys Thr Ser Ile Lys Leu Asn Gly Gln
770 775 780

Ala Glu Leu Phe Tyr Arg Pro Lys Ser Arg Met Lys Arg Met Ala His
785 790 795 800

Arg Leu Gly Glu Lys Met Leu Asn Lys Lys Leu Lys Asp Gln Lys Thr
805 810 815

Pro Ile Pro Asp Thr Leu Tyr Gln Glu Leu Tyr Asp Tyr Val Asn His
820 825 830

Arg Leu Ser His Asp Leu Ser Asp Glu Ala Arg Ala Leu Leu Pro Asn
835 840 845

Val Ile Thr Lys Glu Val Ser His Glu Ile Ile Lys Asp Arg Arg Phe
850 855 860

Thr Ser Asp Lys Phe Phe Phe His Val Pro Ile Thr Leu Asn Tyr Gln
865 870 875 880

Ala Ala Asn Ser Pro Ser Lys Phe Asn Gln Arg Val Asn Ala Tyr Leu
885 890 895

```
Lys Glu His Pro Glu Thr Pro Ile Ile Gly Ile Asp Arg Gly Glu Arg
            900                 905                 910

Asn Leu Ile Tyr Ile Thr Val Ile Asp Ser Thr Gly Lys Ile Leu Glu
        915                 920                 925

Gln Arg Ser Leu Asn Thr Ile Gln Gln Phe Asp Tyr Gln Lys Lys Leu
    930                 935                 940

Asp Asn Arg Glu Lys Glu Arg Val Ala Ala Arg Gln Ala Trp Ser Val
945                 950                 955                 960

Val Gly Thr Ile Lys Asp Leu Lys Gln Gly Tyr Leu Ser Gln Val Ile
                965                 970                 975

His Glu Ile Val Asp Leu Met Ile His Tyr Gln Ala Val Val Val Leu
            980                 985                 990

Glu Asn Leu Asn Phe Gly Phe Lys  Ser Lys Arg Thr Gly  Ile Ala Glu
        995                 1000                1005

Lys Ala  Val Tyr Gln Gln Phe  Glu Lys Met Leu Ile  Asp Lys Leu
    1010                1015                1020

Asn Cys  Leu Val Leu Lys Asp  Tyr Pro Ala Glu Lys  Val Gly Gly
    1025                1030                1035

Val Leu  Asn Pro Tyr Gln Leu  Thr Asp Gln Phe Thr  Ser Phe Ala
    1040                1045                1050

Lys Met  Gly Thr Gln Ser Gly  Phe Leu Phe Tyr Val  Pro Ala Pro
    1055                1060                1065

Tyr Thr  Ser Lys Ile Asp Pro  Leu Thr Gly Phe Val  Asp Pro Phe
    1070                1075                1080

Val Trp  Lys Thr Ile Lys Asn  His Glu Ser Arg Lys  His Phe Leu
    1085                1090                1095

Glu Gly  Phe Asp Phe Leu His  Tyr Asp Val Lys Thr  Gly Asp Phe
```

1100 1105 1110

Ile Leu His Phe Lys Met Asn Arg Asn Leu Ser Phe Gln Arg Gly
1115 1120 1125

Leu Pro Gly Phe Met Pro Ala Trp Asp Ile Val Phe Glu Lys Asn
1130 1135 1140

Glu Thr Gln Phe Asp Ala Lys Gly Thr Pro Phe Ile Ala Gly Lys
1145 1150 1155

Arg Ile Val Pro Val Ile Glu Asn His Arg Phe Thr Gly Arg Tyr
1160 1165 1170

Arg Asp Leu Tyr Pro Ala Asn Glu Leu Ile Ala Leu Leu Glu Glu
1175 1180 1185

Lys Gly Ile Val Phe Arg Asp Gly Ser Asn Ile Leu Pro Lys Leu
1190 1195 1200

Leu Glu Asn Asp Asp Ser His Ala Ile Asp Thr Met Val Ala Leu
1205 1210 1215

Ile Arg Ser Val Leu Gln Met Arg Asn Ser Asn Ala Ala Thr Gly
1220 1225 1230

Glu Asp Tyr Ile Asn Ser Pro Val Arg Asp Leu Asn Gly Val Cys
1235 1240 1245

Phe Asp Ser Arg Phe Gln Asn Pro Glu Trp Pro Met Asp Ala Asp
1250 1255 1260

Ala Asn Gly Ala Tyr His Ile Ala Leu Lys Gly Gln Leu Leu Leu
1265 1270 1275

Asn His Leu Lys Glu Ser Lys Asp Leu Lys Leu Gln Asn Gly Ile
1280 1285 1290

Ser Asn Gln Asp Trp Leu Ala Tyr Ile Gln Glu Leu Arg Asn
1295 1300 1305

<210> 871
<211> 1228
<212> PRT
<213> Desconocido

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Lachnospiraceae bacterium ND2006"

<400> 871

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Ala Ala Ser Lys Leu Glu Lys Phe Thr Asn Cys Tyr Ser Leu Ser Lys
1               5                  10                  15

Thr Leu Arg Phe Lys Ala Ile Pro Val Gly Lys Thr Gln Glu Asn Ile
            20                  25                  30

Asp Asn Lys Arg Leu Leu Val Glu Asp Glu Lys Arg Ala Glu Asp Tyr
        35                  40                  45

Lys Gly Val Lys Lys Leu Leu Asp Arg Tyr Tyr Leu Ser Phe Ile Asn
    50                  55                  60

Asp Val Leu His Ser Ile Lys Leu Lys Asn Leu Asn Asn Tyr Ile Ser
65                  70                  75                  80

Leu Phe Arg Lys Lys Thr Arg Thr Glu Lys Glu Asn Lys Glu Leu Glu
                85                  90                  95

Asn Leu Glu Ile Asn Leu Arg Lys Glu Ile Ala Lys Ala Phe Lys Gly
            100                 105                 110

Ala Ala Gly Tyr Lys Ser Leu Phe Lys Lys Asp Ile Ile Glu Thr Ile
        115                 120                 125

Leu Pro Glu Ala Ala Asp Asp Lys Asp Glu Ile Ala Leu Val Asn Ser
    130                 135                 140

Phe Asn Gly Phe Thr Thr Ala Phe Thr Gly Phe Phe Asp Asn Arg Glu
145                 150                 155                 160

Asn Met Phe Ser Glu Glu Ala Lys Ser Thr Ser Ile Ala Phe Arg Cys
                165                 170                 175
```

```
Ile Asn Glu Asn Leu Thr Arg Tyr Ile Ser Asn Met Asp Ile Phe Glu
            180                 185                 190

Lys Val Asp Ala Ile Phe Asp Lys His Glu Val Gln Glu Ile Lys Glu
        195                 200                 205

Lys Ile Leu Asn Ser Asp Tyr Asp Val Glu Asp Phe Phe Glu Gly Glu
    210                 215                 220

Phe Phe Asn Phe Val Leu Thr Gln Glu Gly Ile Asp Val Tyr Asn Ala
225                 230                 235                 240

Ile Ile Gly Gly Phe Val Thr Glu Ser Gly Glu Lys Ile Lys Gly Leu
                245                 250                 255

Asn Glu Tyr Ile Asn Leu Tyr Asn Ala Lys Thr Lys Gln Ala Leu Pro
            260                 265                 270

Lys Phe Lys Pro Leu Tyr Lys Gln Val Leu Ser Asp Arg Glu Ser Leu
        275                 280                 285

Ser Phe Tyr Gly Glu Gly Tyr Thr Ser Asp Glu Glu Val Leu Glu Val
    290                 295                 300

Phe Arg Asn Thr Leu Asn Lys Asn Ser Glu Ile Phe Ser Ser Ile Lys
305                 310                 315                 320

Lys Leu Glu Lys Leu Phe Lys Asn Phe Asp Glu Tyr Ser Ser Ala Gly
                325                 330                 335

Ile Phe Val Lys Asn Gly Pro Ala Ile Ser Thr Ile Ser Lys Asp Ile
            340                 345                 350

Phe Gly Glu Trp Asn Leu Ile Arg Asp Lys Trp Asn Ala Glu Tyr Asp
        355                 360                 365

Asp Ile His Leu Lys Lys Lys Ala Val Val Thr Glu Lys Tyr Glu Asp
    370                 375                 380
```

```
Asp Arg Arg Lys Ser Phe Lys Lys Ile Gly Ser Phe Ser Leu Glu Gln
385                 390                 395                 400

Leu Gln Glu Tyr Ala Asp Ala Asp Leu Ser Val Val Glu Lys Leu Lys
                405                 410                 415

Glu Ile Ile Ile Gln Lys Val Asp Glu Ile Tyr Lys Val Tyr Gly Ser
            420                 425                 430

Ser Glu Lys Leu Phe Asp Ala Asp Phe Val Leu Glu Lys Ser Leu Lys
        435                 440                 445

Lys Asn Asp Ala Val Val Ala Ile Met Lys Asp Leu Leu Asp Ser Val
    450                 455                 460

Lys Ser Phe Glu Asn Tyr Ile Lys Ala Phe Phe Gly Glu Gly Lys Glu
465                 470                 475                 480

Thr Asn Arg Asp Glu Ser Phe Tyr Gly Asp Phe Val Leu Ala Tyr Asp
                485                 490                 495

Ile Leu Leu Lys Val Asp His Ile Tyr Asp Ala Ile Arg Asn Tyr Val
            500                 505                 510

Thr Gln Lys Pro Tyr Ser Lys Asp Lys Phe Lys Leu Tyr Phe Gln Asn
        515                 520                 525

Pro Gln Phe Met Gly Gly Trp Asp Lys Asp Lys Glu Thr Asp Tyr Arg
    530                 535                 540

Ala Thr Ile Leu Arg Tyr Gly Ser Lys Tyr Tyr Leu Ala Ile Met Asp
545                 550                 555                 560

Lys Lys Tyr Ala Lys Cys Leu Gln Lys Ile Asp Lys Asp Asp Val Asn
                565                 570                 575

Gly Asn Tyr Glu Lys Ile Asn Tyr Lys Leu Leu Pro Gly Pro Asn Lys
            580                 585                 590

Met Leu Pro Lys Val Phe Phe Ser Lys Lys Trp Met Ala Tyr Tyr Asn
        595                 600                 605
```

```
Pro Ser Glu Asp Ile Gln Lys Ile Tyr Lys Asn Gly Thr Phe Lys Lys
    610                 615                 620

Gly Asp Met Phe Asn Leu Asn Asp Cys His Lys Leu Ile Asp Phe Phe
625                 630                 635                 640

Lys Asp Ser Ile Ser Arg Tyr Pro Lys Trp Ser Asn Ala Tyr Asp Phe
                645                 650                 655

Asn Phe Ser Glu Thr Glu Lys Tyr Lys Asp Ile Ala Gly Phe Tyr Arg
            660                 665                 670

Glu Val Glu Glu Gln Gly Tyr Lys Val Ser Phe Glu Ser Ala Ser Lys
        675                 680                 685

Lys Glu Val Asp Lys Leu Val Glu Glu Gly Lys Leu Tyr Met Phe Gln
    690                 695                 700

Ile Tyr Asn Lys Asp Phe Ser Asp Lys Ser His Gly Thr Pro Asn Leu
705                 710                 715                 720

His Thr Met Tyr Phe Lys Leu Leu Phe Asp Glu Asn Asn His Gly Gln
                725                 730                 735

Ile Arg Leu Ser Gly Gly Ala Glu Leu Phe Met Arg Arg Ala Ser Leu
            740                 745                 750

Lys Lys Glu Glu Leu Val Val His Pro Ala Asn Ser Pro Ile Ala Asn
        755                 760                 765

Lys Asn Pro Asp Asn Pro Lys Lys Thr Thr Thr Leu Ser Tyr Asp Val
    770                 775                 780

Tyr Lys Asp Lys Arg Phe Ser Glu Asp Gln Tyr Glu Leu His Ile Pro
785                 790                 795                 800

Ile Ala Ile Asn Lys Cys Pro Lys Asn Ile Phe Lys Ile Asn Thr Glu
                805                 810                 815
```

```
Val Arg Val Leu Leu Lys His Asp Asp Asn Pro Tyr Val Ile Gly Ile
            820                 825                 830

Asp Arg Gly Glu Arg Asn Leu Leu Tyr Ile Val Val Val Asp Gly Lys
        835                 840                 845

Gly Asn Ile Val Glu Gln Tyr Ser Leu Asn Glu Ile Ile Asn Asn Phe
    850                 855                 860

Asn Gly Ile Arg Ile Lys Thr Asp Tyr His Ser Leu Leu Asp Lys Lys
865                 870                 875                 880

Glu Lys Glu Arg Phe Glu Ala Arg Gln Asn Trp Thr Ser Ile Glu Asn
                885                 890                 895

Ile Lys Glu Leu Lys Ala Gly Tyr Ile Ser Gln Val Val His Lys Ile
            900                 905                 910

Cys Glu Leu Val Glu Lys Tyr Asp Ala Val Ile Ala Leu Glu Asp Leu
        915                 920                 925

Asn Ser Gly Phe Lys Asn Ser Arg Val Lys Val Glu Lys Gln Val Tyr
    930                 935                 940

Gln Lys Phe Glu Lys Met Leu Ile Asp Lys Leu Asn Tyr Met Val Asp
945                 950                 955                 960

Lys Lys Ser Asn Pro Cys Ala Thr Gly Gly Ala Leu Lys Gly Tyr Gln
                965                 970                 975

Ile Thr Asn Lys Phe Glu Ser Phe Lys Ser Met Ser Thr Gln Asn Gly
            980                 985                 990

Phe Ile Phe Tyr Ile Pro Ala Trp  Leu Thr Ser Lys Ile  Asp Pro Ser
        995                 1000                1005

Thr Gly  Phe Val Asn Leu Leu  Lys Thr Lys Tyr Thr  Ser Ile Ala
    1010                1015                1020

Asp Ser  Lys Lys Phe Ile Ser  Ser Phe Asp Arg Ile  Met Tyr Val
    1025                1030                1035
```

```
Pro Glu  Glu Asp Leu Phe Glu  Phe Ala Leu Asp Tyr  Lys Asn Phe
    1040                1045                1050

Ser Arg  Thr Asp Ala Asp Tyr  Ile Lys Lys Trp Lys  Leu Tyr Ser
    1055                1060                1065

Tyr Gly  Asn Arg Ile Arg Ile  Phe Ala Ala Ala Lys  Lys Asn Asn
    1070                1075                1080

Val Phe  Ala Trp Glu Glu Val  Cys Leu Thr Ser Ala  Tyr Lys Glu
    1085                1090                1095

Leu Phe  Asn Lys Tyr Gly Ile  Asn Tyr Gln Gln Gly  Asp Ile Arg
    1100                1105                1110

Ala Leu  Leu Cys Glu Gln Ser  Asp Lys Ala Phe Tyr  Ser Ser Phe
    1115                1120                1125

Met Ala  Leu Met Ser Leu Met  Leu Gln Met Arg Asn  Ser Ile Thr
    1130                1135                1140

Gly Arg  Thr Asp Val Asp Phe  Leu Ile Ser Pro Val  Lys Asn Ser
    1145                1150                1155

Asp Gly  Ile Phe Tyr Asp Ser  Arg Asn Tyr Glu Ala  Gln Glu Asn
    1160                1165                1170

Ala Ile  Leu Pro Lys Asn Ala  Asp Ala Asn Gly Ala  Tyr Asn Ile
    1175                1180                1185

Ala Arg  Lys Val Leu Trp Ala  Ile Gly Gln Phe Lys  Lys Ala Glu
    1190                1195                1200

Asp Glu  Lys Leu Asp Lys Val  Lys Ile Ala Ile Ser  Asn Lys Glu
    1205                1210                1215

Trp Leu  Glu Tyr Ala Gln Thr  Ser Val Lys
    1220                1225
```

<210> 872
<211> 4101
<212> ADN
<213> Staphylococcus pyogenes

<400> 872
gacaagaagt acagcatcgg cctggacatc ggcaccaact ctgtgggctg ggccgtgatc
60

accgacgagt acaaggtgcc cagcaagaaa ttcaaggtgc tgggcaacac cgaccggcac
120

agcatcaaga agaacctgat cggagccctg ctgttcgaca gcggcgaaac agccgaggcc
180

acccggctga agagaaccgc cagaagaaga tacaccagac ggaagaaccg gatctgctat
240

ctgcaagaga tcttcagcaa cgagatggcc aaggtggacg acagcttctt ccacagactg
300

gaagagtcct tcctggtgga agaggataag aagcacgagc ggcaccccat cttcggcaac
360

atcgtggacg aggtggccta ccacgagaag taccccacca tctaccacct gagaaagaaa
420

ctggtggaca gcaccgacaa ggccgacctg cggctgatct atctggccct ggcccacatg
480

atcaagttcc ggggccactt cctgatcgag ggcgacctga accccgacaa cagcgacgtg
540

gacaagctgt tcatccagct ggtgcagacc tacaaccagc tgttcgagga aaaccccatc
600

aacgccagcg gcgtggacgc caaggccatc ctgtctgcca gactgagcaa gagcagacgg
660

ctggaaaatc tgatcgccca gctgcccggc gagaagaaga atggcctgtt cggcaacctg
720

attgccctga gcctgggcct gacccccaac ttcaagagca acttcgacct ggccgaggat
780

gccaaactgc agctgagcaa ggacacctac gacgacgacc tggacaacct gctggcccag
840

atcggcgacc agtacgccga cctgtttctg gccgccaaga acctgtccga cgccatcctg
900

ctgagcgaca tcctgagagt gaacaccgag atcaccaagg ccccccctgag cgcctctatg
960

atcaagagat acgacgagca ccaccaggac ctgaccctgc tgaaagctct cgtgcggcag
1020

cagctgcctg agaagtacaa agagattttc ttcgaccaga gcaagaacgg ctacgccggc
1080

tacattgacg gcggagccag ccaggaagag ttctacaagt tcatcaagcc catcctggaa
1140

aagatggacg gcaccgagga actgctcgtg aagctgaaca gagaggacct gctgcggaag
1200

cagcggacct tcgacaacgg cagcatcccc caccagatcc acctgggaga gctgcacgcc
1260

attctgcggc ggcaggaaga tttttaccca ttcctgaagg acaaccggga aaagatcgag
1320

aagatcctga ccttccgcat cccctactac gtgggccctc tggccagggg aaacagcaga
1380

ttcgcctgga tgaccagaaa gagcgaggaa accatcaccc cctggaactt cgaggaagtg
1440

gtggacaagg gcgcttccgc ccagagcttc atcgagcgga tgaccaactt cgataagaac
1500

ctgcccaacg agaaggtgct gcccaagcac agcctgctgt acgagtactt caccgtgtat
1560

aacgagctga ccaaagtgaa atacgtgacc gagggaatga gaaagcccgc cttcctgagc
1620

ggcgagcaga aaaaggccat cgtggacctg ctgttcaaga ccaaccggaa agtgaccgtg
1680

aagcagctga aagaggacta cttcaagaaa atcgagtgct tcgactccgt ggaaatctcc
1740

ggcgtggaag atcggttcaa cgcctccctg ggcacatacc acgatctgct gaaaattatc
1800

aaggacaagg acttcctgga caatgaggaa aacgaggaca ttctggaaga tatcgtgctg
1860

accctgacac tgtttgagga cagagagatg atcgaggaac ggctgaaaac ctatgcccac
1920

ctgttcgacg acaaagtgat gaagcagctg aagcggcgga gatacaccgg ctggggcagg
1980

ctgagccgga agctgatcaa cggcatccgg gacaagcagt ccggcaagac aatcctggat
2040

ttcctgaagt ccgacggctt cgccaacaga aacttcatgc agctgatcca cgacgacagc
2100

ctgaccttta aagaggacat ccagaaagcc caggtgtccg gccagggcga tagcctgcac
2160

gagcacattg ccaatctggc cggcagcccc gccattaaga agggcatcct gcagacagtg
2220

aaggtggtgg acgagctcgt gaaagtgatg ggccggcaca agcccgagaa catcgtgatc
2280

gaaatggcca gagagaacca gaccacccag aagggacaga agaacagccg cgagagaatg
2340

aagcggatcg aagagggcat caaagagctg ggcagccaga tcctgaaaga acaccccgtg
2400

gaaaacaccc agctgcagaa cgagaagctg tacctgtact acctgcagaa tgggcgggat
2460

atgtacgtgg accaggaact ggacatcaac cggctgtccg actacgatgt ggaccatatc
2520

gtgcctcaga gctttctgaa ggacgactcc atcgacaaca aggtgctgac cagaagcgac
2580

aagaaccggg gcaagagcga caacgtgccc tccgaagagg tcgtgaagaa gatgaagaac
2640

tactggcggc agctgctgaa cgccaagctg attacccaga gaaagttcga caatctgacc
2700

aaggccgaga gaggcggcct gagcgaactg gataaggccg gcttcatcaa gagacagctg
2760

gtggaaaccc ggcagatcac aaagcacgtg gcacagatcc tggactcccg gatgaacact
2820

aagtacgacg agaatgacaa gctgatccgg gaagtgaaag tgatcaccct gaagtccaag
2880

ctggtgtccg atttccggaa ggatttccag ttttacaaag tgcgcgagat caacaactac
2940

caccacgccc acgacgccta cctgaacgcc gtcgtgggaa ccgccctgat caaaaagtac
3000

cctaagctgg aaagcgagtt cgtgtacggc gactacaagg tgtacgacgt gcggaagatg
3060

atcgccaaga gcgagcagga aatcggcaag gctaccgcca agtacttctt ctacagcaac
3120

atcatgaact ttttcaagac cgagattacc ctggccaacg gcgagatccg gaagcggcct
3180

ctgatcgaga caaacggcga aaccggggag atcgtgtggg ataagggccg ggattttgcc
3240

accgtgcgga aagtgctgag catgccccaa gtgaatatcg tgaaaaagac cgaggtgcag
3300

acaggcggct tcagcaaaga gtctatcctg cccaagagga acagcgataa gctgatcgcc
3360

agaaagaagg actgggaccc taagaagtac ggcggcttcg acagccccac cgtggcctat
3420

tctgtgctgg tggtggccaa agtggaaaag ggcaagtcca agaaactgaa gagtgtgaaa
3480

gagctgctgg ggatcaccat catggaaaga agcagcttcg agaagaatcc catcgacttt
3540

ctggaagcca agggctacaa agaagtgaaa aaggacctga tcatcaagct gcctaagtac
3600

tccctgttcg agctggaaaa cggccggaag agaatgctgg cctctgccgg cgaactgcag
3660

aagggaaacg aactggccct gccctccaaa tatgtgaact tcctgtacct ggccagccac
3720

tatgagaagc tgaagggctc ccccgaggat aatgagcaga aacagctgtt tgtggaacag
3780

cacaagcact acctggacga gatcatcgag cagatcagcg agttctccaa gagagtgatc
3840

ctggccgacg ctaatctgga caaagtgctg tccgcctaca acaagcaccg ggataagccc
3900

atcagagagc aggccgagaa tatcatccac ctgtttaccc tgaccaatct gggagccccct
3960

gccgccttca agtactttga caccaccatc gaccggaaga ggtacaccag caccaaagag
4020

gtgctggacg ccaccctgat ccaccagagc atcaccggcc tgtacgagac acggatcgac
4080

ctgtctcagc tgggaggcga c
4101

<210> 873
<211> 1053

<212> PRT
<213> Staphylococcus aureus

<400> 873

```
Met Lys Arg Asn Tyr Ile Leu Gly Leu Asp Ile Gly Ile Thr Ser Val
1               5                  10                  15

Gly Tyr Gly Ile Ile Asp Tyr Glu Thr Arg Asp Val Ile Asp Ala Gly
            20                  25                  30

Val Arg Leu Phe Lys Glu Ala Asn Val Glu Asn Asn Glu Gly Arg Arg
        35                  40                  45

Ser Lys Arg Gly Ala Arg Arg Leu Lys Arg Arg Arg Arg His Arg Ile
    50                  55                  60

Gln Arg Val Lys Lys Leu Leu Phe Asp Tyr Asn Leu Leu Thr Asp His
65                  70                  75                  80

Ser Glu Leu Ser Gly Ile Asn Pro Tyr Glu Ala Arg Val Lys Gly Leu
                85                  90                  95

Ser Gln Lys Leu Ser Glu Glu Glu Phe Ser Ala Ala Leu Leu His Leu
            100                 105                 110

Ala Lys Arg Arg Gly Val His Asn Val Asn Glu Val Glu Glu Asp Thr
        115                 120                 125

Gly Asn Glu Leu Ser Thr Lys Glu Gln Ile Ser Arg Asn Ser Lys Ala
    130                 135                 140

Leu Glu Glu Lys Tyr Val Ala Glu Leu Gln Leu Glu Arg Leu Lys Lys
145                 150                 155                 160

Asp Gly Glu Val Arg Gly Ser Ile Asn Arg Phe Lys Thr Ser Asp Tyr
                165                 170                 175

Val Lys Glu Ala Lys Gln Leu Leu Lys Val Gln Lys Ala Tyr His Gln
            180                 185                 190

Leu Asp Gln Ser Phe Ile Asp Thr Tyr Ile Asp Leu Leu Glu Thr Arg
        195                 200                 205
```

```
Arg Thr Tyr Tyr Glu Gly Pro Gly Glu Gly Ser Pro Phe Gly Trp Lys
    210                 215                 220

Asp Ile Lys Glu Trp Tyr Glu Met Leu Met Gly His Cys Thr Tyr Phe
225                 230                 235                 240

Pro Glu Glu Leu Arg Ser Val Lys Tyr Ala Tyr Asn Ala Asp Leu Tyr
                245                 250                 255

Asn Ala Leu Asn Asp Leu Asn Asn Leu Val Ile Thr Arg Asp Glu Asn
            260                 265                 270

Glu Lys Leu Glu Tyr Tyr Glu Lys Phe Gln Ile Ile Glu Asn Val Phe
        275                 280                 285

Lys Gln Lys Lys Lys Pro Thr Leu Lys Gln Ile Ala Lys Glu Ile Leu
    290                 295                 300

Val Asn Glu Glu Asp Ile Lys Gly Tyr Arg Val Thr Ser Thr Gly Lys
305                 310                 315                 320

Pro Glu Phe Thr Asn Leu Lys Val Tyr His Asp Ile Lys Asp Ile Thr
                325                 330                 335

Ala Arg Lys Glu Ile Ile Glu Asn Ala Glu Leu Leu Asp Gln Ile Ala
            340                 345                 350

Lys Ile Leu Thr Ile Tyr Gln Ser Ser Glu Asp Ile Gln Glu Glu Leu
        355                 360                 365

Thr Asn Leu Asn Ser Glu Leu Thr Gln Glu Glu Ile Glu Gln Ile Ser
    370                 375                 380

Asn Leu Lys Gly Tyr Thr Gly Thr His Asn Leu Ser Leu Lys Ala Ile
385                 390                 395                 400

Asn Leu Ile Leu Asp Glu Leu Trp His Thr Asn Asp Asn Gln Ile Ala
                405                 410                 415
```

```
Ile Phe Asn Arg Leu Lys Leu Val Pro Lys Lys Val Asp Leu Ser Gln
            420                 425                 430

Gln Lys Glu Ile Pro Thr Thr Leu Val Asp Asp Phe Ile Leu Ser Pro
        435                 440                 445

Val Val Lys Arg Ser Phe Ile Gln Ser Ile Lys Val Ile Asn Ala Ile
    450                 455                 460

Ile Lys Lys Tyr Gly Leu Pro Asn Asp Ile Ile Ile Glu Leu Ala Arg
465                 470                 475                 480

Glu Lys Asn Ser Lys Asp Ala Gln Lys Met Ile Asn Glu Met Gln Lys
                485                 490                 495

Arg Asn Arg Gln Thr Asn Glu Arg Ile Glu Glu Ile Ile Arg Thr Thr
            500                 505                 510

Gly Lys Glu Asn Ala Lys Tyr Leu Ile Glu Lys Ile Lys Leu His Asp
        515                 520                 525

Met Gln Glu Gly Lys Cys Leu Tyr Ser Leu Glu Ala Ile Pro Leu Glu
    530                 535                 540

Asp Leu Leu Asn Asn Pro Phe Asn Tyr Glu Val Asp His Ile Ile Pro
545                 550                 555                 560

Arg Ser Val Ser Phe Asp Asn Ser Phe Asn Asn Lys Val Leu Val Lys
                565                 570                 575

Gln Glu Glu Asn Ser Lys Lys Gly Asn Arg Thr Pro Phe Gln Tyr Leu
            580                 585                 590

Ser Ser Ser Asp Ser Lys Ile Ser Tyr Glu Thr Phe Lys Lys His Ile
        595                 600                 605

Leu Asn Leu Ala Lys Gly Lys Gly Arg Ile Ser Lys Thr Lys Lys Glu
    610                 615                 620

Tyr Leu Leu Glu Glu Arg Asp Ile Asn Arg Phe Ser Val Gln Lys Asp
625                 630                 635                 640
```

```
Phe Ile Asn Arg Asn Leu Val Asp Thr Arg Tyr Ala Thr Arg Gly Leu
                645                 650                 655

Met Asn Leu Leu Arg Ser Tyr Phe Arg Val Asn Asn Leu Asp Val Lys
            660                 665                 670

Val Lys Ser Ile Asn Gly Gly Phe Thr Ser Phe Leu Arg Arg Lys Trp
        675                 680                 685

Lys Phe Lys Lys Glu Arg Asn Lys Gly Tyr Lys His His Ala Glu Asp
    690                 695                 700

Ala Leu Ile Ile Ala Asn Ala Asp Phe Ile Phe Lys Glu Trp Lys Lys
705                 710                 715                 720

Leu Asp Lys Ala Lys Lys Val Met Glu Asn Gln Met Phe Glu Glu Lys
                725                 730                 735

Gln Ala Glu Ser Met Pro Glu Ile Glu Thr Glu Gln Glu Tyr Lys Glu
            740                 745                 750

Ile Phe Ile Thr Pro His Gln Ile Lys His Ile Lys Asp Phe Lys Asp
        755                 760                 765

Tyr Lys Tyr Ser His Arg Val Asp Lys Lys Pro Asn Arg Glu Leu Ile
    770                 775                 780

Asn Asp Thr Leu Tyr Ser Thr Arg Lys Asp Asp Lys Gly Asn Thr Leu
785                 790                 795                 800

Ile Val Asn Asn Leu Asn Gly Leu Tyr Asp Lys Asp Asn Asp Lys Leu
                805                 810                 815

Lys Lys Leu Ile Asn Lys Ser Pro Glu Lys Leu Leu Met Tyr His His
            820                 825                 830

Asp Pro Gln Thr Tyr Gln Lys Leu Lys Leu Ile Met Glu Gln Tyr Gly
        835                 840                 845
```

```
Asp Glu Lys Asn Pro Leu Tyr Lys Tyr Tyr Glu Glu Thr Gly Asn Tyr
    850                 855                 860

Leu Thr Lys Tyr Ser Lys Lys Asp Asn Gly Pro Val Ile Lys Lys Ile
865                 870                 875                 880

Lys Tyr Tyr Gly Asn Lys Leu Asn Ala His Leu Asp Ile Thr Asp Asp
                885                 890                 895

Tyr Pro Asn Ser Arg Asn Lys Val Val Lys Leu Ser Leu Lys Pro Tyr
            900                 905                 910

Arg Phe Asp Val Tyr Leu Asp Asn Gly Val Tyr Lys Phe Val Thr Val
        915                 920                 925

Lys Asn Leu Asp Val Ile Lys Lys Glu Asn Tyr Tyr Glu Val Asn Ser
    930                 935                 940

Lys Cys Tyr Glu Glu Ala Lys Lys Leu Lys Lys Ile Ser Asn Gln Ala
945                 950                 955                 960

Glu Phe Ile Ala Ser Phe Tyr Asn Asn Asp Leu Ile Lys Ile Asn Gly
                965                 970                 975

Glu Leu Tyr Arg Val Ile Gly Val Asn Asn Asp Leu Leu Asn Arg Ile
            980                 985                 990

Glu Val Asn Met Ile Asp Ile Thr  Tyr Arg Glu Tyr Leu  Glu Asn Met
        995                 1000                1005

Asn Asp  Lys Arg Pro Pro Arg  Ile Ile Lys Thr Ile  Ala Ser Lys
    1010                1015                1020

Thr Gln  Ser Ile Lys Lys Tyr  Ser Thr Asp Ile Leu  Gly Asn Leu
    1025                1030                1035

Tyr Glu  Val Lys Ser Lys Lys  His Pro Gln Ile Ile  Lys Lys Gly
    1040                1045                1050
```

<210> 874
<211> 450

<212> ADN
<213> Desconocido

<220>
<221> fuente
<223> /nota="Descripción de desconocido: Polinucleótido promotor CK8"

<400> 874
ctagactagc atgctgccca tgtaaggagg caaggcctgg ggacacccga gatgcctggt
60

tataattaac ccagacatgt ggctgccccc ccccccccaa cacctgctgc ctctaaaaat
120

aaccctgcat gccatgttcc cggcgaaggg ccagctgtcc cccgccagct agactcagca
180

cttagtttag gaaccagtga gcaagtcagc ccttggggca gcccatacaa ggccatgggg
240

ctgggcaagc tgcacgcctg ggtccggggt gggcacggtg cccgggcaac gagctgaaag
300

ctcatctgct ctcaggggcc cctccctggg gacagcccct cctggctagt cacaccctgt
360

aggctcctct atataaccca ggggcacagg ggctgccctc attctaccac cacctccaca
420

gcacagacag acactcagga gccagccagc
450

<210> 875
<211> 436
<212> ADN
<213> Desconocido

<220>
<221> fuente
<223> /nota="Descripción de desconocido: Polinucleótido promotor CK8e"

<400> 875
tgcccatgta aggaggcaag gcctggggac acccgagatg cctggttata attaacccag
60

acatgtggct gccccccccc ccccaacacc tgctgcctct aaaaataacc ctgcatgcca
120

tgttcccggc gaagggccag ctgtcccccg ccagctagac tcagcactta gtttaggaac
180

cagtgagcaa gtcagccctt ggggcagccc atacaaggcc atggggctgg gcaagctgca
240

cgcctgggtc cggggtgggc acggtgcccg ggcaacgagc tgaaagctca tctgctctca
300

ggggcccctc cctggggaca gcccctcctg gctagtcaca ccctgtaggc tcctctatat
360

aacccagggg cacaggggct gccctcattc taccaccacc tccacagcac agacagacac
420

tcaggagcca gccagc
436

<210> 876
<211> 18
<212> PRT
<213> Thosea asigna

<400> 876
Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro
1 5 10 15

Gly Pro

<210> 877
<211> 20
<212> PRT
<213> Virus de la rinitis equina A

<400> 877
Gln Cys Thr Asn Tyr Ala Leu Leu Lys Leu Ala Gly Asp Val Glu Ser
1 5 10 15

Asn Pro Gly Pro
20

<210> 878
<211> 19
<212> PRT
<213> Teschovirus porcino-1

<400> 878
Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn
1 5 10 15

Pro Gly Pro

<210> 879
<211> 23
<212> PRT
<213> Virus de la fiebre aftosa

<400> 879
Pro Val Lys Gln Leu Leu Asn Phe Asp Leu Leu Lys Leu Ala Gly Asp
1 5 10 15

Val Glu Ser Asn Pro Gly Pro
20

<210> 880
<211> 115
<212> ADN
<213> Virus adenoasociado

<400> 880
ggccactccc tctctgcgcg ctcgctcgct cactgaggcc gggcgaccaa aggtcgcccg
60

acgcccgggc tttgcccggg cggcctcagt gagcgagcga gcgcgcagag aggga
115

<210> 881
<211> 141
<212> ADN
<213> Virus adenoasociado

<400> 881
cctgcaggca gctgcgcgct cgctcgctca ctgaggccgc ccgggcaaag cccgggcgtc
60

gggcgacctt tggtcgcccg gcctcagtga gcgagcgagc gcgcagagag ggagtggcca
120

actccatcac taggggttcc t
141

<210> 882
<211> 141
<212> ADN
<213> Virus adenoasociado

<400> 882
aggaacccct agtgatggag ttggccactc cctctctgcg cgctcgctcg ctcactgagg
60

ccgggcgacc aaaggtcgcc cgacgcccgg gctttgcccg ggcggcctca gtgagcgagc
120

gagcgcgcag ctgcctgcag g
141

<210> 883
<211> 141
<212> ADN
<213> Virus adenoasociado

<400> 883
ccactccctc tatgcgcgct cgctcactca ctcggccctg gagaccaaag gtctccagac
60

tgccggcctc tggccggcag ggccgagtga gtgagcgagc gcgcatagag ggagtgggta
120

cctccatcat ctaggtttgc c
141

<210> 884
<211> 9
<212> PRT
<213> Desconocido

<220>
<221> fuente
<223> /nota="Descripción de desconocido: Secuencia NLS C-myc"

<400> 884
Pro Ala Ala Lys Arg Val Lys Leu Asp
1   5

<210> 885
<211> 51
<212> ADN
<213> Virus del simio 40

<400> 885
atggccccaa agaagaagcg gaaggtcggt atccacggag tcccagcagc c
51

<210> 886
<211> 42
<212> PRT
<213> Homo sapiens

<400> 886
Gly Asn Tyr Asn Asn Gln Ser Ser Asn Phe Gly Pro Met Lys Gly Gly

1 5 10 15

Asn Phe Gly Gly Arg Ser Ser Gly Pro Tyr Gly Gly Gly Gly Gln Tyr
20 25 30

Phe Ala Lys Pro Arg Asn Gln Gly Gly Tyr
35 40

<210> 887
<211> 48
<212> ADN
<213> Desconocido

<220>
<221> fuente
<223> /nota="Descripción de desconocido: Secuencia NLS de nucleoplasmina"

<400> 887
aagcgtcctg ctgctactaa gaaagctggt caagctaaga aaaagaaa
48

<210> 888
<211> 41
<212> PRT
<213> Desconocido

<220>
<221> fuente
<223> /nota="Descripción de desconocido:
Dominio IBB de la alfasecuencia de importina"

<400> 888
Arg Met Arg Lys Phe Lys Asn Lys Gly Lys Asp Thr Ala Glu Leu Arg
1 5 10 15

Arg Arg Arg Val Glu Val Ser Val Glu Leu Arg Lys Ala Lys Lys Asp
20 25 30

Glu Gln Ile Leu Lys Arg Arg Asn Val
35 40

<210> 889
<211> 8
<212> PRT
<213> Desconocido

<220>
<221> fuente
<223> /nota="Descripción de desconocido:
Secuencia de proteína de Mioma T"

<400> 889
Val Ser Arg Lys Arg Pro Arg Pro
1 5

<210> 890
<211> 8
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<213> Desconocido

<220>
<221> fuente
<223> /nota="Descripción de desconocido:
Secuencia de proteína de Mioma T"

<400> 890
Pro Pro Lys Lys Ala Arg Glu Asp
1 5

<210> 891
<211> 8
<212> PRT
<213> Homo sapiens

<400> 891
Pro Gln Pro Lys Lys Lys Pro Leu
1 5

<210> 892
<211> 12
<212> PRT
<213> Mus musculus

<400> 892
Ser Ala Leu Ile Lys Lys Lys Lys Lys Met Ala Pro
1 5 10

<210> 893
<211> 5
<212> PRT
<213> Virus de la influenza

<400> 893
Asp Arg Leu Arg Arg
1 5

<210> 894
<211> 7
<212> PRT
<213> Virus de la influenza

<400> 894
Pro Lys Gln Lys Lys Arg Lys
1   5

<210> 895
<211> 10
<212> PRT
<213> Virus de la hepatitis delta

<400> 895
Arg Lys Leu Lys Lys Lys Ile Lys Lys Leu
1   5   10

<210> 896
<211> 10
<212> PRT
<213> Mus musculus

<400> 896
Arg Glu Lys Lys Lys Phe Leu Lys Arg Arg
1   5   10

<210> 897
<211> 20
<212> PRT
<213> Homo sapiens

<400> 897
Lys Arg Lys Gly Asp Glu Val Asp Gly Val Asp Glu Val Ala Lys Lys
1   5   10   15

Lys Ser Lys Lys
            20

<210> 898
<211> 17
<212> PRT
<213> Homo sapiens

<400> 898
Arg Lys Cys Leu Gln Ala Gly Met Asn Leu Glu Ala Arg Lys Thr Lys
1   5   10   15

Lys

<210> 899
<211> 5133
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Polinucleótido sintético"

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120

caactccatc actaggggtt ccttgtagtt aatgattaac ccgccatgct acttatctac
180

gtagccatgc tctagattaa ttaatgccca tgtaaggagg caaggcctgg ggacacccga
240

gatgcctggt tataattaac ccagacatgt ggctgccccc ccccccccaa cacctgctgc
300

ctctaaaaat aaccctgcat gccatgttcc cggcgaaggg ccagctgtcc cccgccagct
360

agactcagca cttagtttag gaaccagtga gcaagtcagc ccttggggca gcccatacaa
420

ggccatgggg ctgggcaagc tgcacgcctg ggtccggggt gggcacggtg cccgggcaac
480

gagctgaaag ctcatctgct ctcaggggcc cctccctggg gacagcccct cctggctagt
540

cacaccctgt aggctcctct atataaccca ggggcacagg ggctgccctc attctaccac
600

cacctccaca gcacagacag acactcagga gccagccagc gctagcgcca ccatgatggc
660

cccaaagaag aagcggaagg tcggtatcca cggagtccca gcagccgaca agaagtacag
720

catcggcctg gacatcggca ccaactctgt gggctgggcc gtgatcaccg acgagtacaa
780

ggtgcccagc aagaaattca aggtgctggg caacaccgac cggcacagca tcaagaagaa
840

cctgatcgga gccctgctgt tcgacagcgg cgaaacagcc gaggccaccc ggctgaagag
900

aaccgccaga agaagataca ccagacggaa gaaccggatc tgctatctgc aagagatctt
960

cagcaacgag atggccaagg tggacgacag cttcttccac agactggaag agtccttcct
1020

ggtggaagag gataagaagc acgagcggca ccccatcttc ggcaacatcg tggacgaggt
1080

ggcctaccac gagaagtacc ccaccatcta ccacctgaga aagaaactgg tggacagcac
1140

cgacaaggcc gacctgcggc tgatctatct ggccctggcc cacatgatca agttccgggg
1200

ccacttcctg atcgagggcg acctgaaccc cgacaacagc gacgtggaca agctgttcat
1260

ccagctggtg cagacctaca accagctgtt cgaggaaaac cccatcaacg ccagcggcgt
1320

ggacgccaag gccatcctgt ctgccagact gagcaagagc agacggctgg aaaatctgat
1380

cgcccagctg cccggcgaga agaagaatgg cctgttcggc aacctgattg ccctgagcct
1440

gggcctgacc cccaacttca agagcaactt cgacctggcc gaggatgcca aactgcagct
1500

gagcaaggac acctacgacg acgacctgga caacctgctg gcccagatcg gcgaccagta
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cgccgacctg tttctggccg ccaagaacct gtccgacgcc atcctgctga gcgacatcct
1620

gagagtgaac accgagatca ccaaggcccc cctgagcgcc tctatgatca agagatacga
1680

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1740

gtacaaagag attttcttcg accagagcaa gaacggctac gccggctaca ttgacggcgg
1800

agccagccag gaagagttct acaagttcat caagcccatc ctggaaaaga tggacggcac
1860

cgaggaactg ctcgtgaagc tgaacagaga ggacctgctg cggaagcagc ggaccttcga
1920

caacggcagc atcccccacc agatccacct gggagagctg cacgccattc tgcggcggca
1980

ggaagatttt tacccattcc tgaaggacaa ccgggaaaag atcgagaaga tcctgacctt
2040

ccgcatcccc tactacgtgg gccctctggc caggggaaac agcagattcg cctggatgac
2100

cagaaagagc gaggaaacca tcacccccctg gaacttcgag gaagtggtgg acaagggcgc
2160

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2220

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2280

agtgaaatac gtgaccgagg gaatgagaaa gcccgccttc ctgagcggcg agcagaaaaa
2340

ggccatcgtg gacctgctgt tcaagaccaa ccggaaagtg accgtgaagc agctgaaaga
2400

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2460

gttcaacgcc tccctgggca cataccacga tctgctgaaa attatcaagg acaaggactt
2520

cctggacaat gaggaaaacg aggacattct ggaagatatc gtgctgaccc tgacactgtt
2580

tgaggacaga gagatgatcg aggaacggct gaaaacctat gcccacctgt tcgacgacaa
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2700

gatcaacggc atccgggaca agcagtccgg caagacaatc ctggatttcc tgaagtccga
2760

cggcttcgcc aacagaaact tcatgcagct gatccacgac gacagcctga cctttaaaga
2820

ggacatccag aaagcccagg tgtccggcca gggcgatagc ctgcacgagc acattgccaa
2880

tctggccggc agccccgcca ttaagaaggg catcctgcag acagtgaagg tggtggacga
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3000

gaaccagacc acccagaagg gacagaagaa cagccgcgag agaatgaagc ggatcgaaga
3060

gggcatcaaa gagctgggca gccagatcct gaaagaacac cccgtggaaa acacccagct
3120

gcagaacgag aagctgtacc tgtactacct gcagaatggg cgggatatgt acgtggacca
3180

ggaactggac atcaaccggc tgtccgacta cgatgtggac catatcgtgc ctcagagctt
3240

tctgaaggac gactccatcg acaacaaggt gctgaccaga agcgacaaga accggggcaa
3300

gagcgacaac gtgccctccg aagaggtcgt gaagaagatg aagaactact ggcggcagct
3360

gctgaacgcc aagctgatta cccagagaaa gttcgacaat ctgaccaagg ccgagagagg
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3480

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3600

ccggaaggat ttccagtttt acaaagtgcg cgagatcaac aactaccacc acgcccacga
3660

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3720

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3840

caagaccgag attaccctgg ccaacggcga gatccggaag cggcctctga tcgagacaaa
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cggcgaaacc ggggagatcg tgtgggataa gggccgggat tttgccaccg tgcggaaagt
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caaagagtct atcctgccca agaggaacag cgataagctg atcgccagaa agaaggactg
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4140

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4200

caccatcatg gaaagaagca gcttcgagaa gaatcccatc gactttctgg aagccaaggg
4260

ctacaaagaa gtgaaaaagg acctgatcat caagctgcct aagtactccc tgttcgagct
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4560

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4620

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4680

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cctgatccac cagagcatca ccggcctgta cgagacacgg atcgacctgt ctcagctggg
4800

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4860

cgattagcaa taaaggatcg tttattttca ttggaagcgt gtgttggttt tttgatcagg
4920

cgcgggtacc aggtcgcggc cgctctagag catggctacg tagataagta gcatggcggg
4980

ttaatcatta actacaagga acccctagtg atggagttgg ccactccctc tctgcgcgct
5040

cgctcgctca ctgaggccgg gcgaccaaag gtcgcccgac gcccgggctt tgcccgggcg
5100

gcctcagtga gcgagcgagc gcgcagagag gga
5133

<210> 900
<211> 5185
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Polinucleótido sintético"

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120

actccatcac taggggttcc tgtggccaac tccatcacta ggggttcctt gtagttaatg
180

attaacccgc catgctactt atctacgtag ccatgctcta gattaattaa tgcccatgta
240

aggaggcaag gcctggggac acccgagatg cctggttata attaacccag acatgtggct
300

gccccccccc ccccaacacc tgctgcctct aaaaataacc ctgcatgcca tgttcccggc
360

gaagggccag ctgtcccccg ccagctagac tcagcactta gtttaggaac cagtgagcaa
420

gtcagccctt ggggcagccc atacaaggcc atggggctgg gcaagctgca cgcctgggtc
480

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540

cctggggaca gcccctcctg gctagtcaca ccctgtaggc tcctctatat aacccagggg
600

cacaggggct gccctcattc taccaccacc tccacagcac agacagacac tcaggagcca
660

gccagcgcta gcgccaccat gatggcccca aagaagaagc ggaaggtcgg tatccacgga
720

gtcccagcag ccgacaagaa gtacagcatc ggcctggaca tcggcaccaa ctctgtgggc
780

tgggccgtga tcaccgacga gtacaaggtg cccagcaaga aattcaaggt gctgggcaac
840

accgaccggc acagcatcaa gaagaacctg atcggagccc tgctgttcga cagcggcgaa
900

acagccgagg ccacccggct gaagagaacc gccagaagaa gatacaccag acggaagaac
960

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1080

atcttcggca acatcgtgga cgaggtggcc taccacgaga agtaccccac catctaccac
1140

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1200

ctggcccaca tgatcaagtt ccggggccac ttcctgatcg agggcgacct gaaccccgac
1260

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1320

gaaaacccca tcaacgccag cggcgtggac gccaaggcca tcctgtctgc cagactgagc
1380

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1500

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1800

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1920

ctgctgcgga agcagcggac cttcgacaac ggcagcatcc cccaccagat ccacctggga
1980

gagctgcacg ccattctgcg gcggcaggaa gatttttacc cattcctgaa ggacaaccgg
2040

gaaaagatcg agaagatcct gaccttccgc atcccctact acgtgggccc tctggccagg
2100

ggaaacagca gattcgcctg gatgaccaga aagagcgagg aaaccatcac cccctggaac
2160

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2280

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2400

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2460

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2700

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3000

aacatcgtga tcgaaatggc cagagagaac cagaccaccc agaagggaca gaagaacagc
3060

cgcgagagaa tgaagcggat cgaagagggc atcaaagagc tgggcagcca gatcctgaaa
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3180

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3240

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3300

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3360

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3480

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3600

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3660

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accgtggcct attctgtgct ggtggtggcc aaagtggaaa agggcaagtc caagaaactg
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4260

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4620

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4680

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4740

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4800

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4860

ggtcaagcta agaaaaagaa atgaatcgat tagcaataaa ggatcgttta ttttcattgg
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aagcgtgtgt tggtttttg atcaggcgcg ggtaccaggt cgcggccgct ctagagcatg
4980

gctacgtaga taagtagcat ggcgggttaa tcattaacta caaggaaccc ctagtgatgg
5040

agttaggaac ccctagtgat ggagttggcc actccctctc tgcgcgctcg ctcgctcact
5100

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5185

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<211> 6909
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Polinucleótido
sintético"

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120

tttaaggatt atttagggaa gagtgacaaa atagatggga actgggtgta gcgtcgtaag
180

ctaatacgaa aattaaaaat gacaaaatag tttggaacta gatttcactt atctggttcg
240

gatctcctag gcgatatcag tgatcacgga tctcgaccaa ttgacattat tgaagcaact
300

agtatcgatt ttatcagggt tattgtctca gacctgcagg cagctgcgcg ctcgctcgct
360

cactgaggcc gcccgggcaa agcccgggcg tcgggcgacc tttggtcgcc cggcctcagt
420

gagcgagcga gcgcgcagag agggagtggc caactccatc actaggggtt cctgtggcca
480

actccatcac taggggttcc ttgtagttaa tgattaaccc gccatgctac ttatctacgt
540

agccatgctc tagattaatt aatgcccatg taaggaggca aggcctgggg acacccgaga
600

tgcctggtta taattaaccc agacatgtgg ctgccccccc ccccccaaca cctgctgcct
660

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6600

ggtaaattgt cacaacgccg cgaatatagt ctttaccatg cccttggcca cgcccctctt
6660

taatacgacg ggcaatttgc acttcagaaa atgaagagtt tgctttagcc ataacaaaag
6720

tccagtatgc tttttcacag cataactgga ctgatttcag tttacaacta ttctgtctag
6780

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6840

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<212> ADN
<213> Secuencia artificial

<220>
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sintético"

<400> 903
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<210> 904
<211> 3
<212> ADN
<213> Desconocido

<220>
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oligonucleótido de codón de detención"

<400> 904
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<210> 905

<211> 3
<212> ADN
<213> Desconocido

<220>
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oligonucleótido de codón de detención"

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3

<210> 906
<211> 3
<212> ADN
<213> Desconocido

<220>
<221> fuente
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oligonucleótido de codón de detención"

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3

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<211> 166
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<213> Secuencia artificial

<220>
<221> fuente
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sintético"

<400> 907
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ttagggaaga gtgacaaaat agatgggaac tgggtgtagc gtcgtaagct aatacgaaaa
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ttaaaaatga caaaatagtt tggaactaga tttcacttat ctggtt
166

<210> 908
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<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
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ataactggac tgatttcagt ttacaactat tctgtctagt ttaagacttt attgtcatag 180

tttagatcta ttttgttcag tttaagactt tattgtccgc ccaca 225

<210> 909
<211> 1155
<212> ADN
<213> Secuencia artificial

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<221> fuente
<223> /note="Descripción de la secuencia artificial: Polinucleótido sintético"

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cgccgcgacg gccgaggtct tccgatctcc tgaagccagg gcagatccgt gcacagcacc 180

ttgccgtaga agaacagcaa ggccgccaat gcctgacgat gcgtggagac cgaaaccttg 240

cgctcgttcg ccagccagga cagaaatgcc tcgacttcgc tgctgcccaa ggttgccggg 300

tgacgcacac cgtggaaacg gatgaaggca cgaacccagt tgacataagc ctgttcggtt 360

cgtaaactgt aatgcaagta gcgtatgcgc tcacgcaact ggtccagaac cttgaccgaa 420

cgcagcggtg gtaacggcgc agtggcggtt ttcatggctt gttatgactg ttttttgta 480

cagtctatgc ctcgggcatc caagcagcaa gcgcgttacg ccgtgggtcg atgtttgatg
540

ttatggagca gcaacgatgt tacgcagcag caacgatgtt acgcagcagg gcagtcgccc
600

taaaacaaag ttaggtggct caagtatggg catcattcgc acatgtaggc tcggccctga
660

ccaagtcaaa tccatgcggg ctgctcttga tcttttcggt cgtgagttcg gagacgtagc
720

cacctactcc caacatcagc cggactccga ttacctcggg aacttgctcc gtagtaagac
780

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840

tctgcccaag tttgagcagc cgcgtagtga gatctatatc tatgatctcg cagtctccgg
900

cgagcaccgg aggcagggca ttgccaccgc gctcatcaat ctcctcaagc atgaggccaa
960

cgcgcttggt gcttatgtga tctacgtgca agcagattac ggtgacgatc ccgcagtggc
1020

tctctataca aagttgggca tacgggaaga agtgatgcac tttgatatcg acccaagtac
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1140

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<210> 910
<211> 2861
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Polinucleótido
sintético"

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120

cctccatcat ctaggtttgc cagatctgat atcggcgcgc ccctgggcgc gcccgagtcc
180

aacacccgtg ggaatcccat gggcaccatg gcccctcgct ccaaaaatgc tttcgcgtcg
240

cgcagacact gctcggtagt ttcggggatc agcgtttgag taagagcccg cgtctgaacc
300

ctccgcgccg ccccggcccc agtggaaaga cgcgcaggca aaacgcacca cgtgacggag
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cgtgaccgcg cgccgagcgc gcgccaaggt cgggcaggaa gagggcctat ttcccatgat
420

tccttcatat ttgcatatac gatacaaggc tgttagagag ataattagaa ttaatttgac
480

tgtaaacaca aagatattag tacaaaatac gtgacgtaga aagtaataat ttcttgggta
540

gtttgcagtt ttaaaattat gttttaaaat ggactatcat atgcttaccg taacttgaaa
600

gtatttcgat ttcttggctt tatatatctt gtggaaagga cgaaacaccg cactagagta
660

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720

cgttatcaac ttgaaaaagt ggcaccgagt cggtgctttt tttgcggccg cgctcggcgc
780

gcccatattt gcatgtcgct atgtgttctg ggaaatcacc ataaacgtga aatgtctttg
840

gatttgggaa tcttataagt tctgtatgag accacggtac accgcactag agtaacagtc
900

tgacgtttaa gagctatgct ggaaacagca tagcaagttt aaataaggct agtccgttat
960

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1020

cagtatttag catgccccac ccatctgcaa ggcattctgg atagtgtcaa aacagccgga
1080

aatcaagtcc gtttatctca aactttagca ttttgggaat aaatgatatt tgctatgctg
1140

gttaaattag attttagtta aatttcctgc tgaagctcta gtacgataag taacttgacc
1200

taagtgtaaa gttgagattt ccttcaggtt tatatagctt gtgcgccgcc tgggtacacc
1260

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1320

taaggctagt ccgttatcaa cttgaaaaag tggcaccgag tcggtgcttt ttttgcggcc
1380

gcgcttgcgg ccgcctcgag tgatcaaaaa aaccaacaca cgcttccaat gaaaataaac
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1500

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1560

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1620

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1680

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1740

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1800

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1920

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1980

aggtcagggt ggtcacgagg gtgggccagg gcacgggcag cttgccggtg gtgcagatga
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2100

tgtggccgtt tacgtcgccg tccagctcga ccaggatggg caccaccccg gtgaacagct
2160

cctcgccctt gctcaccatg gtggcgaccg gtggatcccg ggcccgcggg gtggctttac
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caacagtacc cggaatgcca agcttactta gatcgcagtc tcgacgctgg ctggctcctg
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2460

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2580

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2640

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2760

cgctcgctcg ctcactgagg ccgcccgggc aaagcccggg cgtcgggcga cctttggtcg
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2861

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<211> 2861
<212> ADN
<213> Secuencia artificial

<220>
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<223> /note="Descripción de la secuencia artificial: Polinucleótido
sintético"

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120

actccatcac taggggttcc tagatctgat atcggcgcgc ccctgggcgc gcccgagtcc
180

aacacccgtg ggaatcccat gggcaccatg gcccctcgct ccaaaaatgc tttcgcgtcg
240

cgcagacact gctcggtagt ttcggggatc agcgtttgag taagagcccg cgtctgaacc
300

ctccgcgccg ccccggcccc agtggaaaga cgcgcaggca aaacgcacca cgtgacggag
360

cgtgaccgcg cgccgagcgc gcgccaaggt cgggcaggaa gagggcctat ttcccatgat
420

tccttcatat ttgcatatac gatacaaggc tgttagagag ataattagaa ttaatttgac
480

tgtaaacaca aagatattag tacaaaatac gtgacgtaga aagtaataat ttcttgggta
540

gtttgcagtt ttaaaattat gttttaaaat ggactatcat atgcttaccg taacttgaaa
600

gtatttcgat ttcttggctt tatatatctt gtggaaagga cgaaacaccg cactagagta
660

acagtctgac gtttaagagc tatgctggaa acagcatagc aagtttaaat aaggctagtc
720

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780

gcccatattt gcatgtcgct atgtgttctg ggaaatcacc ataaacgtga aatgtctttg
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900

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960

caacttgaaa aagtggcacc gagtcggtgc tttttttgcg gccgctgacg gcgcgccctg
1020

cagtatttag catgccccac ccatctgcaa ggcattctgg atagtgtcaa aacagccgga
1080

aatcaagtcc gtttatctca aactttagca ttttgggaat aaatgatatt tgctatgctg
1140

gttaaattag attttagtta aatttcctgc tgaagctcta gtacgataag taacttgacc
1200

taagtgtaaa gttgagattt ccttcaggtt tatatagctt gtgcgccgcc tgggtacacc
1260

gcactagagt aacagtctga cgtttaagag ctatgctgga aacagcatag caagtttaaa
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taaggctagt ccgttatcaa cttgaaaaag tggcaccgag tcggtgcttt ttttgcggcc
1380

gcgcttgcgg ccgcctcgag tgatcaaaaa aaccaacaca cgcttccaat gaaaataaac
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1500

cggtcacgaa ctccagcagg accatgtgat cgcgcttctc gttggggtct ttgctcaggg
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1680

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1860

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1920

acttgaagaa gtcgtgctgc ttcatgtggt cggggtagcg gctgaagcac tgcacgccgt
1980

aggtcagggt ggtcacgagg gtgggccagg gcacgggcag cttgccggtg gtgcagatga
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acttcagggt cagcttgccg taggtggcat cgccctcgcc ctcgccggac acgctgaact
2100

tgtggccgtt tacgtcgccg tccagctcga ccaggatggg caccaccccg gtgaacagct
2160

cctcgcccct gctcaccatg gtggcgaccg gtggatcccg ggcccgcggg gtggctttac
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caacagtacc cggaatgcca agcttactta gatcgcagtc tcgacgctgg ctggctcctg
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atggcatgca gggttatttt tagaggcagc aggtgttggg gggggggggg cagccacatg
2640

tctgggttaa ttataaccag gcatctcggg tgtccccagg ccttgcctcc ttacatgggc
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acgtcgacga tatcagatct aggaacccct agtgatggag ttggccactc cctctctgcg
2760

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2861

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<213> Secuencia artificial

<220>
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sintético"

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120

tttaaggatt atttagggaa gagtgacaaa atagatggga actgggtgta gcgtcgtaag
180

ctaatacgaa aattaaaaat gacaaaatag tttggaacta gatttcactt atctggttcg
240

gatctcctag gcgatatcag tgatcacgga tctcgaccaa ttgacattat tgaagcaact
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agtatcgatt ttatcagggt tattgtctca gacctgcagg cagctgcgcg ctcgctcgct
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cactgaggcc gcccgggcaa agcccgggcg tcgggcgacc tttggtcgcc cggcctcagt
420

gagcgagcga gcgcgcagag agggagtggc caactccatc actaggggtt cctagatctg
480

atatcggcgc gcccctgggc gcgcccgagt ccaacacccg tgggaatccc atgggcacca
540

tggcccctcg ctccaaaaat gctttcgcgt cgcgcagaca ctgctcggta gtttcgggga
600

tcagcgtttg agtaagagcc cgcgtctgaa ccctccgcgc cgccccggcc ccagtggaaa
660

gacgcgcagg caaaacgcac cacgtgacgg agcgtgaccg cgcgccgagc gcgcgccaag
720

gtcgggcagg aagagggcct atttcccatg attccttcat atttgcatat acgatacaag
780

gctgttagag agataattag aattaatttg actgtaaaca caaagatatt agtacaaaat
840

acgtgacgta gaaagtaata atttcttggg tagtttgcag ttttaaaatt atgttttaaa
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aaacagcata gcaagtttaa ataaggctag tccgttatca acttgaaaaa gtggcaccga
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1200

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1320

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1380

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1980

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2100

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3180

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3240

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3360

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3840

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3900

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660

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720

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780

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900

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120

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gcctcagtga gcgagcgagc gcgcagctgc ctgcaggcat gcaagctgta gccaaccact
2640

agaactatag ctagagtcct gggcgaacaa acgatgctcg ccttccagaa aaccgaggat
2700

gcgaaccact tcatccgggg tcagcaccac cggcaagcgc cgcgacggcc gaggtcttcc
2760

gatctcctga agccagggca gatccgtgca cagcaccttg ccgtagaaga acagcaaggc
2820

cgccaatgcc tgacgatgcg tggagaccga aaccttgcgc tcgttcgcca gccaggacag
2880

aaatgcctcg acttcgctgc tgcccaaggt tgccgggtga cgcacaccgt ggaaacggat
2940

gaaggcacga acccagttga cataagcctg ttcggttcgt aaactgtaat gcaagtagcg
3000

tatgcgctca cgcaactggt ccagaacctt gaccgaacgc agcggtggta acggcgcagt
3060

ggcggttttc atggcttgtt atgactgttt ttttgtacag tctatgcctc gggcatccaa
3120

gcagcaagcg cgttacgccg tgggtcgatg tttgatgtta tggagcagca acgatgttac
3180

gcagcagcaa cgatgttacg cagcagggca gtcgccctaa aacaaagtta ggtggctcaa
3240

gtatgggcat cattcgcaca tgtaggctcg gccctgacca agtcaaatcc atgcgggctg
3300

ctcttgatct tttcggtcgt gagttcggag acgtagccac ctactcccaa catcagccgg
3360

actccgatta cctcgggaac ttgctccgta gtaagacatt catcgcgctt gctgccttcg
3420

accaagaagc ggttgttggc gctctcgcgg cttacgttct gcccaagttt gagcagccgc
3480

gtagtgagat ctatatctat gatctcgcag tctccggcga gcaccggagg cagggcattg
3540

ccaccgcgct catcaatctc ctcaagcatg aggccaacgc gcttggtgct tatgtgatct
3600

acgtgcaagc agattacggt gacgatcccg cagtggctct ctatacaaag ttgggcatac
3660

gggaagaagt gatgcacttt gatatcgacc caagtaccgc cacctaacaa ttcgttcaag
3720

ccgagatcgg cttcccggcc gcggagttgt tcggtaaatt gtcacaacgc cgcgaatata
3780

gtctttacca tgcccttggc cacgcccctc tttaatacga cgggcaattt gcacttcaga
3840

aaatgaagag tttgctttag ccataacaaa agtccagtat gctttttcac agcataactg
3900

gactgatttc agtttacaac tattctgtct agtttaagac tttattgtca tagtttagat
3960

ctattttgtt cagtttaaga ctttattgtc cgcccacacc cgcttacgc
4009

<210> 921
<211> 4009
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente

<223> /note="Descripción de la secuencia artificial: Polinucleótido sintético"

<400> 921
aagatgacgg tttgtcacat ggagttggca ggatgtttga ttaaaaacat aacaggaaga 60

aaaatgcccc gctgtgggcg gacaaaatag ttgggaactg ggaggggtgg aaatggagtt 120

tttaaggatt atttagggaa gagtgacaaa atagatggga actgggtgta gcgtcgtaag 180

ctaatacgaa aattaaaaat gacaaaatag tttggaacta gatttcactt atctggttcg 240

gatctcctag gcgatatcag tgatcacgga tctcgaccaa ttgacattat tgaagcaact 300

agtatcgatt ttatcagggt tattgtctca gaccactccc tctatgcgcg ctcgctcact 360

cactcggccc tggagaccaa aggtctccag actgccggcc tctggccggc agggccgagt 420

gagtgagcga gcgcgcatag agggagtggg tacctccatc atctaggttt gccagatctg 480

atatcggcgc gcccctgggc gcgcccgagt ccaacacccg tgggaatccc atgggcacca 540

tggcccctcg ctccaaaaat gctttcgcgt cgcgcagaca ctgctcggta gtttcgggga 600

tcagcgtttg agtaagagcc cgcgtctgaa ccctccgcgc cgccccggcc ccagtggaaa 660

gacgcgcagg caaaacgcac cacgtgacgg agcgtgaccg cgcgccgagc gcgcgccaag 720

gtcgggcagg aagagggcct atttcccatg attccttcat atttgcatat acgatacaag 780

gctgttagag agataattag aattaatttg actgtaaaca caaagatatt agtacaaaat 840

acgtgacgta gaaagtaata atttcttggg tagtttgcag ttttaaaatt atgttttaaa 900

atggactatc atatgcttac cgtaacttga aagtatttcg atttcttggc tttatatatc 960

ttgtggaaag gacgaaacac cgcaccagag taacagtctg acgtttaaga gctatgctgg 1020

aaacagcata gcaagtttaa ataaggctag tccgttatca acttgaaaaa gtggcaccga
1080

gtcggtgctt tttttgcggc cgcgctcggc gcgcccatat ttgcatgtcg ctatgtgttc
1140

tgggaaatca ccataaacgt gaaatgtctt tggatttggg aatcttataa gttctgtatg
1200

agaccacggt acaccgcacc agagtaacag tctgacgttt aagagctatg ctggaaacag
1260

catagcaagt ttaaataagg ctagtccgtt atcaacttga aaaagtggca ccgagtcggt
1320

gctttttttg cggccgctga cggcgcgccc tgcagtattt agcatgcccc acccatctgc
1380

aaggcattct ggatagtgtc aaaacagccg gaaatcaagt ccgtttatct caaactttag
1440

cattttggga ataaatgata tttgctatgc tggttaaatt agattttagt taaatttcct
1500

gctgaagctc tagtacgata agtaacttga cctaagtgta aagttgagat ttccttcagg
1560

tttatatagc ttgtgcgccg cctgggtaca ccgcaccaga gtaacagtct gacgtttaag
1620

agctatgctg gaaacagcat agcaagttta aataaggcta gtccgttatc aacttgaaaa
1680

agtggcaccg agtcggtgct ttttttgcgg ccgcgctgtt taaaccaaca aaatcagcag
1740

ctaatgaagg caagtcagca ggtcactcat cattttccac ttcggcaatg cagtgggatt
1800

attccaacag aggtttttca cagcattcct tcagttaact ggagatcgaa tcttgatttt
1860

cacagatata cttggcaagg tccgccctgt catcagcaca ttcaagcaga tctccatggc
1920

agcattccgt gtggacttag gtaagatctg tcactaactt ggaaacttct gcaaactcag
1980

cttagggaaa tctctggctc aggcgagcta ctgcctcagc ttagaaagct ctttctccaa
2040

attattggag actggcacac ttaagtccct gttaggcaga cgaagccttc ccttcatccc
2100

gaagttcatc gagctttggc aacaggcagg cagctttatc agcagcttgg caacattctg
2160

taaaagcagc tttatacctt taagcaaaga aaaggagttc cggggcataa aagtaaggat
2220

gtcttctggc aatttataat aagtattttt tcaaaaatgt ctcttcattg tcatgaaaag
2280

cagtgcatca cacatcaacc tctggtctca ccaatcgggg gaggtttggg ttgtttactt
2340

agtgttgcaa gaattatttt attctctcag gttcttgttt tgcacagcag tcagctcatt
2400

caccataggt ttcacgaaga gttgctgcgg ccgcctcgat aatacgactc actatagggt
2460

cgacgatatc agatctagga acccctagtg atggagttgg ccactccctc tctgcgcgct
2520

cgctcgctca ctgaggccgc ccgggcaaag cccgggcgtc gggcgacctt tggtcgcccg
2580

gcctcagtga gcgagcgagc gcgcagagag ggagtggcat gcaagctgta gccaaccact
2640

agaactatag ctagagtcct gggcgaacaa acgatgctcg ccttccagaa aaccgaggat
2700

gcgaaccact tcatccgggg tcagcaccac cggcaagcgc cgcgacggcc gaggtcttcc
2760

gatctcctga agccagggca gatccgtgca cagcaccttg ccgtagaaga acagcaaggc
2820

cgccaatgcc tgacgatgcg tggagaccga aaccttgcgc tcgttcgcca gccaggacag
2880

aaatgcctcg acttcgctgc tgcccaaggt tgccgggtga cgcacaccgt ggaaacggat
2940

gaaggcacga acccagttga cataagcctg ttcggttcgt aaactgtaat gcaagtagcg
3000

tatgcgctca cgcaactggt ccagaacctt gaccgaacgc agcggtggta acggcgcagt
3060

ggcggttttc atggcttgtt atgactgttt ttttgtacag tctatgcctc gggcatccaa
3120

gcagcaagcg cgttacgccg tgggtcgatg tttgatgtta tggagcagca acgatgttac
3180

gcagcagcaa cgatgttacg cagcagggca gtcgccctaa aacaaagtta ggtggctcaa
3240

gtatgggcat cattcgcaca tgtaggctcg gccctgacca agtcaaatcc atgcgggctg
3300

ctcttgatct tttcggtcgt gagttcggag acgtagccac ctactcccaa catcagccgg
3360

actccgatta cctcgggaac ttgctccgta gtaagacatt catcgcgctt gctgccttcg
3420

accaagaagc ggttgttggc gctctcgcgg cttacgttct gcccaagttt gagcagccgc
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gtagtgagat ctatatctat gatctcgcag tctccggcga gcaccggagg cagggcattg
3540

ccaccgcgct catcaatctc ctcaagcatg aggccaacgc gcttggtgct tatgtgatct
3600

acgtgcaagc agattacggt gacgatcccg cagtggctct ctatacaaag ttgggcatac
3660

gggaagaagt gatgcacttt gatatcgacc caagtaccgc cacctaacaa ttcgttcaag
3720

ccgagatcgg cttcccggcc gcggagttgt tcggtaaatt gtcacaacgc cgcgaatata
3780

gtctttacca tgcccttggc cacgcccctc tttaatacga cgggcaattt gcacttcaga
3840

aaatgaagag tttgctttag ccataacaaa agtccagtat gctttttcac agcataactg
3900

gactgatttc agtttacaac tattctgtct agtttaagac tttattgtca tagtttagat
3960

ctattttgtt cagtttaaga ctttattgtc cgcccacacc cgcttacgc
4009

<210> 922
<211> 472
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Polinucleótido
sintético"

<400> 922
cgagtccaac acccgtggga atcccatggg caccatggcc cctcgctcca aaaatgcttt
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cgcgtcgcgc agacactgct cggtagtttc ggggatcagc gtttgagtaa gagcccgcgt
120

ctgaaccctc cgcgccgccc cggccccagt ggaaagacgc gcaggcaaaa cgcaccacgt
180

gacggagcgt gaccgcgcgc cgagcgcgcg ccaaggtcgg gcaggaagag ggcctatttc
240

ccatgattcc ttcatatttg catatacgat acaaggctgt tagagagata attagaatta
300

atttgactgt aaacacaaag atattagtac aaaatacgtg acgtagaaag taataatttc
360

ttgggtagtt tgcagtttta aaattatgtt ttaaaatgga ctatcatatg cttaccgtaa
420

cttgaaagta tttcgatttc ttggctttat atatcttgtg gaaaggacga aa
472

<210> 923
<211> 108
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Polinucleótido
sintético"

<400> 923
gctcggcgcg cccatatttg catgtcgcta tgtgttctgg gaaatcacca taaacgtgaa
60

atgtctttgg atttgggaat cttataagtt ctgtatgaga ccacggta
108

<210> 924
<211> 251
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Polinucleótido
sintético"

<400> 924
tgacggcgcg ccctgcagta tttagcatgc cccacccatc tgcaaggcat tctggatagt
60

gtcaaaacag ccggaaatca agtccgttta tctcaaactt tagcattttg ggaataaatg
120

atatttgcta tgctggttaa attagatttt agttaaattt cctgctgaag ctctagtacg
180

ataagtaact tgacctaagt gtaaagttga gatttccttc aggtttatat agcttgtgcg
240

ccgcctgggt a
251

<210> 925
<211> 251
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Polinucleótido
sintético"

<400> 925
tgacggcgcg ccctgcagta tttagcatgc cccacccatc tgcaaggcat tctggatagt
60

gtcaaaacag ccggaaatca agtccgttta tctcaaactt tagcattttg ggaataaatg
120

atatttgcta tgctggttaa attagatttt agttaaattt cctgctgaag ctctagtacg
180

ataagtaact tgacctaagt gtaaagttga gatttccttc aggtttatat agcttgtgcg
240

ccgcctgggt a
251

<210> 926
<211> 26
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador
sintético"

<400> 926
caccgaaatg atgagtgaag ttatat
26

<210> 927
<211> 26
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador sintético"

<400> 927
aaacatataa cttcactcat catttc
26

<210> 928
<211> 25
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador sintético"

<400> 928
caccggtttg ttcaaaagcg tggct
25

<210> 929
<211> 24
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador sintético"

<400> 929
aaacagccac gcttttgaac aaac
24

<210> 930
<211> 45
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador
sintético"

<400> 930
gaattgtaat acgactcact ataggaatga tgagtgaagt tatat
45

<210> 931
<211> 45
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador
sintético"

<400> 931
gaattgtaat acgactcact atagggtttg ttcaaaagcg tggct
45

<210> 932
<211> 22
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador
sintético"

<400> 932
aaaagcaccg actcggtgcc ac
22

<210> 933
<211> 24
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador
sintético"

<400> 933
caccggacac aatgtaggaa gcct
24

<210> 934
<211> 24
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador
sintético"

<400> 934
aaacaggctt cctacattgt gtcc
24

<210> 935
<211> 40
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador
sintético"

<400> 935
gaattgtaat acgactcact ggacacaatg taggaagcct
40

<210> 936
<211> 22
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador
sintético"

<400> 936
aaaagcaccg actcggtgcc ac
22

<210> 937
<211> 25
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente

<223> /note="Descripción de la secuencia artificial: Cebador sintético"

<400> 937
ggattgactg aaatgatggc caagg
25

<210> 938
<211> 24
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador sintético"

<400> 938
ctgccacgat tactctgctt ccag
24

<210> 939
<211> 20
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador sintético"

<400> 939
agcaggcaga gaaggtggta
20

<210> 940
<211> 22
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador sintético"

<400> 940
gggcgtatct cttcatagcc tt
22

<210> 941

<211> 20
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador
sintético"

<400> 941
gcgtgtgtgt ttgtttaggg
20

<210> 942
<211> 24
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador
sintético"

<400> 942
caccgagagt aacagtctga ctgg
24

<210> 943
<211> 25
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador
sintético"

<400> 943
aaacgtcaga ctgttactct agtgc
25

<210> 944
<211> 25
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador
sintético"

<400> 944
caccgcacta gagtaacagt ctgac
25

<210> 945
<211> 24
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador
sintético"

<400> 945
aaacccagtc agactgttac tctc
24

<210> 946
<211> 141
<212> ADN
<213> Virus adenoasociado

<400> 946
aggaacccct agtgatggag ttggccactc cctctctgcg cgctcgctcg ctcactgagg
60

ccgcccgggc aaagcccggg cgtcgggcga cctttggtcg cccggcctca gtgagcgagc
120

gagcgcgcag agagggagtg g
141

<210> 947
<211> 20
<212> ADN
<213> Homo sapiens

<400> 947
cagagtaaca gtctgagtag
20

<210> 948
<211> 22
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /note="Descripción de la secuencia artificial: Cebador

sintético”

<400> 948
gtatgttgtg tggaattgtg ag
22

<210> 949
<211> 11
<212> PRT
<213> Homo sapiens

<400> 949
Met Leu Trp Trp Glu Glu Val Glu Asp Cys Tyr
1 5 10

<210> 950
<211> 7
<212> PRT
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota=“Descripción de la secuencia artificial: Péptido sintético”

<400> 950
Met Ser Glu Val Ser Ser Asp
1 5

<210> 951
<211> 16
<212> PRT
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota=“Descripción de la secuencia artificial: Péptido sintético”

<400> 951
Met Thr Glu Ile Ile Leu Leu Ile Phe Phe Pro Ala Tyr Phe Leu Asn
1 5 10 15

<210> 952
<211> 13
<212> PRT
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota=“Descripción de la secuencia artificial: Péptido sintético”

<400> 952
Met Ser Ala Arg Lys Leu Arg Asn Leu Ser Tyr Lys Lys
1 5 10

<210> 953
<211> 10
<212> PRT
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Péptido sintético"

<400> 953
Met Leu His Arg Lys Thr Tyr His Val Lys
1 5 10

<210> 954
<211> 26
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 954
ctgccagtca gactgttact ctagtg
26

<210> 955
<211> 28
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 955
ctttactagt agtttgtctt ccatacct
28

<210> 956
<211> 26
<212> ADN
<213> Mus musculus

<400> 956
cactagagta acagtctgac tggcag
26

<210> 957
<211> 28
<212> ADN
<213> Mus musculus

<400> 957
aggtatggaa gacaaactac tagtaaag
28

<210> 958
<211> 34
<212> ADN
<213> Secuencia artificial

<220>
<221> fuente
<223> /nota="Descripción de la secuencia artificial: Oligonucleótido sintético"

<400> 958
aacactagct gccagtcaga ctgttactct agtg
34

<210> 959
<211> 34
<212> ADN
<213> Mus musculus

<400> 959
cactagagta acagtctgac tggcagctag tgtt
34

<210> 960
<211> 50
<212> ADN
<213> Mus musculus

<400> 960
ctttctttca aaaacactag ctgccagtca gactgttact ctagtgacac
50

<210> 961
<211> 51
<212> ADN
<213> Mus musculus

<400> 961
ctttctttca aaaacactag ctgccagtca agactgttac tctagtgaca c
51

<210> 962
<211> 14
<212> ADN
<213> Mus musculus

<400> 962
ctttctagtg acac
14

<210> 963
<211> 11
<212> ADN
<213> Mus musculus

<400> 963
ctttctttca c
11

<210> 964
<211> 18
<212> ADN
<213> Mus musculus

<400> 964
ctttctttct agtgacac
18

<210> 965
<211> 44
<212> ADN
<213> Mus musculus

<400> 965
ctttctttca aaaacactag ctgccactgt tactctagtg acac
44

<210> 966
<211> 46
<212> ADN
<213> Mus musculus

<400> 966
ctttctttca aaaacactag ctgccagact gttactctag tgacac
46

<210> 967
<211> 233
<212> ADN
<213> Mus musculus

<400> 967
ctgccagtca gactgttact ctagtgacac aatctgtggt tactaaggaa actgtcatct
60

ccaaactaga aatgccatct tctttgctgt tggaggtacc tgcactggca gacttcaacc
120

gagcttggac agaacttaca gactggctgt ctctgcttga tcgagttata aaatcacaga
180

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DESCRIPCIÓN

ESTRATEGIA OPTIMIZADA PARA MODIFICACIONES DE OMISIÓN DE EXONES MEDIANTE EL USO DE CRISPR/CAS9 CON SECUENCIAS GUÍA TRIPLES

REIVINDICACIÓN DE PRIORIDAD

La presente solicitud reivindica beneficio de prioridad de la solicitud provisional estadounidense n.º de serie 62/596.298, presentada el 8 de diciembre de 2017, la solicitud provisional estadounidense n.º de serie 62/544.499, presentada el 11 de agosto de 2017 y la solicitud provisional estadounidense n.º de serie 62/442.606 presentada el 5 de enero de 2017, el contenido de las cuales se incorpora a la presente en su totalidad mediante referencia.

CLÁUSULA DE APOYO FEDERAL DE FINANCIAMIENTO

Esta invención se hizo con el apoyo del gobierno conforme a la concesión n.º U54 HD 087351 otorgado por el Instituto Nacional de Salud. El gobierno tiene determinados derechos con respecto a la invención.

LISTADO DE SECUENCIAS

La presente solicitud contiene un listado de secuencias presentado en forma electrónica en formato ASCII e incorporado a la presente en su totalidad mediante referencia. Dicha copia de ASCII, creada el viernes, 5 de enero de 2018, se denomina UTFD_P3178WO.txt y tiene un tamaño de 1.316.974 bytes.

CAMPO DE LA DESCRIPCIÓN

La presente descripción hace referencia al campo de biología molecular, la medicina y la genética. Más particularmente, la descripción se refiere a composiciones y usos de estas para la edición genómica para corregir mutaciones *in vivo* mediante el uso de un enfoque de omisión de exones.

ANTECEDENTES

Las distrofias musculares (DM) son un grupo de más de 30 enfermedades genéticas caracterizadas por debilidad progresiva y degeneración de los músculos esqueléticos que controlan el movimiento. La distrofia muscular de Duchenne (DMD) es una de las formas más graves de DM que afecta aproximadamente a 1 de cada 5000 niños y se caracteriza por debilidad muscular progresiva y muerte prematura. La cardiomiopatía y la insuficiencia cardíaca son características comunes,

incurables y letales de la DMD. La enfermedad es causada por mutaciones en el gen que codifica la distrofina (*DMD*), una proteína intracelular grande que une el complejo de distroglicano en la superficie celular con el citoesqueleto subyacente, manteniendo de ese modo la integridad de la membrana de las células musculares durante la contracción. Las mutaciones en el gen de la distrofina causan la pérdida de la expresión de la distrofina, lo que causa fragilidad de la membrana muscular y atrofia muscular progresiva.

COMPENDIO

A pesar de los intensos esfuerzos para encontrar curas a través de una variedad de enfoques, que incluyen la transferencia de mioblastos, la administración viral y la omisión de exones mediada por oligonucleótidos, aún no hay ninguna cura para ningún tipo de distrofia muscular. Los autores de la presente invención usaron recientemente edición genómica mediada por repeticiones palindrómicas cortas agrupadas y regularmente espaciadas/Cas9 (CRISPR/Cas9) para corregir la mutación del gen de la distrofina (DMD) en ratones *mdx* después del nacimiento, un modelo para DMD. El suministro mediado por AAV *in vivo* de componentes de edición génica eliminó con éxito la secuencia genómica mutante mediante omisión de exones en las células musculares esqueléticas y cardíacas de ratones *mdx*. Mediante el uso de diferentes modos de administración de AAV9, los inventores restauraron la expresión de la proteína distrofina en el músculo esquelético y cardíaco de ratones *mdx*. El modelo de ratón mdx y la corrección del exón 23 mediante el uso de AAV de maquinaria de mioedición han sido útiles para demostrar el concepto de prueba del enfoque de omisión de exones mediante el uso de varios cortes en la región genómica que abarca la mutación *in vivo*. Sin embargo, enfoques más eficientes y seguros para la edición genómica y la DMD podrían proporcionar un medio más poderoso para intervenir en esta enfermedad.

En algunas modalidades, un ácido nucleico comprende una secuencia que codifica un primer ARN guía de DMD que se dirige a una primera secuencia diana genómica, una secuencia que codifica un segundo ARN guía de DMD que se dirige a una segunda secuencia diana genómica, una secuencia que codifica un primer promotor, en donde el primer promotor dirige la expresión de la secuencia que codifica el primer ARN guía de DMD, y una secuencia que codifica un segundo promotor, en donde el segundo promotor dirige la expresión de la secuencia que codifica el segundo ARN guía de DMD, en donde la primera secuencia diana genómica y la segunda secuencia diana genómica comprenden cada una un sitio aceptor de corte y empalme de distrofina. En algunas modalidades, la secuencia que codifica el primer promotor y la secuencia que codifica el segundo promotor son idénticas. En algunas modalidades, la secuencia que codifica el primer promotor y la secuencia que codifica el segundo promotor no son idénticas. En algunas modalidades, la secuencia que codifica el primer

promotor y la secuencia que codifica el segundo promotor comparten al menos 50 %, 60 %, 70 %, 80 %, 90 % o 95 % de identidad de secuencia. En algunas modalidades, la primera secuencia diana genómica y la segunda secuencia diana genómica son idénticas. En algunas modalidades, la primera secuencia diana genómica y la segunda secuencia diana genómica no son idénticas. En algunas modalidades, la primera secuencia diana genómica y la segunda secuencia diana genómica comparten al menos 50 %, 60 %, 70 %, 80 %, 90 % o 95 % de identidad de secuencia. En algunas modalidades, la primera secuencia diana genómica y la segunda secuencia diana genómica son complementarias. En algunas modalidades, el ácido nucleico comprende, además, una secuencia que codifica un tercer ARN guía de DMD que se dirige a una tercera secuencia diana genómica, y una secuencia que codifica un tercer promotor, en donde el tercer promotor dirige la expresión de la secuencia que codifica el tercer ARN guía de DMD, y en donde la tercera secuencia diana genómica comprende un sitio aceptor de corte y empalme de distrofina. En algunas modalidades, al menos dos de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor y la secuencia que codifica el tercer promotor son idénticas. En algunas modalidades, al menos dos de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor y la secuencia que codifica el tercer promotor no son idénticas. En algunas modalidades, al menos dos de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor y la secuencia que codifica el tercer promotor comparten al menos 50 %, 60 %, 70 %, 80 %, 90 % o 95 % de identidad de secuencia. En algunas modalidades, al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica y la tercera secuencia diana genómica son idénticas. En algunas modalidades, al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica y la tercera secuencia diana genómica no son idénticas. En algunas modalidades, al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica y la tercera secuencia diana genómica comparten al menos 50 %, 60 %, 70 %, 80 %, 90 % o 95 % de identidad de secuencia. En algunas modalidades, al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica y la tercera secuencia diana genómica son complementarias. En algunas modalidades, el ácido nucleico comprende, además, una secuencia que codifica un cuarto ARN guía de DMD que se dirige a una cuarta secuencia diana genómica, y una secuencia que codifica un cuarto promotor, en donde el cuarto promotor dirige la expresión de la cuarta secuencia que codifica un ARN guía de DMD, y en donde la cuarta secuencia diana genómica comprende un sitio aceptor de corte y empalme de distrofina. En algunas modalidades, al menos dos de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor y la secuencia que codifica el cuarto promotor son idénticas. En algunas modalidades, al menos dos de la secuencia que codifica el

primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor y la secuencia que codifica el cuarto promotor no son idénticas. En algunas modalidades, al menos dos de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor y la secuencia que codifica el cuarto promotor comparten al menos 50 %, 60 %, 70 %, 80 %, 90 % o 95 % de identidad de secuencia. En algunas modalidades, al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica, la tercera secuencia diana genómica y la cuarta secuencia diana genómica son idénticas. En algunas modalidades, al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica, la tercera secuencia diana genómica y la cuarta secuencia diana genómica no son idénticas. En algunas modalidades, al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica, la tercera secuencia diana genómica y la cuarta secuencia diana genómica comparten al menos 50 %, 60 %, 70 %, 80 %, 90 % o 95 % de identidad de secuencia. En algunas modalidades, al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica, la tercera secuencia diana genómica y la cuarta secuencia diana genómica son complementarias. En algunas modalidades, el ácido nucleico comprende, además, una secuencia que codifica un quinto ARN guía de DMD que se dirige a una quinta secuencia diana genómica, y una secuencia que codifica un quinto promotor, en donde el quinto promotor dirige la expresión de la secuencia que codifica el quinto ARN guía de DMD, en donde la quinta secuencia diana genómica comprende un sitio aceptor de corte y empalme de distrofina. En algunas modalidades, al menos dos de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor y la secuencia que codifica el quinto promotor son idénticas. En algunas modalidades, al menos dos de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor son idénticas y la secuencia que codifica el quinto promotor no son idénticas. En algunas modalidades, al menos dos de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor son idénticas y la secuencia que codifica el quinto promotor comparten al menos 50 %, 60 %, 70 %, 80 %, 90 % o 95 % de identidad de secuencia. En algunas modalidades, al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica, la tercera secuencia diana genómica, la cuarta secuencia diana genómica y la quinta secuencia diana genómica son idénticas. En algunas modalidades, al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica, la tercera secuencia diana genómica, la cuarta secuencia diana genómica y la quinta secuencia diana genómica no son idénticas. En algunas modalidades, al menos

dos de la primera secuencia diana genómica, la segunda secuencia diana genómica, la tercera secuencia diana genómica, la cuarta secuencia diana genómica y la quinta secuencia diana genómica comparten al menos 50 %, 60 %, 70 %, 80 %, 90 % o 95 % de identidad de secuencia. En algunas modalidades, al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica, la tercera secuencia diana genómica, la cuarta secuencia diana genómica y la quinta secuencia diana genómica son complementarias. En algunas modalidades, el ácido nucleico comprende, además, al menos una secuencia que codifica un ARN guía de DMD adicional que se dirige a una secuencia diana genómica, y al menos un promotor adicional, en donde el promotor adicional dirige la expresión de la secuencia que codifica el ARN guía de DMD adicional, en donde la secuencia diana genómica adicional comprende un sitio aceptor de corte y empalme de distrofina. En algunas modalidades, el sitio aceptor de corte y empalme de distrofina comprende el sitio aceptor de corte y empalme 5' del exón 51. En algunas modalidades, la secuencia que codifica el primer promotor o la secuencia que codifica el segundo promotor comprende una secuencia que codifica un promotor constitutivo. En algunas modalidades, el primer promotor o el segundo promotor comprende un promotor constitutivo. En algunas modalidades, al menos una de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor y la secuencia que codifica el quinto promotor comprende una secuencia que codifica un promotor constitutivo. En algunas modalidades, al menos uno del primer promotor, el segundo promotor, el tercer promotor, el cuarto promotor y el quinto promotor comprenden un promotor constitutivo. En algunas modalidades, la secuencia que codifica el primer promotor o la secuencia que codifica el segundo promotor comprende una secuencia que codifica un promotor inducible. En algunas modalidades, al menos uno del primer promotor, el segundo promotor, el tercer promotor, el cuarto promotor y el quinto promotor comprende un promotor inducible. En algunas modalidades, la secuencia que codifica el primer promotor o la secuencia que codifica el segundo promotor comprende una secuencia que codifica un promotor específico del tipo celular. En algunas modalidades, al menos una de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor y la secuencia que codifica el quinto promotor comprende una secuencia que codifica un promotor específico del tipo celular. En algunas modalidades, el promotor específico de tipo celular comprende un promotor específico de los músculos. En algunas modalidades, la secuencia que codifica el primer promotor o la secuencia que codifica el segundo promotor comprende una secuencia que codifica un promotor U6, un promotor H1 o un promotor 7SK. En algunas modalidades, al menos una de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que

codifica el cuarto promotor y la secuencia que codifica el quinto promotor comprende una secuencia que codifica un promotor U6, un promotor H1 o un promotor 7SK. En algunas modalidades, al menos una de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor y la secuencia que codifica el quinto promotor comprende una secuencia que codifica un promotor U6. En algunas modalidades, al menos una de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor y la secuencia que codifica el quinto promotor comprende una secuencia que codifica un promotor H1. En algunas modalidades, al menos una de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor y la secuencia que codifica el quinto promotor comprende una secuencia que codifica un promotor 7SK. En algunas modalidades, la secuencia que codifica el primer ARN guía de DMD, la secuencia que codifica el segundo ARN de guía DMD y la secuencia que codifica el tercer ARN guía de DMD son idénticas y el sitio aceptor de corte y empalme 5’ comprende un sitio aceptor de corte y empalme 5’ del exón 51 . En algunas modalidades, la secuencia que codifica el primer promotor comprende una secuencia que codifica un promotor U6, la secuencia que codifica el segundo promotor comprende una secuencia que codifica un promotor H1, y la secuencia que codifica el tercer promotor comprende un promotor 7SK. En algunas modalidades, el ácido nucleico comprende una secuencia de ADN. En algunas modalidades, el ácido nucleico comprende una secuencia de ARN. En algunas modalidades, el ácido nucleico comprende, además, una o más secuencias que codifican una repetición terminal invertida (ITR). En algunas modalidades, el ácido nucleico comprende, además, una secuencia que codifica una repetición terminal invertida (ITR) 5’ y una secuencia que codifica una ITR 3’. En algunas modalidades, la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un virus adenoasociado (AAV). En algunas modalidades, la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un virus adenoasociado (AAV) del serotipo 2 (AAV2). En algunas modalidades, la secuencia que codifica la repetición terminal invertida 5’ (ITR) y la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un AAV2. En algunas modalidades, la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un virus adenoasociado (AAV) del serotipo 4 (AAV4). En algunas modalidades, la secuencia que codifica la repetición terminal invertida 5’ (ITR) y la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un AAV4. En algunas modalidades, la secuencia que codifica la repetición terminal invertida 5’

(ITR) o la secuencia que codifica una ITR 3' comprende o consiste en 145 nucleótidos. En algunas modalidades, la secuencia que codifica la repetición terminal invertida 5' (ITR) o la secuencia que codifica una ITR 3' comprende o consiste en 115 nucleótidos. En algunas modalidades, la secuencia que codifica la repetición terminal invertida 5' (ITR) o la secuencia que codifica una ITR 3' comprende o consiste en 141 nucleótidos. En algunas modalidades, el ácido nucleico comprende, además, una secuencia de poliadenosina (poli A). En algunas modalidades, la secuencia de poli A es una secuencia de poli A mini. En algunas modalidades, la secuencia que codifica el primer ARN guía de DMD o la secuencia que codifica el segundo ARN guía de DMD comprende la secuencia de cualquiera de las SEQ ID NO. 60-382, 706-708 y 712-789. En algunas modalidades, la secuencia que codifica el primer ARN guía de DMD o la secuencia que codifica el segundo ARN guía de DMD comprende la secuencia de la SEQ ID NO. 714.

También se proporciona un vector que comprende un ácido nucleico que comprende una secuencia que codifica un primer ARN guía de DMD que se dirige a una primera secuencia diana genómica, una secuencia que codifica un segundo ARN guía de DMD que se dirige a una segunda secuencia diana genómica, una secuencia que codifica un primer promotor, en donde el primer promotor dirige la expresión de la secuencia que codifica el primer ARN guía de DMD, y una secuencia que codifica un segundo promotor, en donde el segundo promotor dirige la expresión de la secuencia que codifica el segundo ARN guía de DMD, en donde la primera secuencia diana genómica y la segunda secuencia diana genómica comprenden cada una un sitio aceptor de corte y empalme de distrofina. En algunas modalidades, el vector comprende, además, una secuencia que codifica una repetición terminal invertida de un elemento transponible. En algunas modalidades, el elemento transponible es un transposón. En algunas modalidades, el transposón es un transposón Tn7. En algunas modalidades, el vector es un vector no viral. En algunas modalidades, el vector no viral es un plásmido. En algunas modalidades, el vector es un vector viral. En algunas modalidades, el vector viral es un vector viral adenoasociado (AAV). En algunas modalidades, el vector AAV tiene defectos en la replicación o tiene defectos condicionales en la replicación. En algunas modalidades, el vector AAV es un vector AAV recombinante. En algunas modalidades, el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 1 (AAV1), 2 (AAV2), 3 (AAV3), 4 (AAV4), 5 (AAV5), 6 (AAV6), 7 (AAV7), 8 (AAV8), 9 (AAV9), 10 (AAV10), 11 (AAV11) o cualquier combinación de estos. En algunas modalidades, el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 9 (AAV9). En algunas modalidades, el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 2 (AAV2). En algunas modalidades, el vector AAV comprende una secuencia aislada o derivada de un AAV2 y una secuencia aislada o derivada de un AAV9. En algunas modalidades, el vector AAV comprende una secuencia aislada o derivada de un vector AAV4

y una secuencia aislada o derivada de un vector AAV9. En algunas modalidades, el vector está optimizado para la expresión en células de mamíferos. En algunas modalidades, el vector está optimizado para la expresión en células humanas. En algunas modalidades, el vector comprende la secuencia de la SEQ ID NO. 914, la SEQ ID NO. 915, la SEQ ID NO. 916 o la SEQ ID NO. 917.

También se proporciona un ácido nucleico que comprende una secuencia que codifica un promotor y una secuencia que codifica una Cas9 o un dominio de nucleasa de esta, en donde la secuencia que codifica el promotor comprende una secuencia que codifica un promotor específico de los músculos. En algunas modalidades, la secuencia que codifica el promotor específico de los músculos comprende una secuencia que codifica un promotor CK8. En algunas modalidades, la secuencia que codifica el promotor específico de los músculos comprende una secuencia que codifica un promotor CK8e. En algunas modalidades, la secuencia que codifica la Cas9 o el dominio de nucleasa de esta se aísla o deriva de una secuencia que codifica un dominio de nucleasa o Cas9 de *S. pyogenes* de este. En algunas modalidades, la secuencia que codifica la Cas9 o el dominio de nucleasa de esta se aísla o deriva de una secuencia que codifica Cas9 de *S. aureus* o un dominio de nucleasa de esta. En algunas modalidades, la secuencia que codifica la Cas9 o el dominio de nucleasa de esta optimizada con codones para la expresión en un mamífero. En algunas modalidades, la secuencia que codifica la Cas9 o el dominio de nucleasa de esta optimizada con codones para la expresión en un ser humano. En algunas modalidades, el ácido nucleico comprende, además, una secuencia de poliA. En algunas modalidades, la secuencia de poliA es una secuencia de poliA mini. En algunas modalidades, el ácido nucleico comprende, además, una o más secuencias que codifican una repetición terminal invertida (ITR). En algunas modalidades, el ácido nucleico comprende, además, una secuencia que codifica una repetición terminal invertida (ITR) 5’ y una secuencia que codifica una ITR 3’. En algunas modalidades, la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un virus adenoasociado (AAV). En algunas modalidades, la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un virus adenoasociado (AAV) del serotipo 2 (AAV2). En algunas modalidades, la secuencia que codifica la repetición terminal invertida 5’ (ITR) y la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un AAV2. En algunas modalidades, la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un virus adenoasociado (AAV) del serotipo 4 (AAV4). En algunas modalidades, la secuencia que codifica la repetición terminal invertida 5’ (ITR) y la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un AAV4. En algunas modalidades, la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende o

consiste en 145 nucleótidos, 115 nucleótidos o 141 nucleótidos. En algunas modalidades, el ácido nucleico comprende, además, una señal de localización nuclear. En algunas modalidades, el ácido nucleico está optimizado para la expresión en células de mamíferos. En algunas modalidades, el ácido nucleico está optimizado para la expresión en células humanas.

También se proporciona un vector que comprende un ácido nucleico que comprende una secuencia que codifica un promotor y una secuencia que codifica una Cas9 o un dominio de nucleasa de esta, en donde la secuencia que codifica el promotor comprende una secuencia que codifica un promotor específico de los músculos tal como el promotor CK8 o CK8e. En algunas modalidades, el vector comprende, además, una secuencia que codifica una repetición terminal invertida (ITR) de un elemento transponible. En algunas modalidades, el elemento transponible es un transposón. En algunas modalidades, el transposón es un transposón Tn7. En algunas modalidades, el vector comprende, además, una secuencia que codifica una ITR 5' de un transposón T7 y una secuencia que codifica una ITR 3' de un transposón T7. En algunas modalidades, el vector es un vector no viral. En algunas modalidades, el vector no viral es un plásmido. En algunas modalidades, el vector es un vector viral. En algunas modalidades, el vector viral es un vector viral adenoasociado (AAV). En algunas modalidades, el vector AAV tiene defectos en la replicación o tiene defectos condicionales en la replicación. En algunas modalidades, el vector AAV es un vector AAV recombinante. En algunas modalidades, el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 1 (AAV1), 2 (AAV2), 3 (AAV3), 4 (AAV4), 5 (AAV5), 6 (AAV6), 7 (AAV7), 8 (AAV8), 9 (AAV9), 10 (AAV10), 11 (AAV11) o cualquier combinación de estos. En algunas modalidades, el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 9 (AAV9). En algunas modalidades, el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 2 (AAV2). En algunas modalidades, el vector AAV comprende una secuencia aislada o derivada de un AAV2 y una secuencia aislada o derivada de un AAV9. En algunas modalidades, el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 4 (AAV4). En algunas modalidades, el vector AAV comprende una secuencia aislada o derivada de un vector AAV4 y una secuencia aislada o derivada de un vector AAV9. En algunas modalidades, el vector está optimizado para la expresión en células de mamíferos. En algunas modalidades, el vector está optimizado para la expresión en células humanas. En algunas modalidades, el vector comprende el ácido nucleico de la secuencia de la SEQ ID NO. 899, la SEQ ID NO. 900, la SEQ ID NO. 901 o la SEQ ID NO. 902.

También se proporciona una célula que comprende uno o más ácidos nucleicos de la descripción. En algunas modalidades, la célula es una célula humana. En algunas modalidades, la célula es una célula muscular o una célula satélite. En algunas modalidades, la célula es una célula madre

pluripotente inducida (iPS).

También se proporciona una composición que comprende uno o más ácidos nucleicos de la descripción. En algunas modalidades, la composición comprende, además, un portador farmacéuticamente aceptable.

También se proporciona una composición que comprende una célula que comprende uno o más ácidos nucleicos de la descripción. En algunas modalidades, la composición comprende, además, un portador farmacéuticamente aceptable.

También se proporciona una composición que comprende uno o más vectores de la descripción. En algunas modalidades, la composición comprende, además, un portador farmacéuticamente aceptable.

También se proporciona una célula que comprende una composición que comprende uno o más vectores de la descripción. En algunas modalidades, la célula es una célula humana. En algunas modalidades, la célula es una célula muscular o una célula satélite. En algunas modalidades, la célula es una célula madre pluripotente inducida (iPS).

En algunas modalidades, una composición comprende (i) una primera secuencia de ácido nucleico que comprende una secuencia que codifica un primer ARN guía de DMD que se dirige a una primera secuencia diana genómica, una secuencia que codifica un segundo ARN guía de DMD que se dirige a una segunda secuencia diana genómica, una secuencia que codifica un primer promotor, en donde el primer promotor dirige la expresión de la secuencia que codifica el primer ARN guía de DMD, y una secuencia que codifica un segundo promotor, en donde el primer promotor controla la expresión de la secuencia que codifica el segundo ARN guía de DMD, en donde cada una de la primera secuencia diana genómica y la segunda secuencia diana genómica comprende cada una un aceptor de corte y empalme de distrofina, y (ii) una segunda secuencia de ácido nucleico que comprende una secuencia que codifica un promotor y una secuencia que codifica una Cas9 o un dominio de nucleasa de esta, en donde la secuencia que codifica el promotor comprende una secuencia que codifica un promotor específico de los músculos tal como el promotor CK8 o CK8e. En algunas modalidades, la composición comprende, además, un portador farmacéuticamente aceptable.

En algunas modalidades, una composición comprende (i) un primer vector que comprende una secuencia de ácido nucleico que comprende una secuencia que codifica un primer ARN guía de DMD que se dirige a una primera secuencia diana genómica, una secuencia que codifica un segundo ARN guía de DMD que se dirige a una segunda secuencia diana genómica, una secuencia que codifica un primer promotor, en donde el primer promotor dirige la expresión de la secuencia que codifica el primer ARN guía de DMD, y una secuencia que codifica un segundo promotor, en donde el primer promotor controla la expresión de la secuencia que codifica el segundo ARN guía de DMD, en donde

cada una de la primera secuencia diana genómica y la segunda secuencia diana genómica comprende cada una un aceptor de corte y empalme de distrofina, y (ii) un segundo vector que comprende una secuencia de ácido nucleico que comprende una secuencia que codifica un promotor y una secuencia que codifica una Cas9 o un dominio de nucleasa de esta, en donde la secuencia que codifica el promotor comprende una secuencia que codifica un promotor específico de los músculos tal como el promotor CK8 o CK8e. En algunas modalidades, al menos uno del primer vector y el segundo vector son AAV. En algunas modalidades, la composición comprende, además, un portador farmacéuticamente aceptable.

También se proporciona un método para corregir un defecto de distrofina, el método comprende poner en contacto una célula con una o más composiciones de la descripción en condiciones adecuadas para la expresión del primer ARN guía de DMD, el segundo ARN guía de DMD y la proteína Cas9 o un dominio de nucleasa de esta, en donde al menos uno del primer ARN guía de DMD o el segundo ARN guía de DMD forma un complejo con la proteína Cas9 o el dominio de nucleasa de esta para formar al menos un complejo de Cas9-ARN guía de DMD, en donde el al menos un complejo de Cas9-ARN guía de DMD interrumpe un sitio de corte y empalme de distrofina e induce la omisión selectiva de un exón de DMD.

También se proporciona un método para corregir un defecto de distrofina, el método comprende poner en contacto una célula con una o más composiciones de la descripción en condiciones adecuadas para la expresión del primer ARN guía de DMD, el segundo ARN guía de DMD y la proteína Cas9 o un dominio de nucleasa de esta, en donde al menos uno del primer ARN guía de DMD o el segundo ARN guía de DMD forma un complejo con la proteína Cas9 o el dominio de nucleasa de esta para formar al menos un complejo de Cas9-ARN guía de DMD, en donde el al menos un complejo de Cas9-ARN guía de DMD induce la reestructuración de un marco de lectura de distrofina. En algunas modalidades, la reestructuración de un marco de lectura de distrofina induce una inserción. En algunas modalidades, la inserción comprende o consiste en un único nucleótido de adenosina.

También se proporciona un método para inducir la omisión selectiva de un exón de DMD, el método comprende poner en contacto una célula con una o más composiciones de la descripción en condiciones adecuadas para la expresión del primer ARN guía de DMD, el segundo ARN guía de DMD y la proteína Cas9 o un dominio de nucleasa de esta, en donde al menos uno del primer ARN guía de DMD o el segundo ARN guía de DMD forma un complejo con la proteína Cas9 o el dominio de nucleasa de esta para formar al menos un complejo de Cas9-ARN guía de DMD, en donde el al menos un complejo de Cas9-ARN guía de DMD interrumpe un sitio de corte y empalme de distrofina e induce la omisión selectiva de un exón de DMD.

También se proporciona un método para inducir un evento de reestructuración en el marco de lectura de distrofina, el método comprende poner en contacto una célula con una o más composiciones de la descripción en condiciones adecuadas para la expresión del primer ARN guía de DMD, el segundo ARN guía de DMD y la proteína Cas9 o un dominio de nucleasa de esta, en donde al menos uno del primer ARN guía de DMD o el segundo ARN guía de DMD forma un complejo con la proteína Cas9 o el dominio de nucleasa de esta para formar al menos un complejo de Cas9-ARN guía de DMD, en donde el al menos un complejo de Cas9-ARN guía de DMD interrumpe un sitio de corte y empalme de distrofina e induce la omisión selectiva de un exón de DMD. En algunas modalidades, el al menos un complejo Cas9-ARN guía de DMD interrumpe un sitio de corte y empalme de distrofina e induce la omisión selectiva del exón 51 de un gen de DMD humana.

También se proporciona un método para tratar la distrofia muscular en un sujeto que lo necesita, que comprende administrar al sujeto una cantidad terapéuticamente eficaz de una o más composiciones de la descripción. En algunas modalidades, la composición se administra por vía local. En algunas modalidades, la composición se administra directamente en un tejido muscular. En algunas modalidades, la composición se administra mediante infusión o inyección intramuscular. En algunas modalidades, el tejido muscular comprende un tejido tibial anterior, un tejido de cuádriceps, un tejido del sóleo, un tejido del diafragma o un tejido del corazón. En algunas modalidades, la composición se administra mediante inyección intracardíaca. En algunas modalidades, la composición se administra de forma sistémica. En algunas modalidades, la composición se administra mediante una infusión o inyección intravenosa. En algunas modalidades, después de la administración de la composición, el sujeto muestra miofibras positivas a distrofina normales y miofibras positivas a distrofina de mosaico que contienen núcleos centralizados, o una combinación de estas. En algunas modalidades, después de la administración de la composición, el sujeto muestra una aparición o un aumento en el nivel de abundancia de miofibras positivas a distrofina normales en comparación con una ausencia o un nivel de abundancia de miofibras positivas a distrofina normales antes de la administración de la composición. En algunas modalidades, después de la administración de la composición, el sujeto muestra una aparición o un aumento en el nivel de abundancia de miofibras positivas a distrofina de mosaico que contienen núcleos centralizados en comparación con una ausencia o un nivel de abundancia de miofibras positivas a distrofina de mosaico que contienen centralizada núcleos centralizados antes de la administración de la composición. En algunas modalidades, después de la administración de la composición, el sujeto muestra un nivel menor de CK en suero en comparación con un nivel de CK en suero antes de la administración de la composición. En algunas modalidades, después de la administración de la composición, el sujeto presenta una mejor resistencia de agarre en comparación con una resistencia de agarre antes de la administración de la composición. En

algunas modalidades, el sujeto es un neonato, un bebé, un niño, un adulto joven o un adulto. En algunas modalidades, el sujeto tiene distrofia muscular. En algunas modalidades, el sujeto es un portador genético de distrofia muscular. En algunas modalidades, el sujeto es un hombre. En algunas modalidades, el sujeto es una mujer. En algunas modalidades, el sujeto parece ser asintomático y en el que un diagnóstico genético revela una mutación en una o ambas copias de un gen de *DMD* que altera la función del producto génico de *DMD*. En algunas modalidades, el sujeto presenta un signo o síntoma temprano de distrofia muscular. En algunas modalidades, el signo o síntoma temprano de la distrofia muscular comprende la pérdida de masa muscular o debilidad muscular proximal. En algunas modalidades, la pérdida de masa muscular o debilidad muscular proximal se produce en una o ambas piernas y/o la pelvis, seguido por uno o más músculos de la parte superior del cuerpo. En algunas modalidades, el signo o síntoma temprano de distrofia muscular comprende, además, pseudohipertrofia, baja resistencia, dificultad para pararse, dificultad para caminar, dificultad para subir una escalera o una combinación de estas. En algunas modalidades, el sujeto presenta un signo o síntoma progresivo de distrofia muscular. En algunas modalidades, el signo o síntoma progresivo de distrofia muscular comprende desgaste del tejido muscular, reemplazo del tejido muscular con grasa o reemplazo del tejido muscular con tejido fibrótico. En algunas modalidades, el sujeto presenta un signo o síntoma tardío de distrofia muscular. En algunas modalidades, el signo o síntoma tardío de distrofia muscular comprende desarrollo óseo anormal, curvatura de la columna vertebral, pérdida de movimiento y parálisis. En algunas modalidades, el sujeto presenta un signo o síntoma neurológico de distrofia muscular. En algunas modalidades, el signo o síntoma neurológico de distrofia muscular comprende deficiencia intelectual y parálisis. En algunas modalidades, la administración de la composición se produce antes de que el sujeto presente uno o más signos o síntomas progresivos, tardíos o neurológicos de distrofia muscular. En algunas modalidades, el sujeto tiene menos de 10 años de edad, menos de 5 años de edad o menos de 2 años de edad.

También se proporciona el uso de una cantidad terapéuticamente eficaz de una o más composiciones de la descripción para el tratamiento de la distrofia muscular en un sujeto que lo necesita.

Tal como se usan en la memoria descriptiva, «un» o «uno/a» pueden significar uno o más. Tal como se usan en la o las reivindicaciones, cuando se usan junto con la expresión «que comprende», las palabras «un» o «uno/a» pueden significar uno o más de uno.

El uso del término «o» en las reivindicaciones se emplea para hacer referencia a «y/o», a menos que se indique expresamente que hace referencia solamente a alternativas o que las alternativas sean mutuamente excluyentes, aunque la descripción respalda una definición que hace referencia solamente a alternativas y a «y/o». Tal como se usa en la presente, «otro» puede significar al menos un segundo o más.

A lo largo de esta solicitud, la expresión «alrededor de» se utiliza para indicar que un valor incluye la variación inherente de error para el dispositivo, para el método que se utiliza para determinar el valor o que existe entre los sujetos del estudio. Dicha variación inherente puede ser una variación de ±10 % del valor indicado.

A lo largo de esta solicitud, las secuencias de nucleótidos se enumeran en la dirección 5' a 3', y las secuencias de aminoácidos se enumeran en la dirección del extremo N al extremo C, a menos que se indique lo contrario.

Otros objetos, características y beneficios de la presente invención resultarán evidentes a partir de la siguiente descripción detallada. Sin embargo, debería tenerse en cuenta que la descripción detallada y los ejemplos específicos, si bien indican modalidades preferidas de la invención, se brindan únicamente a modo de ejemplo, ya que varios cambios y modificaciones comprendidos por el espíritu y el alcance de la invención resultarán evidentes para los expertos en la técnica a partir de la presente descripción detallada.

BREVE DESCRIPCIÓN DE LAS FIGURAS

El archivo de la patente o la solicitud contiene al menos un dibujo a color. Si se solicitara, y luego de efectuado el pago de la tasa necesaria, la oficina entregará copias de esta publicación de patente o solicitud de patente con una o más figuras a color.

Las siguientes figuras forman parte de la presente memoria descriptiva y se incluyen para demostrar adicionalmente determinados aspectos de la presente descripción. La descripción puede entenderse mejor mediante referencia a uno o más de estas figuras en combinación con la descripción detallada de las modalidades específicas que se presentan en la presente.

Figuras 1A-F. Modelo de ratón ΔEx50 «humanizado». (Figura 1A) Estrategia que muestra el enfoque de edición genómica mediada por CRISPR/Cas9 para generar un modelo de ratón humanizado. (Figura 1B) Análisis de RT-PCR para validar la eliminación del exón 50 (ΔEx50). (Figura 1C) Secuencia del producto de RT-PCR para validar la eliminación del exón 50 y la generación de una secuencia fuera de marco (secuencia de ácido nucleico = SEQ ID NO: 1; secuencia de aminoácidos = SEQ ID NO: 2). (Figura 1E) Análisis de transferencia Western de distrofina y expresión de vinculina en tejidos del corazón y tibial anterior. (Figura 1F) Los niveles de CK en suero, un marcador de distrofia muscular que refleja el daño muscular y la filtración de la membrana, se midieron en ratones de tipo salvaje(WT), ΔEx50 y mdx. (Figura 1D) Histoquímica de los músculos cardíacas y esqueléticos mediante tinción de hematoxilina y eosina (H&E), e inmunohistoquímica mediante el uso de un anticuerpo de distrofina. Escala gráfica: 50 μm.

Figuras 2A-B. Omisión del exón 51. (Figura 2A) RT-PCR de ARN de ratones ΔEx50, 3 semanas

después de la inyección intramuscular indica la eliminación del exón 51 (denominado ΔEx50-51, banda inferior). (Figura 2B) La secuencia de los productos de RT-PCR de la banda de ΔEx50-51 confirmó que el exón 49 se cortó y empalmó directamente con el exón 52, con exclusión del exón 51 (secuencia de ácido nucleico = SEQ ID NO: 3; secuencia de aminoácidos = SEQ ID NO: 4).

Figuras 3A-G. Corrección de la expresión de distrofina mediante el uso de la estrategia de ARNg por triplicado, 3 semanas después de la inyección intramuscular. (Figura 3A) Estrategia que muestra el enfoque de edición genómica mediada por CRISPR/Cas9 para corregir el marco de lectura en el modelo de ratón ΔEx50. (Figura 3B) ARNgs que se dirige a la secuencia del sitio aceptor de corte y empalme (ARNgs-ex51-SA) y una ilustración esquemática de la posición de unión del ARNgs. La Figura 3B describe las SEQ ID NO 954-957, respectivamente, en orden de aparición. (Figura 3C) Ilustración esquemática de estrategia y plásmidos de inyección de AAV. Estrategia de guía doble mediante el uso del plásmido rAAV9-ARNgs para ARNgs-ex51-SA y ARNgs-ex51-SD. Triplicado mediante el uso del plásmido rAAV9-ARNgs que contiene 3 copias de ARNgs-ex51-SA. Promotor de la creatina quinasa 8 (CK8) muscular para expresar SpCas9. Promotor U6, H1 y 7SK para la ARN polimerasa III para expresar ARNgs. (Figura 3D) Tinción inmunohistoquímica de distrofina del músculo tibial anterior. (Figura 3E) Cuantificación de fibras positivas a distrofina normalizadas por área. (Figura 3F) Análisis de transferencia Western de la expresión de distrofina (DMD) y vinculina (VCL), 3 semanas después de la inyección intramuscular. (Figura 3G) Cuantificación de la expresión de distrofina después de la normalización a vinculina. Los datos se representan como promedio ± SEM. ** *P*<0,005. Escala gráfica: 50 µm

Figuras 4A-B. Mejora histológica del músculo inyectado después de 3 semanas. (Figura 4A) Histoquímica del músculo tibial anterior mediante tinción con hematoxilina y eosina (H&E). (Figura 4B) Cuantificación del tamaño de las fibras y el porcentaje de frecuencia. Los datos se representan como promedio ± SEM. Escala gráfica: 50 µm. Cada conjunto de cuatro puntos de datos para un tamaño de fibra dado son Δ50-CTL, WT-CTL, Δ50-AAV-TriSA y Δ50-AAV-SA+SD, de izquierda a derecha.

Figura 5. Análisis de ARNgs en células 293 humanas y células 10T de ratón. Productos de PCR no digeridos (panel superior) y digestión con T7E1 (panel inferior) en un gel de agarosa al 2 %. M denota la banda del marcador de tamaño. pb indica la longitud de las bandas marcadoras.

Figura 6. Tinción inmunohistoquímica de distrofina del músculo tibial anterior entero.

Figuras 7A-B. Estrategia para la edición genómica mediada por CRISPR/Cas9 en ratones ΔEx50. (Figura 7A) Estrategia que muestra el enfoque de edición genómica mediada por CRISPR/Cas9 para corregir el marco de lectura en el modelo de ratón ΔEx50. (Figura 7B) ARNgs que se dirige a la secuencia del sitio aceptor de corte y empalme (ARNgs-ex51-SA2) y una ilustración esquemática de la posición de unión del ARNgs. La Figura 7B describe las SEQ ID NO 958-959,

respectivamente, en orden de aparición.

Figura 8A-F. Análisis genómico de ARNgs en células humanas y de ratón. (Figura 8A) Cas9 se expresó en presencia o ausencia de ARNgs-ARNgs-51-SA2 de ratón en células 10T1/2 y la edición génica se controló mediante el ensayo de T7E1 en células clasificadas mediante fluorescencia (FACS) (+) y no clasificadas (-). Se usó GFP como control. Los productos de PCR no digeridos (panel superior) y digestión con T7E1 (panel inferior) se muestran en un gel de agarosa al 2 %. La punta de flecha negra indica la banda de PCR de 771 pb no digerida. Las puntas de flecha verdes en el panel inferior indican las bandas cortadas mediante el ensayo de T7E1. M denota la banda del marcador de tamaño. pb indica la longitud de las bandas marcadoras. (Figura 8B) Análisis de secuenciación genética profunda de los amplicones de PCR generados en el sitio diana del exón 51 en células 10T1/2. Secuencia de indels representativas alineadas con la secuencia de ARNgs (indicada en azul) que revela inserciones (resaltadas en verde) y eliminaciones (resaltadas en rojo) (SEQ ID NO 960-966, respectivamente, en orden de aparición). La línea indica la secuencia de potenciadores de corte y empalme de exones (ESE) previstos ubicados en el sitio del ARNgs. La flecha negra indica el sitio de escisión. (Figura 8C) La secuencia del Exón 51 de ratón (SEQ ID NO: 967) con los potenciadores de corte y empalme de exones (ESE) previstos ubicados en el sitio del ARNgs se indica en rojo. Humano Secuencia Exón 51 (SEQ ID NO: 968) con los potenciadores de corte y empalme de exones (ESE) previstos ubicados en el sitio del ARNgs se indica en rojo. (Figura 8D) Sitios de ESE de ratón y humanos del exón 51 previstos mediante el uso de ESEfinder3. (Figura 8E) Cas9 se expresó en presencia o ausencia de ARNgs-ARNgs-51-SA2 de ratón en células 293 T humanas y la edición génica se controló mediante el ensayo de T7E1 en células clasificadas mediante fluorescencia (FACS) (+) y no clasificadas (-). Se usó GFP como control. Los productos de PCR no digeridos (panel superior) y digestión con T7E1 (panel inferior) se muestran en un gel de agarosa al 2 %. La punta de flecha negra indica la banda de PCR de 771 pb no digerida. Las puntas de flecha verdes en el panel inferior indican las bandas cortadas mediante el ensayo de T7E1. M denota la banda del marcador de tamaño. pb indica la longitud de las bandas marcadoras. (Figura 8F) Secuencia de indels representativas alineadas con la secuencia de ARNgs (indicada en azul) que revela eliminaciones e inserciones (SEQ ID NO 969-978, respectivamente, en orden de aparición). La cabeza de flecha negra indica el sitio de escisión.

Figuras 9A-B. Ilustración esquemática de estrategia y plásmidos de inyección de AAV. (Figura 9A) Promotor de la creatina quinasa 8 (CK8) muscular para expresar SpCas9. (Figura 9B) Triplicado mediante el uso del plásmido rAAV9-ARNgs que contiene 3 copias de ARNgs-ex51-SA2. Promotor U6, H1 y 7SK para la ARN polimerasa III para expresar ARNgs.

Figuras 10A-B. Edición génica de *Dmd* in vivo. (Figura 10A) Los productos de PCR no digeridos

(panel superior) y la digestión de T7E1 (panel inferior) se muestran en un gel de agarosa al 2 % de muestras de músculo TA (tibial anterior) de ratones WT y ΔEx50, 3 semanas después de la inyección intramuscular con los vectores de expresión AAV9-ARNgs-SA2 y AAV9 -Cas9. Los controles se inyectaron solo con AAV9-Cas9, no AAV9-ARNgs-SA2. La punta de flecha negra en el panel superior indica la banda de PCR de 771 pb. Las puntas de flecha verdes en el panel inferior indican las bandas cortadas mediante el ensayo de T7E1. M denota la banda del marcador de tamaño. pb indica la longitud de las bandas marcadoras. N=4. (Figura 10B) Análisis de secuenciación genómica profunda de los amplicones de PCR generados a través del sitio diana del exón 51 en ratones ΔEx50 inyectados con AAV9-ARNgs-51-SA2 y AAV9-Cas9. Secuencia de indels representativas alineadas con la secuencia de ARNgs (indicada en azul) que revela inserciones (resaltadas en verde) y eliminaciones (resaltadas en rojo). (SEQ ID NO 979-1014, respectivamente, en orden de aparición). Las cabezas de flecha negras indican el sitio de escisión. n=3.

Figuras 11A-D. Análisis de RT-PCR de la corrección del marco de lectura. (Figura 11A) RT-PCR de ARN de músculos tibiales anteriores de ratones de tipo salvaje (WT) y ΔEx50, 3 semanas después de la inyección intramuscular de los vectores de expresión ARNgs-51-SA2 y Cas9. Las bandas inferiores de distrofina indican la eliminación del exón 51. Se indican las posiciones de los cebadores en los exones 48 y 53 (Fw, Rv). (Figura 11B) Porcentaje de eventos detectados en el exón 51 después del tratamiento con AAV9-ARNgs-51-SA2 mediante el análisis de secuencia mediante RT-PCR de clones generados mediante TOPO-TA. Para cada una de 4 muestras diferentes, se generaron y secuenciaron 40 clones. Los productos de RT-PCR se dividieron en 4 grupos: sin edición (NE), con omisión del exón 51 (SK), con reestructuración de marco (RF) y fuera del marco (OF). (Figura 11C) La secuencia de los productos de RT-PCR de la banda inferior de distrofina de ratón ΔEx50-51 confirmó que el exón 49 se cortó y empalmó directamente con el exón 52, con exclusión del exón 51. Secuencia de productos de RT-PCR de ΔEx50 con reestructuración de marco (ΔEx50-RF). La Figura 11C describe las SEQ ID NO 1015-1022, respectivamente, en orden de aparición. (Figura 11D) Análisis de secuenciación profunda de productos de RT-PCR de la banda superior que contiene ΔEx50 sin edición (NE) y ΔEx50-RF. Secuencia de productos de RT-PCR que revela inserciones (resaltadas en verde) y eliminaciones (resaltadas en rojo). n=4. Los datos se representan como promedio ± SEM. La Figura 11D describe las SEQ ID NO 1023-1026, respectivamente, en orden de aparición.

Figuras 12A-D. La inyección intramuscular de AAV9-Cas9 y AAV9-ARNgs-51-SA2 corrige la expresión de distrofina. (Figura 12A) Los músculos tibiales anteriores de ratones ΔEx50 se inyectaron con el vector AAV9 que codifica ARNgs y Cas9, y se analizaron 3 semanas después mediante inmunotinción para distrofina. Los ratones de control de tipo salvaje (WT-CTL) y los ratones

de control ΔEx50 (ΔEx50-CTL) se inyectaron con AAV9-Cas9 solo sin ARNgs. En cada panel se indican los porcentajes de miofibras positivas a distrofina en ratones ΔEx50-CTL y en ratones ΔEx50 tratados (ΔEx50-AAV9-ARNgs-51-SA2 y AAV9-Cas9) en comparación con WT-CTL. (Figura 12B) Tinción con hematoxilina y eosina (H&E) de los músculos tibiales anteriores. (Figura 12C) Análisis de transferencia Western de la expresión de distrofina (DMD) y vinculina (VCL) en músculos tibiales anteriores, 3 semanas después de la inyección intramuscular. (Figura 12D) Cuantificación de la expresión de distrofina a partir de transferencias después de la normalización a vinculina. El asterisco indica bandas inmunorreactivas no específicas. n=5 para AAV9-ARNgs-51-SA2. Escala gráfica: 50 µm

Figura 13. Rescate de la expresión de distrofina después de las inyecciones intramusculares de AAV9-Cas9 y AAV9-ARNgs-51-SA2 en el modelo de ratones ΔEx50. Inmunohistoquímica de distrofina del músculo tibial anterior entero. Los ratones CTL se inyectaron con AAV9-Cas9 solo sin AAV9-ARNgs-51-SA2. n=5

Figura 14. Mejora histológica del músculo inyectado después de 3 semanas. Histoquímica del músculo tibial anterior mediante tinción con hematoxilina y eosina (H&E).

Figuras 15A-B. Rescate de la expresión de la distrofina después de las inyecciones intramusculares de AAV9-Cas9 combinadas con diferentes AAV9 que expresan una copia simple o una copia triple de ARNgs en el modelo de ratones ΔEx50. (Figura 15A) Cada uno de los promotores U6, H1 y 7SK para la ARN polimerasa III se usó individualmente para expresar el ARNgs en una copia simple (AAV9-U6-ARNgs-51-SA2; AAV9-H1-ARNgs-51-SA2; AAV9-7SK-ARNgs-51 -SA2) o una copia triple. (Figura 15B) Inmunohistoquímica de distrofina del músculo tibial anterior entero. Los ratones de control (CTL) se inyectaron con AAV9-Cas9 solo sin AAV9-ARNgs-51-SA2.

Figuras 16A-B. Rescate de la expresión de distrofina 4 semanas después de la administración sistémica de AAV9-Cas9 y AAV9-ARNgs-51-SA2 en ratones ΔEx50. (Figura 16A) Inmunotinción de distrofina del tibial anterior (TA), tríceps, diafragma y músculos cardíacos, 8 semanas después de la inyección sistémica de AAV9-ARNgs-51. (Figura 16B) Análisis de transferencia Western de la expresión de distrofina (DMD) y vinculina (VCL) en TA, tríceps, músculos del diafragma y el corazón. n=5 para cada grupo. Escala gráfica: 50 µm.

Figuras 17A-B. Rescate de la expresión de distrofina 8 semanas después de la administración sistémica de AAV9-Cas9 y AAV9-ARNgs-51-SA2 en ratones ΔEx50. (Figura 17A) Inmunotinción de distrofina del tibial anterior (TA), tríceps, diafragma y músculos cardíacos, 8 semanas después de la inyección sistémica de AAV9-ARNgs-51. (Figura 17B) Análisis de transferencia Western de la expresión de distrofina (DMD) y vinculina (VCL) en TA, tríceps, músculos del diafragma y el corazón.

n=5 para cada grupo. Escala gráfica: 50 µm.

Figuras 18A-B. Mejora funcional 4 semanas después de la administración sistémica de AAV9-Cas9 y AAV9-ARNgs-51-SA2 en ratones ΔEx50. (Figura 18A) Los ratones de tipo salvaje (WT), ratones ΔEx50 de control y ratones ΔEx50 tratados con AAV9-ARNgs-51 (ΔEx50-AAV9-ARNgs-51) se sometieron a una prueba de resistencia de agarre para medir el rendimiento muscular (gemos de fuerza). (Figura 18B) Se midió la creatina quinasa (CK) en suero en ratones WT, ΔEx50 y ΔEx50-AAV9-ARNgs-51. n=5. El asterisco indica bandas inmunorreactivas no específicas. Los datos se representan como promedio ± SEM.

Figura 19. Corrección de la expresión de distrofina 6 semanas después de la inyección intramuscular en el modelo de perros ΔEx50-MD. Tinción inmunohistoquímica de distrofina del músculo tibial craneal de un perro de tipo salvaje (Nathan), un perro ΔEx50-MD no tratado, y dos perros ΔEx50-MD (Norman y Newton) con el músculo tibial craneal inyectado con AAV9-Cas9-ARNgs y no inyectado contralateral. Escala gráfica: 50 µm.

Figuras 20A-B. Corrección de la expresión de distrofina 6 semanas después de la inyección intramuscular en el modelo de perros ΔEx50-MD. (Figura 20A) Análisis de transferencia Western de distrofina (DMD) y vinculina (VCL) del músculo tibial craneal de un perro de tipo salvaje (Nathan), un perro ΔEx50-MD no tratado, y dos perros ΔEx50-MD (Norman y Newton) con el músculo tibial craneal inyectado con AAV9-Cas9-ARNgs y no inyectado contralateral. (Figura 20B) Cuantificación de la expresión de distrofina a partir de dos transferencias independientes después de la normalización a vinculina.

Figura 21. Mejora histológica del músculo inyectado después de 6 semanas en el modelo de perros ΔEx50-MD. Histoquímica mediante tinción de hematoxilina y eosina (H&E) del músculo tibial craneal de un perro de tipo salvaje (Nathan), y perros ΔEx50-MD (Norman y Newton) con el músculo tibial craneal inyectado con AAV9-Cas9-ARNgs y no inyectado contralateral. Escala gráfica: 50 µm.

DESCRIPCIÓN DETALLADA

La DMD es un nuevo síndrome de mutación con más de 4000 mutaciones independientes que se han identificado en humanos (sitio web en dmd.nl). La mayoría de las mutaciones en pacientes incluyen eliminaciones que se agrupan en un punto de interés y, por lo tanto, un enfoque terapéutico para omitir determinados exones se aplica a un gran grupo de pacientes. El fundamento del enfoque de omisión de exones se basa en la diferencia genética entre los pacientes con DMD y distrofia muscular de Becker (DMB). En pacientes con DMD, se interrumpe el marco de lectura del ARNm de distrofina, lo que da como resultado proteínas de distrofina no funcionales truncadas prematuramente. Los pacientes con DMB tienen mutaciones en el gen de DMD que mantienen el marco de lectura, lo que

permite la producción de distrofinas eliminadas internamente, pero parcialmente funcionales, lo que conduce a síntomas de la enfermedad mucho más leves en comparación con los pacientes con DMD. En la presente se proporcionan composiciones y métodos para tratar la DMD. En algunas modalidades, se proporciona una construcción de AAV, en donde la construcción de AAV comprende un ácido nucleico que codifica tres promotores que dirigen la expresión de un ARN guía de DMD. Mediante el uso de las composiciones y los métodos que se describen en la presente, se logró una forma más sólida y segura de edición genómica en un modelo de ratón humanizado para DMD con una eliminación en el exón 50 y en un modelo de perro ΔEx50-MD. Estos y otros aspectos de la invención se reproducen a continuación.

I. Distrofia muscular de Duchenne

A. Antecedentes

La distrofia muscular de Duchenne (DMD) es una forma de distrofia muscular recesiva ligada al cromosoma X, que afecta a alrededor de 1 de 5000 varones, que provoca degeneración muscular y muerte prematura. El trastorno es causado por una mutación en el gen distrofina (véase GenBank n.º de acceso NC_000023.11), ubicado en el cromosoma X humano, que codifica la proteína distrofina (GenBank n.º de acceso AAA53189; SEQ ID NO: 5), cuya secuencia se reproduce a continuación:

1 mlwweevedc yeredvqkkt ftkwvnaqfs kfgkqhienl fsdlqdgrrl ldllegltgq
61 klpkekgstr vhalnnvnka lrvlqnnnvd lvnigstdiv dgnhkltlgl iwniilhwqv
121 knvmknimag lqqtnsekil lswvrqstrn ypqvnvinft tswsdglaln alihshrpdl
181 fdwnsvvcqq satqrlehaf niaryqlgie klldpedvdt typdkksilm yitslfqvlp
241 qqvsieaiqe vemlprppkv tkeehfqlhh qmhysqqitv slaqgyerts spkprfksya
301 ytqaayvtts dptrspfpsq hleapedksf gsslmesevn ldryqtalee vlswllsaed
361 tlqaqgeisn dvevvkdqfh thegymmdlt ahqgrvgnil qlgskligtg klsedeetev
421 qeqmnllnsr weclrvasme kqsnlhrvlm dlqnqklkel ndwltkteer trkmeeeplg
481 pdledlkrqv qqhkvlqedl eqeqvrvnsl thmvvvvdes sgdhataale eqlkvlgdrw
541 anicrwtedr wvllqdillk wqrlteeqcl fsawlseked avnkihttgf kdqnemlssl
601 qklavlkadl ekkkqsmgkl yslkqdllst lknksvtqkt eawldnfarc wdnlvqklek
661 staqisqavt ttqpsltqtt vmetvttvtt reqilvkhaq eelpppppqk krqitvdsei
721 rkrldvdite lhswitrsea vlqspefaif rkegnfsdlk ekvnaierek aekfrklqda
781 srsaqalveq mvnegvnads ikqaseqlns rwiefcqlls erlnwleyqn niiafynqlq
841 qleqmtttae nwlkiqpttp septaiksql kickdevnrl sglqpqierl kiqsialkek
901 gqgpmfldad fvaftnhfkq vfsdvqarek elqtifdtlp pmryqetmsa irtwvqqset
961 klsipqlsvt dyeimeqrlg elqalqsslq eqqsglyyls ttvkemskka pseisrkyqs

1021 efeeiegrwk klssqlvehc qkleeqmnkl rkiqnhiqtl kkwmaevdvf lkeewpalgd
1081 seilkkqlkq crllvsdiqt iqpslnsvne ggqkikneae pefasrlete lkelntqwdh
1141 mcqqvyarke alkgglektv slqkdlsemh ewmtqaeeey lerdfeyktp delqkaveem
1201 krakeeaqqk eakvklltes vnsviaqapp vaqealkkel etlttnyqwl ctrlngkckt
1261 leevwacwhe llsylekank wlnevefklk ttenipggae eisevldsle nlmrhsednp
1321 nqirilaqtl tdggvmdeli neeletfnsr wrelheeavr rqklleqsiq saqetekslh
1381 liqesltfid kqlaayiadk vdaaqmpqea qkiqsdltsh eisleemkkh nqgkeaaqrv
1441 lsqidvaqkk lqdvsmkfrl fqkpanfelr lqeskmilde vkmhlpalet ksveqevvqs
1501 qlnhcvnlyk slsevkseve mviktgrqiv qkkqtenpke ldervtalkl hynelgakvt
1561 erkqqlekcl klsrkmrkem nvltewlaat dmeltkrsav egmpsnldse vawgkatqke
1621 iekqkvhlks itevgealkt vlgkketlve dklsllnsnw iavtsraeew lnllleyqkh
1681 metfdqnvdh itkwiiqadt lldesekkkp qqkedvlkrl kaelndirpk vdstrdqaan
1741 lmanrgdhcr klvepqisel nhrfaaishr iktgkasipl keleqfnsdi qkllepleae
1801 iqqgvnlkee dfnkdmnedn egtvkellqr gdnlqqritd erkreeikik qqllqtkhna
1861 lkdlrsqrrk kaleishqwy qykrqaddll kclddiekkl aslpeprder kikeidrelq
1921 kkkeelnavr rqaeglsedg aamaveptqi qlskrwreie skfaqfrrln faqihtvree
1981 tmmvmtedmp leisyvpsty lteithvsqa lleveqllna pdlcakdfed lfkqeeslkn
2041 ikdslqqssg ridiihskkt aalqsatpve rvklqealsq ldfqwekvnk mykdrqgrfd
2101 rsvekwrrfh ydikifnqwl teaeqflrkt qipenwehak ykwylkelqd gigqrqtvvr
2161 tlnatgeeii qqssktdasi lqeklgslnl rwqevckqls drkkrleeqk nilsefqrdl
2221 nefvlwleea dniasiplep gkeqqlkekl eqvkllveel plrqgilkql netggpvlvs
2281 apispeeqdk lenklkqtnl qwikvsralp ekqgeieaqi kdlgqlekkl edleeqlnhl
2341 llwlspirnq leiynqpnqe gpfdvqetei avqakqpdve eilskgqhly kekpatqpvk
2401 rkledlssew kavnrllqel rakqpdlapg lttigasptq tvtlvtqpvv tketaiskle
2461 mpsslmlevp aladfnrawt eltdwlslld qviksqrvmv gdledinemi ikqkatmqdl
2521 eqrrpqleel itaaqnlknk tsnqeartii tdrieriqnq wdevqehlqn rrqqlnemlk
2581 dstqwleake eaeqvlgqar akleswkegp ytvdaiqkki tetkqlakdl rqwqtnvdva
2641 ndlalkllrd ysaddtrkvh miteninasw rsihkrvser eaaleethrl lqqfpldlek
2701 flawlteaet tanvlqdatr kerlledskg vkelmkqwqd lqgeieahtd vyhnldensq
2761 kilrslegsd davllqrrld nmnfkwselr kkslnirshl eassdqwkrl hlslqellvw
2821 lqlkddelsr qapiggdfpa vqkqndvhra fkrelktkep vimstletvr iflteqpleg
2881 leklyqepre lppeeraqnv trllrkqaee vnteweklnl hsadwqrkid etlerlqelq
2941 eatdeldlkl rqaevikgsw qpvgdllids lqdhlekvka lrgeiaplke nvshvndlar
3001 qlttlgiqls pynlstledl ntrwkllqva vedrvrqlhe ahrdfgpasq hflstsvqgp

3061 weraispnkv pyyinhetqt tcwdhpkmte lyqsladlnn vrfsayrtam klrrlqkalc
3121 ldllslsaac daldqhnlkq ndqpmdilqi inclttiydr leqehnnlvn vplcvdmcln
3181 wllnvydtgr tgrirvlsfk tgiislckah ledkyrylfk qvasstgfcd qrrlglllhd
3241 siqiprqlge vasfggsnie psvrscfqfa nnkpeieaal fldwmrlepq smvwlpvlhr
3301 vaaaetakhq akcnickecp iigfryrslk hfnydicqsc ffsgrvakgh kmhypmveyc
3361 tpttsgedvr dfakvlknkf rtkryfakhp rmgylpvqtv legdnmetpv tlinfwpvds
3421 apasspqlsh ddthsriehy asrlaemens ngsylndsis pnesiddehl liqhycqsln
3481 qdsplsqprs paqilisles eergeleril adleeenrnl qaeydrlkqq hehkglsplp
3541 sppemmptsp qsprdaelia eakllrqhkg rlearmqile dhnkqlesql hrlrqlleqp
3601 qaeakvngtt vsspstslqr sdssqpmllr vvgsqtsdsm geedllsppq dtstgleevm
3661 eqlnnsfpss rgrntpgkpm redtm.

En humanos, el ARNm de distrofina contiene 79 exones. Se sabe que el ARNm de distrofina se corta y empalma, de manera alternativa, dando como resultado diversas isoformas. En la Tabla 1 se enumeran ejemplos de isoformas de distrofina.

Tabla 1: Isoformas de distrofina

Nombre de la secuencia	**N.º de acceso de ácido nucleico**	**SEQ ID NO de ácido nucleico:**	**N.º de acceso de proteína**	**SEQ ID NO de proteína:**	**Descripción**
Secuencia genómica de DMD	NC_000023.11 (posiciones 31119219 a 33339609)	Ninguna	Ninguna	Ninguna	Secuencia del cromosoma X humano (en las posiciones Xp21.2 a p21.1) del montaje GRCh38.p7 (GCF_000001405.33)
Isoforma Dp427c de distrofina	NM_000109.3	6	NP_000100.2	7	Variante de transcripción: la transcripción Dp427c se expresa principalmente en las neuronas de la corteza y las regiones CA del hipocampo. Utiliza un promotor/exón 1 único ubicado a alrededor de 130 kb corriente arriba del promotor de transcripción Dp427m. La transcripción incluye el exón común 2 de la transcripción Dp427m y tiene una longitud similar de 14 kb. La isoforma Dp427c contiene una

					secuencia MED del extremo N única, en lugar de la secuencia MLWWEEVEDCY (SEQ ID NO: 949) de la isoforma Dp427m. El resto de la isoforma Dp427c es idéntico a la isoforma Dp427m.
Isoforma Dp427m de distrofina	NM_004006.2	8	NP_003997.1	9	Variante de transcripción: la transcripción Dp427m codifica la proteína distrofina principal que se encuentra en el músculo. Como resultado del uso del promotor alternativo, el exón 1 codifica una secuencia aa de MLWWEEVEDCY de extremo N única (SEQ ID NO: 949).
Isoforma Dp427p1 de distrofina	NM_004009.3	10	NP_004000.1	11	Variante de transcripción: la transcripción Dp427p1 comienza en un promotor/exón 1 único ubicado en lo que corresponde al primer intrón de la transcripción Dp427m. La transcripción agrega el exón común 2 de la transcripción Dp427m y tiene una longitud similar (14 kb). La isoforma Dp427p1 reemplaza el inicio MLWWEEVEDCY (SEQ ID NO: 949) de Dp427m con una secuencia de aa MSEVSSD del extremo N única (SEQ ID NO: 950).
Isoforma Dp260-1 de distrofina	NM_004011.3	12	NP_004002.2	13	Variante de transcripción: la transcripción Dp260-1 usa los exones 30-79, y se origina a partir de una secuencia promotora/exón 1 ubicada en el intrón 29 del gen de distrofina. Como resultado, Dp260-1 contiene un exón 1 de 95 pb que codifica una secuencia de 16 aa MTEIILLIFFPAYFLN del extremo N única (SEQ ID NO: 951) que reemplaza los aminoácidos 1-1357 del producto de distrofina de longitud completa (isoforma Dp427m).
Isoforma	NM_004012.3	14	NP_004003.1	15	Variante de transcripción: la

Dp260-2 de distrofina					transcripción Dp260-2 utiliza los exones 30-79, a partir de una secuencia promotora/exón 1 ubicada en el intrón 29 del gen de distrofina que se corta y empalma de manera alternativa y carece de los aminoácidos 1-1357 del extremo N de la distrofina de longitud completa (isoforma Dp427m). La transcripción Dp260-2 codifica una secuencia MSARKLRNLSYKK del extremo N única (SEQ ID NO: 952).
Isoforma Dp140 de distrofina	NM_004013.2	16	NP_004004.1	17	Variante de transcripción: Las transcripciones Dp140 utilizan los exones 45-79, y comienzan en un promotor/exón 1 ubicado en el intrón 44. Las transcripciones Dp140 tienen una 5' UTR larga (1 kb), ya que la traducción comienza en el exón 51 (correspondiente al aa 2461 de distrofina). Además del promotor alternativo y el exón 1, el corte y empalme diferencial de los exones 71-74 y 78 produce al menos cinco isoformas Dp140. De estas, esta transcripción (Dp140) contiene todos los exones.
Isoforma Dp116 de distrofina	NM_004014.2	18	NP_004005.1	19	Variante de transcripción: la transcripción Dp116 usa los exones 56-79, y comienza en un promotor/exón 1 dentro del intrón 55. Como resultado, la isoforma Dp116 contiene una secuencia de aa MLHRKTYHVK del extremo N única (SEQ ID NO: 953), en lugar de los aa 1-2739 de distrofina. El corte y empalme diferencial produce varios subtipos de Dp116. La isoforma Dp116 también se conoce como S-distrofina o apo-distrofina-2.
Isoforma Dp71	NM_004015.2	20	NP_004006.1	21	Variante de transcripción: Las

de distrofina					transcripciones Dp71 utilizan los exones 63-79 con un exón nuevo de 80 a 100 nt que contiene un sitio de inicio ATG para una secuencia de codificación nueva de 17 nt. La secuencia de codificación corta se encuentra en el marco de la secuencia de distrofina consecutiva del exón 63. El corte y empalme diferencial de los exones 71 y 78 produce al menos cuatro isoformas Dp71. De estas, esta transcripción (Dp71) incluye ambos exones 71 y 78.
Isoforma Dp71b de distrofina	NM_004016.2	22	NP_004007.1	23	Variante de transcripción: Las transcripciones Dp71 utilizan los exones 63-79 con un exón nuevo de 80 a 100 nt que contiene un sitio de inicio ATG para una secuencia de codificación nueva de 17 nt. La secuencia de codificación corta se encuentra en el marco de la secuencia de distrofina consecutiva del exón 63. El corte y empalme diferencial de los exones 71 y 78 produce al menos cuatro isoformas Dp71. De estas, esta transcripción (Dp71b) carece del exón 78 y codifica una proteína con un extremo C diferente a las isoformas Dp71 y Dp71a.
Isoforma Dp71a de distrofina	NM_004017.2	24	NP_004008.1	25	Variante de transcripción: Las transcripciones Dp71 utilizan los exones 63-79 con un exón nuevo de 80 a 100 nt que contiene un sitio de inicio ATG para una secuencia de codificación nueva de 17 nt. La secuencia de codificación corta se encuentra en el marco de la secuencia de distrofina consecutiva del exón 63. El corte y empalme diferencial de los exones 71 y 78 produce al menos cuatro isoformas Dp71. De estas, esta

					transcripción (Dp71a) carece del exón 71.
Isoforma Dp71ab de distrofina	NM_004018.2	26	NP_004009.1	27	Variante de transcripción: Las transcripciones Dp71 utilizan los exones 63-79 con un exón nuevo de 80 a 100 nt que contiene un sitio de inicio ATG para una secuencia de codificación nueva de 17 nt. La secuencia de codificación corta se encuentra en el marco de la secuencia de distrofina consecutiva del exón 63. El corte y empalme diferencial de los exones 71 y 78 produce al menos cuatro isoformas Dp71. De estas, esta transcripción (Dp71ab) carece de ambos exones 71 y 78 y codifica una proteína con un extremo C similar a la isoforma Dp71b.
Isoforma Dp40 de distrofina	NM_004019.2	28	NP_004010.1	29	Variante de la transcripción: la transcripción Dp40 usa los exones 63-70. La 5' UTR y los primeros 7 aa codificados son idénticos a los de la transcripción Dp71, pero el codón de terminación se encuentra en la unión de corte y empalme del exón/intrón 70. La 3' UTR incluye nt del intrón 70, que incluyen un sitio de poliadenilación alternativo. La isoforma Dp40 carece del extremo C normal de la distrofina de longitud completa (aa 3409-3685).
Isoforma Dp140c de distrofina	NM_004020.3	30	NP_004011.2	31	Variante de transcripción: Las transcripciones Dp140 utilizan los exones 45-79, y comienzan en un promotor/exón 1 ubicado en el intrón 44. Las transcripciones Dp140 tienen una 5' UTR larga (1 kb), ya que la traducción comienza en el exón 51 (correspondiente al aa 2461 de distrofina). Además del promotor alternativo y el exón 1, el corte y empalme diferencial de los exones 71-

					74 y 78 produce al menos cinco isoformas Dp140. De estas, esta transcripción (Dp140c) carece de los exones 71-74.
Isoforma Dp140b de distrofina	NM_004021.2	32	NP_004012.1	33	Variante de transcripción: Las transcripciones Dp140 utilizan los exones 45-79, y comienzan en un promotor/exón 1 ubicado en el intrón 44. Las transcripciones Dp140 tienen una 5' UTR larga (1 kb), ya que la traducción comienza en el exón 51 (correspondiente al aa 2461 de distrofina). Además del promotor alternativo y el exón 1, el corte y empalme diferencial de los exones 71-74 y 78 produce al menos cinco isoformas Dp140. De estas, esta transcripción (Dp140b) carece del exón 78 y codifica una proteína con un extremo C único.
Isoforma Dp140ab de distrofina	NM_004022.2	34	NP_004013.1	35	Variante de transcripción: Las transcripciones Dp140 utilizan los exones 45-79, y comienzan en un promotor/exón 1 ubicado en el intrón 44. Las transcripciones Dp140 tienen una 5' UTR larga (1 kb), ya que la traducción comienza en el exón 51 (correspondiente al aa 2461 de distrofina). Además del promotor alternativo y el exón 1, el corte y empalme diferencial de los exones 71-74 y 78 produce al menos cinco isoformas Dp140. De estas, esta transcripción (Dp140ab) carece de los exones 71 y 78 y codifica una proteína con un extremo C único.
Isoforma Dp140bc de distrofina	NM_004023.2	36	NP_004014.1	37	Variante de transcripción: Las transcripciones Dp140 utilizan los exones 45-79, y comienzan en un promotor/exón 1 ubicado en el intrón 44. Las transcripciones Dp140 tienen

					una 5’ UTR larga (1 kb), ya que la traducción comienza en el exón 51 (correspondiente al aa 2461 de distrofina). Además del promotor alternativo y el exón 1, el corte y empalme diferencial de los exones 71-74 y 78 produce al menos cinco isoformas Dp140. De estas, esta transcripción (Dp140bc) carece de los exones 71-74 y 78 y codifica una proteína con un extremo C único.
Isoforma X2 de distrofina	XM_006724469.3	38	XP_006724532.1	39	
Isoforma X5 de distrofina	XM_011545467.1	40	XP_011543769.1	41	
Isoforma X6 de distrofina	XM_006724473.2	42	XP_006724536.1	43	
Isoforma X8 de distrofina	XM_006724475.2	44	XP_006724538.1	45	
Isoforma X4 de distrofina	XM_017029328.1	46	XP_016884817.1	47	
Isoforma X1 de distrofina	XM_006724468.2	48	XP_006724531.1	49	
Isoforma X13 de distrofina	XM_017029331.1	50	XP_016884820.1	51	
Isoforma X3 de distrofina	XM_006724470.3	52	XP_006724533.1	53	
Isoforma X7 de distrofina	XM_006724474.3	54	XP_006724537.1	55	
Isoforma X9 de distrofina	XM_011545468.2	56	XP_011543770.1	57	
Isoforma X11 de distrofina	XM_017029330.1	58	XP_016884819.1	59	
Isoforma X10 de distrofina	XM_017029329.1	865	XP_016884818.1	866	
Isoforma X12 de distrofina	XM_011545469.1	867	XP_011543771.1	868	

La proteína distrofina murina tiene la siguiente secuencia de aminoácidos (n.º de acceso de Uniprot P11531, SEQ. ID. NO: 869):

1 MWWVDCYRDV KKTTKWNASK GKHDNSDDGK RDGTGKKKGS TRVHANNVNK ARVKNNVDVN
61 GSTDVDGNHK TGWNHWVKNV MKTMAGTNSK SWVRSTRNYV NVNTSSWSDG ANAHSHRDDW
121 NSVVSHSATR HANAKCGKDD VATTYDKKSM YTSVVSAVMR TSSKVTRHHH MHYSTVSAGY
181 TSSSKRKSYA TAAYVATSDS TSYSHARDKS DSSMTVNDSY TAVSWSADTR AGSNDVVKHA
241 HGMMDTSHGV GNVGSVGKGK SDAVMNNSRW CRVASMKSKH KVMDNKKDDW TKTRTKKMGD
301 DKCVHKVDVR VNSTHMVVVV DSSGDHATAA KVGDRWANCR WTDRWVDKWH TCSTWSKDAM
361 KNTSGKDNMM SSHKSTKDKK KTMKSSNDSA KNKSVTKMWM NARWDNTKKS SASAVTTTST
421 TTVMTVTMVT TRMVKHAKKR TVDSRKRDVD THSWTRSAVS SAVYRKGNSD KVNAARKAKR
481 KDASRSAAVM ANGVNASRAS NSRWTCSRVN WYTNTYNMTT TANKTSTTST AKSKCKDVNR
541 SAKSKKGGMD ADVATNHNHD GVRAKKTDTM RYTMSSRTWS SKSVYSVTYM RGKASSKNGN
601 YSDTVKMAKK ASCKYSGHWK KSSVSCKHMN KRKNHKTKWM AVDVKWAGDA KKKCRVGDTS
661 NSVNGGKKSA ASRTRNTWDH CRVYTRKAKA GDKTVSKDSM HWMTAYRDYK TDTAVMKRAK
721 AKTKVKTTVN SVAHASAAKK TTTNYWCTRN GKCKTVWACW HSYKANKWNV KKTMNVAGTV
781 SNMHHSNNRA TTDGGVMDNT NSRWRHAVRK KSSAKSHSDK AAYTDKVDAA MAKSDTSHSM
841 KKHNGKDANR VSDVAKKDVS MKRKANRSKM DVKMHATKSV VSSHCVNYKS SVKSVMVKTG
901 RVKKTNKDRV TAKHYNGAKV TRKKCKSRKM RKMNVTWAAT DTTKRSAVGM SNDSVAWGKA
961 TKKKAHKSVT GSKMVGKKTV DKSNSNWAVT SRVWNYKHMT DNTKWHADDS KKKKDKRKAM
1021 NDMRKVDSTR DAAKMANRGD HCRKVVSNRR AASHRKTGKA SKNSDKAGVN KDNKDMSDNG
1081 TVNRGDNRTD RKRKKTKHNA KDRSRRKKAS HWYYKRADDK CDKKASRDRK KDRKKKNAVR
1141 RAGSNGAAMA VTSKRWRSNA RRNAHTHTMV VTTDMDVSYV STYTSHASVD

HNTCAKDDKS

1201 KNKDNSGRDH KKKTAASATS MKVKVAVAMD GKHRMYKRGR DRSVKWRHHY DMKVNWNVKK

1261 TNNWHAKYKW YKDGGRAVVR TNATGSSKTD VNKGSSRWHD CKARRKRKNV SRDNVWADNA

1321 TGDKVKARGK NTGGAVVSAR DKKKKTNWKV SRAKGVHKDR DHWSRNYNSA GDKVTVHGKA

1381 DVRSKGHYKK STVKRKDRSW AVNHRRTKDR AGSTTGASAS TVTVTSVVTK TVSKMSSVAA

1441 DNRAWTTDWS DRVKSRVMVG DDNMKKATDR RTAANKNKTS NARTTDRRWD VNRRNMKDST

1501 WAKAVGVRGK DSWKGHTVDA KKTTKAKDRR SVDVANDAKR DYSADDTRKV HMTNNTSWGN

1561 HKRVSAATHR DKSWTATTAN VDASRKKDSR GVRMKWDGTH TDYHNDNGKR SGSDARRDNM

1621 NKWSKKSNRS HASSDWKRHS VWKDDSRAGG DAVKNDHRAK RKTKVMSTTV RTGKYRRANV

1681 TRRKAVNAWD KNRSADWRKD ARAADDKRAV KGSWVGDDSD HKVKARGAKN VNRVNDAHTT

1741 GSYNSTDNTR WRVAVDRVRH AHRDGASHST SVGWRASNKV YYNHTTTCWD HKMTYSADNN

1801 VRSAYRTAMK RRKACDSSAA CDADHNKNDM DNCTTYDRHN NVNVCVDMCN WNVYDTGRTG

1861 RRVSKTGSCK AHDKYRYKVA SSTGCDRRGH DSRGVASGGS NSVRSCANNK AADWMRSMVW

1921 VHRVAAATAK HAKCNCKCGR YRSKHNYDCS CSGRVAKGHK MHYMVYCTTT SGDVRDAKVK

1981 NKRTKRYAKH RMGYVTVGDN MTVTNWVDSA ASSSHDDTHS RHYASRAMNS NGSYNDSSNS

2041 DDHHYCSNDS SRSASSRGRA DNRNAYDRKH HKGSSMMTSS RDAAAKRHKG RARMDHNKSH

2101 RRAAKVNGTT VSSSTSRSDS SMRVVGSTSS MGDSDTSTGV MNNSSSRGRN AGKMRDTM

La distrofina es un componente importante dentro del tejido muscular que proporciona estabilidad estructural al complejo de distroglicano (DGC) de la membrana celular. Si bien ambos sexos pueden

tener la mutación, el femenino se ve afectado raramente con la forma de la enfermedad de músculo esquelético.

Las mutaciones varían en cuanto a su naturaleza y frecuencia. Las eliminaciones genéticas grandes se encuentran en alrededor de 60-70 % de los casos, las duplicaciones grandes en alrededor de 10 % de los casos, y las mutaciones puntuales u otros cambios pequeños representan alrededor de 15-30 % de los casos. Bladen et ál. (2015), quienes examinaron unas 7000 mutaciones, catalogaron un total de 5682 mutaciones grandes (80 % del total), de las cuales 4894 (86 %) fueron eliminaciones (1 exón o más) y 784 (14 %) fueron duplicaciones (1 exón o más). Hubo 1445 mutaciones pequeñas (menos de 1 exón, 20 % de todas las mutaciones), de las cuales 358 (25 %) fueron eliminaciones pequeñas y 132 (9 %) inserciones pequeñas, mientras que 199 (14 %) afectaron los sitios de corte y empalme. Las mutaciones puntuales totalizaron 756 (52 % de las mutaciones pequeñas) con 726 (50 %) mutaciones sin sentido y 30 (2 %) mutaciones con cambio de sentido. Finalmente, se observaron 22 (0,3 %) mutaciones intrónicas centrales. Además, se identificaron mutaciones dentro de la base de datos que potencialmente se beneficiarían de terapias genéticas novedosas para la DMD que incluyen terapias a través de lectura de codones de terminación (10 % de las mutaciones totales) y terapia de omisión de exones (80 % de las eliminaciones y 55 % de las mutaciones totales).

B. Síntomas

Los síntomas generalmente aparecen en los niños entre 2 y 3 años de edad y pueden ser visibles en la primera infancia. Aunque los síntomas no aparezcan hasta la primera infancia, las pruebas de laboratorio pueden identificar a los niños que portan la mutación activa al momento del nacimiento. En primer lugar, se observa la debilidad muscular proximal progresiva de las piernas y la pelvis asociada con la pérdida de masa muscular. Eventualmente, esta debilidad se extiende a los brazos, el cuello y otras áreas. Los signos tempranos pueden incluir pseudohipertrofia (agrandamiento de los músculos de la pantorrilla y deltoides), resistencia baja y dificultades para pararse sin ayuda o incapacidad para subir escaleras. A medida que la afección avanza, el tejido muscular se atrofia y eventualmente se reemplaza por tejido adiposo y fibrótico (fibrosis). A los 10 años, es posible que se requieran aparatos para ayudar a caminar, pero la mayoría de los pacientes dependen de una silla de ruedas a los 12 años. Los síntomas tardíos pueden incluir un desarrollo óseo anormal que conduce a deformidades esqueléticas, incluida la curvatura de la columna vertebral. Debido al deterioro progresivo del músculo, se produce una pérdida de movimiento, que eventualmente conduce a la parálisis. El deterioro intelectual puede o no estar presente, pero si está presente, no empeora progresivamente a medida que el niño crece. La esperanza de vida promedio para los hombres afectados de DMD es de alrededor de 25 años.

El síntoma principal de la distrofia muscular de Duchenne, un trastorno neuromuscular progresivo, es la debilidad muscular asociada con la atrofia muscular, lo que afecta primero los músculos voluntarios, especialmente los de las caderas, la zona pélvica, los muslos, los hombros y las pantorrillas. La debilidad muscular también se presenta luego en los brazos, el cuello y otras zonas. A menudo se produce un aumento del tamaño de las pantorrillas. Usualmente, los síntomas aparecen antes de los 6 años y pueden aparecer en la primera infancia. Otros síntomas físicos son:

1. Manera incómoda de caminar, pisar o correr - (los pacientes tienden a caminar sobre la parte delantera del pie, debido a un aumento en el tono muscular de la pantorrilla. Además, caminar en puntas de pie es una adaptación compensatoria a la debilidad del extensor de la rodilla.)
2. Caídas frecuentes.
3. Fatiga.
4. Dificultad con las habilidades motoras (correr, brincar, saltar).
5. Hiperlordosis lumbar, que posiblemente produzca un acortamiento de los músculos flexores de la cadera. Esto tiene un efecto en la postura general y la manera de caminar, pisar o correr.
6. Las contracturas musculares del tendón de Aquiles y los isquiotibiales afectan la funcionalidad porque las fibras musculares se acortan y se desarrolla fibrosis en el tejido conectivo.
7. Dificultad progresiva para caminar.
8. Deformidades de la fibra muscular.
9. Pseudohipertrofia (agrandamiento) de los músculos de la lengua y la pantorrilla. El tejido muscular es reemplazado finalmente por tejido conectivo y adiposo, de ahí el término pseudohipertrofia.
10. Mayor riesgo de trastornos neuroconductuales (p.ej., TDAH), trastornos del aprendizaje (dislexia) y debilidades no progresivas en las habilidades cognitivas específicas (en particular, la memoria verbal a corto plazo), que se cree que son el resultado de distrofina ausente o disfuncional en el cerebro.
11. Pérdida eventual de la capacidad para caminar (usualmente, a los 12 años).
12. Deformidades esqueléticas (lo que incluye escoliosis en algunos casos).
13. Dificultad para levantarse de la posición acostada o sentada.

La afección puede observarse, frecuentemente, de forma clínica desde el momento en que el paciente da sus primeros pasos, y la capacidad de caminar usualmente se desintegra por completo entre el momento en que el niño tiene entre 9 y 12 años de edad. La mayoría de los hombres afectados con DMD quedan esencialmente «paralizados desde el cuello hacia abajo» a la edad de 21 años. La atrofia muscular comienza en las piernas y la pelvis, luego avanza hacia los músculos de los hombros y el cuello, seguido por la pérdida de los músculos de los brazos y los músculos

respiratorios. El agrandamiento del músculo de la pantorrilla (pseudohipertrofia) es bastante obvio. La cardiomiopatía (cardiomiopatía dilatada) es particularmente común, pero el desarrollo de insuficiencia cardíaca congestiva o arritmia (latido irregular del corazón) es solo ocasional.

Un signo positivo de Gowers refleja el deterioro más grave de los músculos de las extremidades inferiores. El niño se ayuda a levantarse con las extremidades superiores: primero, se levanta para pararse sobre sus brazos y rodillas, y luego «camina» con las manos sobre las piernas para ponerse de pie. Los niños afectados usualmente se cansan más fácilmente y tienen menos fuerza general que sus compañeros. Los niveles de creatina quinasa (CPK-MM) en el torrente sanguíneo son extremadamente altos. Una electromiografía (EMG) muestra que la debilidad es causada por la destrucción del tejido muscular en lugar de por el daño a los nervios. Las pruebas genéticas pueden revelar errores genéticos en el gen Xp21. Una biopsia muscular (inmunohistoquímica o inmunotransferencia) o una prueba genética (prueba de sangre) confirman la ausencia de distrofina, aunque las mejoras en las pruebas genéticas a menudo hacen que esto no sea necesario.

Los pacientes con DMD pueden sufrir de:

1. Músculo cardíaco anormal (cardiomiopatía).
2. Insuficiencia cardíaca congestiva o ritmo cardíaco irregular (arritmia).
3. Deformidades del tórax y espalda (escoliosis).
4. Músculos agrandados de las pantorrillas, los glúteos y los hombros (alrededor de los 4 o 5 años). Estos músculos son reemplazados finalmente por tejido conectivo y adiposo (pseudohipertrofia).
5. Pérdida de masa muscular (atrofia).
6. Contracturas musculares en los talones, piernas.
7. Deformidades musculares.
8. Trastornos respiratorios, que incluyen neumonía y tragado de alimentos o líquidos que pasan a los pulmones (en las últimas etapas de la enfermedad).

C. Causas

La distrofia muscular de Duchenne (DMD) es causada por una mutación del gen de la distrofina en el locus Xp21, ubicado en el brazo corto del cromosoma X. La distrofina es responsable de conectar el citoesqueleto de cada fibra muscular a la lámina basal subyacente (matriz extracelular), a través de un complejo de proteínas que contiene muchas subunidades. La ausencia de distrofina permite que el exceso de calcio penetre en el sarcolema (la membrana celular). Las alteraciones en el calcio y las vías de señalización hacen que el agua entre en las mitocondrias, que luego se rompen.

En la distrofia del músculo esquelético, la disfunción mitocondrial da lugar a una amplificación de las

señales de calcio citosólico inducidas por el estrés y una amplificación de la producción de especies reactivas de oxígeno (ROS) inducidas por el estrés. En un proceso en cascada complejo que involucra varias vías y no se comprende claramente, el aumento del estrés oxidativo dentro de la célula daña el sarcolema y, finalmente, provoca la muerte de la célula. Las fibras musculares sufren necrosis y finalmente se reemplazan con tejido adiposo y conectivo.

La DMD se hereda en un patrón recesivo vinculado al cromosoma X. Las mujeres generalmente serán portadoras de la enfermedad, mientras que los hombres se verán afectados. Por lo general, una mujer portadora no sabrá que porta una mutación hasta que tenga un hijo afectado. El hijo de una madre portadora tiene un 50 % de probabilidad de heredar el gen defectuoso de su madre. La hija de una madre portadora tiene un 50 % de probabilidad de ser portadora y un 50% de probabilidad de tener dos copias normales del gen. En todos los casos, un padre no afectado pasará una Y normal a su hijo o una X normal a su hija. Las mujeres portadoras de una afección recesiva vinculada al cromosoma X, tal como la DMD, pueden mostrar síntomas dependiendo de su patrón de inactivación de X.

Las eliminaciones de exones que preceden al exón 51 del gen *DMD* humano, que interrumpen el marco de lectura abierto (ORF) mediante la yuxtaposición de los exones de marco, representan el tipo más común de mutación de DMD humana. La omisión del exón 51 puede, en principio, restaurar el ORF de DMD en el 13 % de los pacientes con DMD con eliminaciones de exones.

La distrofia muscular de Duchenne tiene una incidencia de 1 en 5000 en niños varones. Las mutaciones dentro del gen de distrofina pueden heredarse o pueden producirse espontáneamente durante la transmisión de la línea germinal. A continuación, se presenta una tabla de mutaciones ilustrativas no taxativas y modelos correspondientes:

Tabla 2: Mutaciones de distrofina y modelos de ratón correspondientes

Supresión, inserción pequeña y mutaciones sin sentido	**Nombre del modelo de ratón**
Exón 44	ΔEx44
Exón 52	ΔEx52
Exón 43	ΔEx43

D. Diagnóstico

Se aconseja la consulta genética para las personas con antecedentes familiares del trastorno. La distrofia muscular de Duchenne puede detectarse con alrededor de 95 % de precisión en estudios

genéticos realizados durante el embarazo.

Ensayo de ADN. La isoforma específica del músculo del gen de distrofina está compuesta por 79 exones, y las pruebas y análisis de ADN usualmente pueden identificar el tipo específico de mutación del exón o los exones afectados. Las pruebas de ADN confirman el diagnóstico en la mayoría de los casos.

Biopsia muscular. Si la prueba de ADN no encuentra la mutación, se puede realizar una prueba de biopsia muscular. Se extrae una pequeña muestra de tejido muscular (usualmente con un escalpelo en lugar de una aguja) y se aplica un tinte que revela la presencia de distrofina. La ausencia completa de la proteína indica la afección.

En los últimos años, se han desarrollado pruebas de ADN que detectan más de las muchas mutaciones que causan la afección, y no es necesario realizar una biopsia muscular para confirmar la presencia de Duchenne.

Pruebas prenatales. La DMD es portada mediante un gen recesivo vinculado al cromosoma X. Los hombres solo tienen un cromosoma X, por lo que una copia del gen mutado causará la DMD. Los padres no pueden transmitir los rasgos vinculados al cromosoma X a sus hijos, por lo que la mutación es transmitida por la madre.

Si la madre es portadora y, por lo tanto, uno de sus dos cromosomas X tiene una mutación de DMD, hay un 50 % de probabilidades de que una niña herede esa mutación como uno de sus dos cromosomas X y sea portadora. Hay un 50 % de probabilidades de que un niño varón herede esa mutación como su único cromosoma X y, por lo tanto, tenga DMD.

Las pruebas prenatales pueden determinar si su hijo por nacer tiene las mutaciones más comunes. Existen muchas mutaciones responsables de la DMD, y algunas no se han identificado, por lo que las pruebas genéticas solo funcionan cuando los miembros de la familia con DMD tienen una mutación que ha sido identificada.

Antes de las pruebas invasivas, es importante la determinación del sexo fetal; mientras que los hombres a veces se ven afectados por esta enfermedad vinculada al X, la DMD femenina es extremadamente rara. Esto se puede lograr mediante ecografía a las 16 semanas o más recientemente mediante pruebas de ADN fetal gratuitas. La toma de muestras de vellosidades coriónicas (CVS) se puede realizar en las 11-14 semanas y tiene un riesgo de aborto espontáneo de 1 %. La amniocentesis se puede realizar después de 15 semanas y tiene un riesgo de aborto espontáneo de 0,5 %. La toma de muestras de sangre fetal se puede realizar a alrededor de las 18 semanas. Otra opción en el caso de resultados de pruebas genéticas poco claros es la biopsia de músculo fetal.

E. Tratamiento

No existe una cura actual para la DMD, y las autoridades reguladoras han reconocido una necesidad médica continua. Los ensayos de fase 1-2a con tratamiento de omisión de exones para determinadas mutaciones han detenido el deterioro y han producido pequeñas mejoras clínicas al caminar. El tratamiento generalmente está dirigido a controlar el inicio de los síntomas para maximizar la calidad de vida, y puede incluir lo siguiente:

1. Los corticosteroides tales como prednisolona y deflazacort aumentan la energía y la fuerza y difieren la gravedad de algunos síntomas.

2. Los ensayos controlados aleatorios han demostrado que los agonistas beta-2 aumentan la fuerza muscular pero no modifican la evolución de la enfermedad. El tiempo de seguimiento para la mayoría de los ECA con agonistas beta-2 es de alrededor de 12 meses y, por lo tanto, los resultados no se pueden extrapolar más allá de ese plazo.

3. Se incentiva la actividad física leve no discordante tal como la natación. La inactividad (como el reposo en cama) puede empeorar la enfermedad muscular.

4. La fisioterapia es útil para mantener la fuerza, flexibilidad y función muscular.

5. Los aparatos ortopédicos (tales como aparatos ortopédicos y sillas de ruedas) pueden mejorar la movilidad y la capacidad de autocuidado. Los aparatos ortopédicos desmontables para piernas que se ajustan a la forma y que sujetan el tobillo en su lugar durante el sueño pueden diferir la aparición de contracturas.

6. La asistencia respiratoria adecuada es importante medida que evoluciona la enfermedad.

Los Centros para el Control y la Prevención de Enfermedades (CDC) han desarrollado normas/pautas de atención integral multidisciplinaria para la DMD, y están disponibles en www.treat-nmd.eu/dmd/care/diagnosis-management-DMD.

La DMD generalmente evoluciona a través de cinco etapas, tal como se describe en Bushby et ál., Lancet Neurol., 9(1): 77-93 (2010) y Bushby et ál., Lancet Neurol., 9(2): 177-198 (2010), que se incorporan en su totalidad mediante referencia. Durante la etapa presintomática, los pacientes suelen mostrar retraso en el desarrollo, pero no alteración del andar. Durante la etapa ambulatoria temprana, los pacientes suelen mostrar el signo de Gowers, andar como pato y caminar en puntas de pies. Durante la etapa ambulatoria tardía, los pacientes suelen presentar un andar cada vez más difícil y comienzan a perder la capacidad de subir escaleras y levantarse del piso. Durante la etapa no ambulatoria temprana, los pacientes suelen ser capaces de autoimpulsarse durante algún tiempo, pueden mantener la postura y pueden desarrollar escoliosis. Durante la etapa no ambulatoria tardía, la función de las extremidades superiores y el mantenimiento postural son cada vez más limitados.

En algunas modalidades, el tratamiento comienza en la etapa presintomática de la enfermedad. En

algunas modalidades, el tratamiento comienza en la etapa ambulatoria temprana. En algunas modalidades, el tratamiento comienza en la etapa ambulatoria tardía. En algunas modalidades, el tratamiento comienza en la etapa no ambulatoria temprana. En algunas modalidades, el tratamiento comienza en la etapa no ambulatoria tardía.

1. Terapia física

Los fisioterapeutas se preocupan por permitir a los pacientes que alcancen su máximo potencial físico. Su objetivo es:

1. minimizar el desarrollo de contracturas y deformidades mediante el desarrollo de un programa de estiramientos y ejercicios cuando sea apropiado,
2. anticipar y minimizar otras complicaciones secundarias de naturaleza física mediante la recomendación de aparatos y equipo médico duradero, y
3. monitorear la función respiratoria y aconsejar sobre técnicas para ayudar con ejercicios de respiración y métodos para eliminar las secreciones.

2. Asistencia respiratoria

Los «respiradores/ventiladores a volumen» modernos, que suministran un volumen ajustable (cantidad) de aire a la persona con cada respiración, son valiosos en el tratamiento de personas con problemas respiratorios relacionados con la distrofia muscular. El ventilador puede requerir un tubo de traqueotomía o endotraqueal invasivo a través del cual se suministra aire directamente, pero, para algunas personas, el suministro no invasivo a través de una máscara facial o una boquilla es suficiente. Las máquinas de presión positiva de las vías aéreas, particularmente las de dos niveles, se usan a veces de esta última manera. El equipo respiratorio puede ajustarse fácilmente en una bandeja de ventilación en la parte inferior o trasera de una silla de ruedas eléctrica con una batería externa para su transporte.

El tratamiento con ventilador puede comenzar en la adolescencia media o tardía cuando los músculos respiratorios pueden comenzar a colapsarse. Si la capacidad vital ha disminuido por debajo de 40 % de lo normal, se puede usar un respirador/ventilador a volumen durante las horas de sueño, tiempo durante el cual es más probable que la persona se encuentre con ventilación («hipoventilación»). La hipoventilación durante el sueño está determinada por un historial completo de trastornos del sueño con un estudio de oximetría y un gas sanguíneo capilar (véanse las Pruebas de función pulmonar). Un dispositivo de asistencia para la tos puede ayudar con el exceso de mucosidad en los pulmones mediante la hiperinflación de los pulmones con presión de aire positiva, y luego presión negativa para elevar la mucosidad. Si la capacidad vital continúa disminuyendo hasta menos del 30 por ciento de lo normal, también se puede necesitar un respirador/ventilador a volumen durante el día para obtener más asistencia. La persona aumentará gradualmente la cantidad de tiempo usando el

respirador/ventilador durante el día, según sea necesario.

F. Pronóstico

La distrofia muscular de Duchenne es una enfermedad progresiva que eventualmente afecta a todos los músculos voluntarios e involucra al corazón y los músculos respiratorios en etapas posteriores. La esperanza de vida se estima actualmente en alrededor de 25 años, pero esto varía de un paciente a otro. Los avances recientes en la medicina extienden la vida de los afectados. *Muscular Dystrophy Campaign*, que es una organización benéfica líder en el Reino Unido que se centra en todas las enfermedades musculares, afirma que «con estándares altos de atención médica, los hombres jóvenes con distrofia muscular de Duchenne a menudo viven bien hasta los 30 años».

En casos raros, se ha observado que las personas con DMD sobreviven hasta los cuarenta años o principios de los cincuenta, con el uso de una posición adecuada en sillas de ruedas y camas, soporte de ventilación (mediante traqueotomía o boquilla), depuración de las vías respiratorias y medicamentos para el corazón, si es necesario. La planificación temprana de la asistencia necesaria para el cuidado de la vida posterior ha demostrado una mayor longevidad en las personas que viven con DMD.

Curiosamente, en el modelo de ratón mdx de distrofia muscular de Duchenne, la deficiencia de distrofina se asocia con un aumento de los niveles de calcio y mionecrosis del músculo esquelético. Los músculos laríngeos intrínsecos (ILM) están protegidos y no experimentan mionecrosis. Los ILM tienen un perfil de sistema de regulación de calcio que sugiere una mejor capacidad para controlar los cambios de calcio en comparación con otros músculos, y esto puede proporcionar una visión mecanicista de sus propiedades patofisiológicas únicas. Los ILM pueden facilitar el desarrollo de estrategias novedosas para la prevención y el tratamiento de la atrofia muscular en una variedad de escenarios clínicos.

II. Otras enfermedades que se benefician de la edición genómica

Además de encontrar aplicación en el tratamiento de la DMD, el enfoque de guías múltiples de los inventores puede aplicarse ventajosamente a otros estados de enfermedad en los que dicha intervención podría dar como resultado la corrección de los defectos genéticos causales subyacentes. Algunos de estos se describen brevemente a continuación.

Distrofia muscular de la cintura y las extremidades. La distrofia muscular de la cintura y las extremidades (LGMD) o distrofia muscular de Erb es un grupo genéticamente y clínicamente heterogéneo de distrofias musculares raras. Se caracteriza por la atrofia muscular progresiva que afecta principalmente los músculos de la cadera y los hombros. La LGMD tiene un patrón autosómico

de herencia y actualmente no tiene cura conocida. Los síntomas de una persona con distrofia muscular de la cintura y las extremidades (LGMD) generalmente presentan dificultad para caminar, subir y bajar escaleras y levantarse de una silla. La dificultad para inclinarse y las caídas también son comunes regularmente. La dificultad para levantar ciertos objetos también es una presentación común de la LGMD, así como la dificultad para mantener los brazos hacia afuera o por encima de la cabeza. Eventualmente, se deteriora la capacidad de caminar/correr.

La enfermedad empeora inevitablemente con el tiempo, aunque la evolución es más rápida en algunos pacientes que en otros. Eventualmente, la enfermedad puede afectar otros músculos, como los que se encuentran en la cara. La enfermedad generalmente conduce a la dependencia de una silla de ruedas dentro de los años de aparición de los síntomas, pero existe una alta variabilidad entre los pacientes, y algunos pacientes mantienen la movilidad.

La debilidad muscular es generalmente simétrica, proximal y lentamente progresiva. En la mayoría de los casos, el dolor no está presente con la LGMD, y la función mental no se ve afectada. La LGMD puede comenzar en la infancia, la adolescencia, la edad adulta joven o incluso más tarde, la edad de inicio suele ser entre los 10 y los 30 años. Ambos sexos se ven afectados por igual, cuando la distrofia muscular de la cintura y las extremidades comienza en la infancia, la evolución parece ser más rápida y la enfermedad es más incapacitante. Cuando el trastorno comienza en la adolescencia o en la edad adulta, la enfermedad generalmente no es tan grave y evoluciona más lentamente. No hay neuropatía sensorial o disfunción autonómica o visceral en la presentación.

En términos genéticos, la LGMD es un trastorno hereditario, aunque puede heredarse como un defecto genético dominante o recesivo. El resultado del defecto es que los músculos no pueden formar correctamente determinadas proteínas necesarias para la función muscular normal. Varias proteínas diferentes pueden verse afectadas, y la proteína específica que está ausente o es defectuosa identifica el tipo específico de distrofia muscular. Entre las proteínas afectadas en la LGMD se encuentran los sarcoglicanos α, β y γ. Las sarcoglicanopatías posiblemente podrían ser sometidas a la terapia génica.

Disferlinopatía. La disferlinopatía es un trastorno neuromuscular autosómico recesivo causado por una deficiencia de la proteína disferlina funcional debido a mutaciones en el gen de la disferlina. La disferlinopatía se caracteriza por una atrofia muscular progresiva y, en la mayoría de los casos, se diagnostica clínicamente como distrofia muscular de la cintura y las extremidades tipo 2B (LGMD2B) o distrofia muscular de Miyoshi 1 (MMD1; un tipo de distrofia muscular distal), dependiendo del patrón inicial de implicación muscular en el diagnóstico. La disferlinopatía es una enfermedad rara, cuya incidencia exacta aún no se ha determinado.

Los síntomas de la disferlinopatía usualmente se manifiestan en la edad adulta temprana entre los 16

y los 25 años y afectan principalmente el músculo esquelético de las extremidades y las fajas de las extremidades (caderas y hombros), y no afectan en gran medida los músculos cruciales tales como el corazón y el diafragma. La mayoría de los pacientes con disferlinopatía se vuelven no ambulantes dentro de los 10-20 años después del diagnóstico, pero la expectativa de vida es normal. Existe una gran variabilidad en la edad de inicio y evolución de la enfermedad.

Aunque la LGMD2B y MMD1 son causadas por una deficiencia de disferlina, se da un diagnóstico de LGMD2B cuando la debilidad se presenta inicialmente en los músculos proximales (muslos y parte superior de los brazos), mientras que se da un diagnóstico de MMD1 cuando la debilidad se presenta inicialmente en los músculos distales (pantorrillas y parte inferior de los brazos). En ambos casos, la debilidad eventualmente evoluciona para incluir los músculos distales y proximales. Tanto la LGMD2B como la MMD1 son muy difíciles de diagnosticar, y los pacientes a menudo se diagnostican erróneamente muchas veces antes de que se les diagnostique con éxito la disferlinopatía.

Mientras que la «disferlinopatía» simplemente se refiere a la ausencia de la proteína disferlina, la miopatía LGMD2B y de Miyoshi 1 son el diagnóstico confirmado solo cuando se pueden detectar mutaciones en el gen de la disferlina. Es esencial que los pacientes reciban un diagnóstico genético para participar en estudios y ensayos clínicos específicos para la disferlinopatía. La Fundación Jain es una organización familiar sin fines de lucro (www.jain-foundation.org) que ayuda a los pacientes con distrofia muscular de la cintura y las extremidades a lograr un diagnóstico genético mediante la organización de pruebas y la cobertura del costo.

Miopatía de titina. La titina, también conocida como conectina, es una proteína que en humanos es codificada por el gen *TTN*. La titina es una proteína gigante, de más de 1 µm de longitud, que funciona como un resorte molecular que es responsable de la elasticidad pasiva del músculo. Está compuesto por 244 dominios de proteínas plegadas individualmente conectadas por secuencias peptídicas no estructuradas. Estos dominios se despliegan cuando se estira la proteína y se repliegan cuando se elimina la tensión.

La titina es importante en la contracción de los tejidos musculares estriados. Conecta la línea Z a la línea M en el sarcómero. La proteína contribuye a la transmisión de fuerza en la línea Z y la tensión de reposo en la región de la banda I. Limita el rango de movimiento del sarcómero en tensión, contribuyendo de ese modo a la rigidez pasiva del músculo. Las variaciones en la secuencia de la titina entre diferentes tipos de músculo (p.ej., cardíaco o esquelético) se han correlacionado con diferencias en las propiedades mecánicas de estos músculos.

La titina es una proteína abundante grande del músculo estriado. Las funciones principales de la titina son estabilizar el filamento grueso, centrarlo entre los filamentos delgados, evitar el estiramiento excesivo del sarcómero y hacer retroceder el sarcómero como un resorte después de estirarlo. Una

región del disco Z en el extremo N y una región de la línea M en el extremo C se unen a la línea Z y la línea M del sarcómero, respectivamente, de modo que una única molécula de titina se extiende hasta la mitad de la longitud de un sarcómero. La titina también contiene sitios de unión para proteínas asociadas con los músculos, por lo que sirve como plantilla de adhesión para el montaje de la maquinaria contráctil en las células musculares. También se ha identificado como una proteína estructural para los cromosomas. Existe una variabilidad considerable en las regiones de la banda I, la línea M y el disco Z de la titina. La variabilidad en la región de la banda I contribuye con las diferencias en la elasticidad de diferentes isoformas de titina y, por lo tanto, con las diferencias en la elasticidad de diferentes tipos de músculos. De las muchas variantes de titina identificadas, cinco se describen con la información de transcripción completa disponible.

Las mutaciones en cualquier lugar dentro de la secuencia inusualmente larga de este gen pueden causar codones de terminación prematuros u otros defectos. Las mutaciones de titina se asocian con miopatía hereditaria con insuficiencia respiratoria temprana, miopatía de inicio temprano con cardiomiopatía fatal, miopatía central con enfermedad cardíaca, miopatía centronuclear, distrofia muscular de la cintura y las extremidades tipo 2J, cardiomiopatía dilatada familiar 9, cardiomiopatía hipertrófica y distrofia muscular tibial. Las investigaciones adicionales también sugieren que ninguna forma genéticamente vinculada de cualquier distrofia o miopatía puede ser excluida de forma segura de ser causada por una mutación en el gen TTN. Las mutaciones que se truncan en pacientes con cardiomiopatía dilatada se encuentran más comúnmente en la región A; aunque se podría esperar que los truncamientos en la región I corriente arriba impidan la traducción de la región A por completo, el corte y empalme alternativo crea algunas transcripciones que no encuentran el codón de terminación prematuro, lo que mejora su efecto. Se producen autoanticuerpos contra la titina en pacientes con la enfermedad autoinmunitaria esclerodermia.

Miopatía congénita «enfermedad del núcleo central» causada por una mutación en el receptor de rianodina (mutación con pseudoexones). La enfermedad del núcleo central (CCD), también conocida como miopatía del núcleo central, es una miopatía congénita autosómica dominante (trastorno muscular innato). Fue descrita por primera vez por Shy y Magee en 1956. Se caracteriza por la aparición de la miofibrilla bajo el microscopio.

Los síntomas de la CCD son variables, pero generalmente incluyen hipotonía (disminución del tono muscular) al nacer, retraso leve en el desarrollo del niño (altamente variable entre los casos), debilidad de los músculos faciales y malformaciones esqueléticas tales como escoliosis y dislocación de la cadera.

Los síntomas pueden estar presentes al nacer o pueden aparecer en cualquier etapa de la vida. Parece que hay un número creciente de personas que no se vuelven sintomáticas hasta la edad

adulta o mediana edad. Si bien en general no es progresiva, nuevamente parece haber una cantidad creciente de personas que experimentan una evolución lenta de la sintomatología clínicamente significativa. Hipotéticamente, estos casos pueden deberse a la gran cantidad de mutaciones genéticas de la disfunción del receptor de rianodina y, de hecho, con la investigación continua se pueden encontrar variantes clínicas.

El diagnóstico se realiza mediante la combinación de síntomas típicos y la apariencia en la biopsia (muestra de tejido) del músculo. El nombre deriva de la apariencia típica de la biopsia en microscopía óptica, donde las células musculares tienen núcleos que no tienen mitocondrias ni enzimas específicas. La insuficiencia respiratoria se desarrolla en una pequeña proporción de casos. La creatina quinasa y la electromiografía (EMG) tienden a ser normales.

La enfermedad del núcleo central se hereda de manera autosómica dominante. La mayoría de los casos tienen mutaciones demostrables en el gen del receptor de rianodina tipo 1 (*RYR1*), que son a menudo *de novo* (desarrolladas recientemente). Las personas con CCD tienen riesgo de hipertermia maligna (MH) cuando reciben anestesia general.

No hay un tratamiento específico, pero se evitan los anestésicos desencadenantes y se examina a los familiares para detectar mutaciones de *RYR1* dado que estas pueden hacerlos propensos a la MH.

Distrofia miotónica. La distrofia miotónica es un trastorno genético a largo plazo que afecta la función muscular. Los síntomas incluyen de la debilidad y pérdida muscular con empeoramiento gradual. Los músculos a menudo se contraen y son incapaces de relajarse. Otros síntomas pueden incluir cataratas, discapacidad intelectual y problemas de conducción cardíaca. En los hombres puede haber calvicie temprana e incapacidad para tener hijos.

La distrofia miotónica es un trastorno autosómico dominante que generalmente se hereda de los padres de una persona. Hay dos tipos principales: tipo 1 (DM1) debido a mutaciones en el gen DMPK y tipo 2 (DM2) debido a mutaciones en el gen CNBP. El trastorno generalmente empeora en cada generación. Un tipo de DM1 puede ser evidente al nacer. La DM2 generalmente es más suave. Estos son tipos de distrofia muscular. El diagnóstico se confirma mediante pruebas genéticas.

No tiene cura. Los tratamientos pueden incluir aparatos ortopédicos o sillas de ruedas, marcapasos y ventilación con presión positiva no invasiva. Los medicamentos mexiletina o carbamazepina son útiles en algunas ocasiones. El dolor, si se presenta, puede tratarse con antidepresivos tricíclicos y medicamentos antiinflamatorios no esteroides (AINE).

La distrofia miotónica afecta a más de 1 de cada 8000 personas en todo el mundo. Si bien la distrofia miotónica puede aparecer a cualquier edad, el inicio suele ser entre los 20 y los 30 años. Es la forma más común de distrofia muscular que comienza en la edad adulta. Se describió por primera vez en

1909 y la causa subyacente del tipo 1 se determinó en 1992.

La presentación de los síntomas y signos varía considerablemente según la forma (DM1/DM2), la gravedad e incluso los fenotipos inusuales de DM2. Los síntomas de DM1 para DM2 incluyen problemas con la función ejecutiva (p.ej., organización, concentración, búsqueda de palabras) e hipersomnia. Las anomalías de conducción son más comunes en la DM1 que en la DM2, pero se recomienda a todas las personas que se realicen una ECG anual. Ambos tipos también están asociados con la resistencia a la insulina. La distrofia miotónica puede tener una catarata cortical con una apariencia de punto azul, o una catarata subcapsular posterior.

La DM2 es generalmente más leve que la DM1, y menos personas con DM2 requieren dispositivos de asistencia en comparación con las personas con DM1. Además, la forma congénita grave que afecta a los bebés en la DM1 no se ha encontrado en la DM2 y rara vez se observa la aparición temprana de síntomas en personas jóvenes en la bibliografía médica.

Los síntomas pueden aparecer en cualquier momento desde la infancia hasta la edad adulta. La DM causa debilidad general, que usualmente comienza en los músculos de las manos, los pies, el cuello o la cara. Evoluciona lentamente hasta involucrar a otros grupos musculares, incluido el corazón. La DM afecta también a una amplia variedad de otros sistemas de órganos.

La distrofia miotónica es una afección genética que se hereda en un patrón autosómico dominante y, por lo tanto, se transmitirá a un promedio de 50 % de la descendencia de un portador. La distrofia miotónica es uno de varios trastornos de repetición de trinucleótidos conocidos. Determinadas áreas del ADN tienen secuencias repetidas de dos o tres nucleótidos.

La distrofia miotónica (DM) es una enfermedad hereditaria. Una forma grave de DM, la distrofia miotónica congénita, puede aparecer en los recién nacidos de madres que tienen DM. La distrofia miotónica congénita también puede heredarse a través del gen paterno, aunque se considera que es relativamente poco frecuente. Congénito/a significa que la afección está presente desde el nacimiento.

En la DM1, el gen afectado se denomina *DMPK*, que codifica la proteína quinasa de la distrofia miotónica, una proteína que se expresa principalmente en el músculo esquelético. El gen se encuentra en el brazo largo del cromosoma 19.

En la DM1, hay una expansión de la repetición del triplete citosina-timina-guanina (CTG) en el gen *DMPK*. Entre 5 y 37 repeticiones se consideran normales, mientras se considera que los individuos con entre 38 y 49 repeticiones tienen una premutación y corren el riesgo de tener hijos con repeticiones expandidas adicionales y, por lo tanto, la enfermedad sintomática. Los individuos con más de 50 repeticiones son casi invariablemente sintomáticos, con algunas excepciones observadas. Las repeticiones más largas usualmente se asocian con un inicio más temprano y una enfermedad

más grave.

Los alelos de DMPK con más de 37 repeticiones son inestables y pueden insertarse repeticiones de trinucleótidos adicionales durante la división celular en la mitosis y la meiosis. Por consiguiente, los hijos de personas con premutaciones o mutaciones heredan alelos de DMPK más largos que los sus padres y, por lo tanto, tienen más probabilidades de verse afectados o mostrar un inicio más temprano y una mayor gravedad de la afección, un fenómeno conocido como anticipación. Curiosamente, la transmisión paterna de la afección es muy poco frecuente, posiblemente debido a presiones de selección contra espermatozoides con repeticiones expandidas, pero la anticipación tiende a ser menos grave que en los casos de herencia materna.

El ARN de la región de repetición de trinucleótidos expandida forma bucles de horquilla intranucleoplásmicos debido a los enlaces de hidrógeno extensos entre los pares de bases C-G, y se ha demostrado que estos secuestran el regulador de corte y empalme MBNL1 para formar focos distintivos mediante marcado con GFP y un oligonucleótido sonda con el tinte fluorescente rojo Cyanine5 (Cy5).

La DM2 es causada por un defecto del gen *ZNF9* en el cromosoma 3. El defecto específico es una repetición del tetranucleótido citosina-citosina-timina-guanosina (CCTG) en el gen *ZNF9*. Como implica la repetición de cuatro nucleótidos, no es un trastorno de repetición de trinucleótido, sino más bien un trastorno de repetición de tetranucleótido.

La expansión de repetición para DM2 es mucho más grande que para DM1, con un intervalo de 75 a más de 11.000 repeticiones. A diferencia de la DM1, el tamaño de la expansión repetida del ADN en la DM2 no parece hacer una diferencia en la edad de aparición o la gravedad de la enfermedad. La anticipación parece ser menos significativa en la DM2 y la mayoría de las revisiones actuales solo informan una anticipación leve como una característica de la DM2.

Ataxia de Friedreich. La ataxia de Friedreich es una enfermedad hereditaria autosómica recesiva que causa daño progresivo al sistema nervioso. Se manifiesta en síntomas iniciales de mala coordinación tal como la alteración del andar; También puede provocar escoliosis, enfermedades cardíacas y diabetes, pero no afecta la función cognitiva. La enfermedad evoluciona hasta que se requiere una silla de ruedas para la movilidad. Su incidencia en la población general es de aproximadamente 1 en 50.000.

La mutación genética particular (expansión de una repetición del triplete intrónico GAA en el gen FXN) provoca una expresión reducida de la proteína mitocondrial frataxina. Con el transcurso del tiempo, esta deficiencia causa el daño mencionado anteriormente, así como fatiga frecuente debido a los efectos sobre el metabolismo celular.

La ataxia de Friedreich se debe a la degeneración del tejido nervioso en la médula espinal, en

particular, a las neuronas sensoriales esenciales (a través de las conexiones con el cerebelo) para dirigir el movimiento muscular de los brazos y las piernas. La médula espinal se vuelve más delgada y las células nerviosas pierden parte de su vaina de mielina (la cubierta aislante sobre algunas células nerviosas que ayuda a conducir los impulsos nerviosos).

Los síntomas generalmente comienzan en algún momento entre las edades de 5 a 15 años, pero en el inicio tardío la FA puede producirse a los 20 o 30 años. Los síntomas incluyen cualquier combinación, pero no necesariamente todas, de debilidad muscular en los brazos y las piernas, pérdida de coordinación, discapacidad visual, discapacidad auditiva, dificultad para hablar, curvatura de la columna vertebral, arcos plantares altos (deformidad del pie cavo del pie), diabetes (alrededor de 20 % de las personas con ataxia de Friedreich desarrollan intolerancia a los carbohidratos y 10 % desarrolla diabetes mellitus) y trastornos cardíacos (p.ej., fibrilación auricular y taquicardia resultante (frecuencia cardíaca rápida) y cardiomiopatía hipertrófica).

Se presenta antes de los 22 años de edad con un andar tambaleante o con tropiezos progresivo y caídas frecuentes. Las extremidades inferiores se encuentran más gravemente involucradas. Los síntomas son lentos y progresivos. La observación a largo plazo muestra que muchos pacientes alcanzan una meseta en los síntomas en la edad adulta temprana del paciente. En promedio, después de 10-15 años con la enfermedad, los pacientes suelen estar en silla de ruedas y requieren asistencia en todas las actividades de la vida diaria.

Los siguientes signos físicos pueden detectarse en el examen físico: signos cerebelosos tales como nistagmo, movimientos oculares sacádicos rápidos, ataxia troncal, disartria, dismetría; lesiones neuronales motoras inferiores tales como ausencia de reflejos tendinosos profundos; se encuentran comúnmente signos piramidales tales como respuestas plantares extensoras y debilidad distal; aparecen aspectos de la columna dorsal tales como pérdida de la sensación vibratoria y propioceptiva. La afectación cardíaca se produce en 91 % de los pacientes, incluida la cardiomegalia (hasta cardiomiopatía dilatada), hipertrofia simétrica, soplos cardíacos y defectos de la conducción. La edad mediana de muerte es de 35 años, mientras que las mujeres tienen un mejor pronóstico, con una supervivencia de 20 años del 100 % en comparación con 63 % en los hombres. El veinte por ciento de los casos se encuentran en asociación con diabetes mellitus.

La ataxia de Friedreich es un trastorno autosómico recesivo que se produce cuando el gen FXN contiene repeticiones de GAA intrónicas amplificadas (un ejemplo de expansión de repetición de trinucleótidos). El gen FXN codifica la proteína frataxina. La expansión de repeticiones de GAA hace que se reduzcan los niveles de frataxina. La frataxina es una proteína de unión al hierro responsable de la formación de grupos de hierro-azufre. Un resultado de la deficiencia de frataxina es la sobrecarga de hierro mitocondrial que puede causar daño a muchas proteínas. El papel exacto de la

frataxina en la fisiología normal sigue siendo confuso. El gen se encuentra en el cromosoma 9.

El gen mutante contiene repeticiones del triplete GAA expandidas en el primer intrón; en unos pocos linajes, se han detectado mutaciones puntuales. Debido a que el defecto se encuentra en un intrón (que se elimina de la transcripción del ARNm entre la transcripción y la traducción), esta mutación no provoca la producción de proteínas frataxina anormales. En cambio, la mutación provoca el silenciamiento de genes (es decir, la mutación disminuye la transcripción del gen) a través de la inducción de una estructura de heterocromatina de manera similar a la variación de posición y efecto.

Además de reducir la expresión de frataxina, los tramos largos de repeticiones de GAA inducen interrupciones de cromosomas en estudios de levadura *in vivo*.

Enfermedad de Huntington. La enfermedad de Huntington (HD), también conocida como corea de Huntington, es un trastorno hereditario que provoca la muerte de las células cerebrales. Los primeros síntomas son a menudo problemas sutiles con el estado de ánimo o las habilidades mentales. A menudo sigue una falta de coordinación y un andar inestable. A medida que avanza la enfermedad, los movimientos del cuerpo descoordinados y bruscos se hacen más evidentes. Las habilidades físicas empeoran gradualmente hasta que el movimiento coordinado se vuelve difícil y la persona no puede hablar. Las habilidades mentales generalmente se convierten en demencia. Los síntomas específicos varían algo entre las personas. Los síntomas generalmente comienzan entre los 30 y 50 años de edad, pero pueden comenzar a cualquier edad. La enfermedad puede desarrollarse más temprano en la vida en cada generación sucesiva. Alrededor de 8 % de los casos comienzan antes de los 20 años y, generalmente, presentan síntomas más similares a los de la enfermedad de Parkinson. Las personas con HD a menudo subestiman el grado de sus problemas.

La HD se hereda típicamente de los padres de una persona con 10 % de los casos debido a una nueva mutación. La enfermedad es causada por una mutación autosómica dominante en cualquiera de las dos copias en un individuo de un gen denominado *Huntingtin*. Esto significa que un hijo de una persona afectada generalmente tiene 50 % de probabilidad de heredar la enfermedad. El gen *Huntingtin* proporciona la información genética para una proteína que también se denomina «huntingtin». La expansión de las repeticiones del triplete CAG (citosina-adenina-guanina) en el gen que codifica la proteína Huntingtin produce una proteína anormal, que daña gradualmente las células en el cerebro, a través de mecanismos que no se comprenden por completo. El diagnóstico se realiza mediante pruebas genéticas, que pueden llevarse a cabo en cualquier momento, independientemente de si los síntomas están presentes o no. Este hecho plantea varios debates éticos: la edad a la que una persona se considera lo suficientemente madura como para elegir hacerse las pruebas; si los padres tienen derecho a que sus hijos sean examinados; y la gestión de la confidencialidad y divulgación de los resultados de las pruebas.

No existe cura para la HD. Se requiere atención a tiempo completo en las últimas etapas de la enfermedad. Los tratamientos pueden aliviar algunos síntomas y en algunos mejorar la calidad de vida. La mejor evidencia para el tratamiento de los problemas de movimiento es con tetrabenazina. La HD afecta de alrededor de 4 a 15 de cada 100.000 personas de origen europeo. Es poco frecuente entre los japoneses y se produce a un ritmo desconocido en África. La enfermedad afecta a hombres y mujeres por igual. Las complicaciones tales como neumonía, enfermedad cardíaca y lesiones físicas causadas por las caídas reducen la expectativa de vida. El suicidio es la causa de muerte en alrededor de 9 % de los casos. La muerte se produce típicamente de quince a veinte años desde que se detectó la enfermedad.

Los síntomas de la enfermedad de Huntington se notan con mayor frecuencia entre los 35 y los 44 años, pero pueden comenzar a cualquier edad desde la infancia hasta la vejez. En las primeras etapas, hay cambios sutiles en la personalidad, la cognición y las habilidades físicas. Los síntomas físicos suelen ser los primeros en notarse, ya que los síntomas cognitivos y de comportamiento generalmente no son lo suficientemente graves como para ser reconocidos por sí mismos en las etapas iniciales. Casi todas las personas con la enfermedad de Huntington eventualmente presentan síntomas físicos similares, pero la aparición, evolución y grado de los síntomas cognitivos y de comportamiento varían significativamente entre las personas.

Los síntomas físicos iniciales más característicos son movimientos espasmódicos, aleatorios e incontrolables, denominados corea. La corea puede mostrarse inicialmente como inquietud general, pequeños movimientos iniciados involuntariamente o incompletos, falta de coordinación o movimientos oculares sacádicos lentos. Estas anomalías motoras menores suelen preceder a los signos más evidentes de disfunción motora durante al menos tres años. La aparición clara de síntomas tales como rigidez, movimientos de retorcimiento o postura anormal aparecen a medida que avanza el trastorno. Estas son señales de que se ha visto afectado el sistema responsable del movimiento en el cerebro. Las funciones psicomotoras se deterioran cada vez más, de modo que se ve afectada cualquier acción que requiera control muscular. Las consecuencias comunes son la inestabilidad física, la expresión facial anormal y las dificultades para masticar, tragar y hablar. Las dificultades para comer comúnmente causan pérdida de peso y pueden llevar a la desnutrición. Los trastornos del sueño también son síntomas asociados. La HD juvenil difiere de estos síntomas dado que generalmente avanza más rápido y la corea se presenta brevemente, si es que lo hace, siendo la rigidez el síntoma dominante. Las convulsiones también son un síntoma común de esta forma de HD.

Las habilidades cognitivas se deterioran de forma progresiva. Las funciones ejecutivas que se ven especialmente afectadas son las que incluyen la planificación, flexibilidad cognitiva, pensamiento abstracto, adquisición de reglas, inicio de acciones apropiadas y presentación de acciones

inapropiadas. A medida que avanza la enfermedad, tienden a aparecer déficits de memoria. Las deficiencias informadas van desde déficits de la memoria a corto plazo hasta dificultades de la memoria a largo plazo, incluidos los déficits en la memoria episódica (memoria de la vida), de los procedimientos (memoria del cuerpo de cómo realizar una actividad) y del trabajo. Los problemas cognitivos tienden a empeorar con el transcurso del tiempo y, en última instancia, provocan demencia. Este patrón de déficit se ha denominado síndrome de demencia subcortical para distinguirlo de los efectos típicos de las demencias corticales, p.ej., la enfermedad de Alzheimer.

Las manifestaciones neuropsiquiátricas informadas son ansiedad, depresión, una disminución al mostrar las emociones (embotamiento afectivo), egocentrismo, agresión y comportamiento compulsivo, el último de los cuales puede causar o empeorar las adicciones, incluido el alcoholismo, el juego y la hipersexualidad. También se han observado dificultades para reconocer las expresiones negativas de otras personas. La prevalencia de estos síntomas es altamente variable entre los estudios, con tasas estimadas de prevalencia en la vida de trastornos psiquiátricos entre 33 % y 76 %. Para muchas personas que padecen la enfermedad y sus familias, estos síntomas se encuentran entre los aspectos más angustiantes de la enfermedad, que a menudo afectan el funcionamiento diario y constituyen una razón para la institucionalización. Los pensamientos suicidas y los intentos de suicidio son más comunes que en la población general. A menudo, las personas tienen una conciencia reducida sobre la corea, las discapacidades cognitivas y emocionales.

La Huntingtin mutante se expresa en todo el cuerpo y se asocia con anomalías en los tejidos periféricos que son causadas directamente por dicha expresión fuera del cerebro. Estas anomalías incluyen atrofia muscular, insuficiencia cardíaca, tolerancia a la glucosa alterada, pérdida de peso, osteoporosis y atrofia testicular.

Todos los humanos tienen dos copias del gen Huntingtin (*HTT*), que codifica la proteína Huntingtin (HTT). El gen también se denomina *HD* y *IT15*, que significa «transcripción interesante 15». Parte de este gen es una sección repetida denominada repetición de trinucleótidos, cuya longitud varía entre las personas y puede cambiar la longitud entre las generaciones. Si la repetición está presente en un gen sano, una mutación dinámica puede aumentar el conteo de repeticiones y dar como resultado un gen defectuoso. Cuando la longitud de esta sección repetida alcanza un umbral determinado, se produce una forma alterada de la proteína, denominada proteína Huntingtin mutante (mHTT). Las diferentes funciones de estas proteínas son la causa de cambios patológicos que a su vez causan los síntomas de la enfermedad. La mutación de la enfermedad de Huntington es genéticamente dominante y casi totalmente penetrante: la mutación de cualquiera de los dos alelos de *HTT* de uan persona causa la enfermedad. No se hereda según el sexo, pero la longitud de la sección repetida del gen y, por lo tanto, su gravedad puede verse influida por el sexo del progenitor afectado.

La HD es uno de los varios trastornos de repetición de trinucleótidos que son causados por la longitud de una sección repetida de un gen que excede un intervalo normal. El gen *HTT* se encuentra en el brazo corto del cromosoma 4 en 4p16.3. El *HTT* contiene una secuencia de tres bases de ADN: citosina, adenina, guanina (CAG), que se repite varias veces (es decir, ... CAGCAGCAG...), conocida como una repetición de trinucleótido. CAG es el código genético de 3 letras (codón) para el aminoácido glutamina, por lo que una serie de ellos resulta en la producción de una cadena de glutamina conocida como tramo de poliglutamina (o tramo poliQ), y la parte repetida del gen, la *región PoliQ*.

En general, las personas tienen menos de 36 glutaminas repetidas en la región poliQ, lo que da como resultado la producción de la proteína citoplasmática Huntingtin. Sin embargo, una secuencia de 36 o más glutaminas da como resultado la producción de una proteína que tiene características diferentes. Esta forma alterada, denominada huntingtin mutante (mHTT), aumenta la la velocidad de deterioro de determinados tipos de neuronas. Las regiones del cerebro tienen cantidades diferentes y dependen de estos tipos de neuronas, y se ven afectadas en consecuencia. En general, el número de repeticiones de CAG se relaciona con qué parte de este proceso que se ve afectada y representa alrededor de 60 % de la variación de la edad de aparición de los síntomas. La variación restante se atribuye al medio ambiente y otros genes que modifican el mecanismo de la HD. 36–39 repeticiones dan como resultado una forma con penetrancia reducida de la enfermedad, con un inicio muy posterior y una evolución más lenta de los síntomas. En algunos casos, la aparición puede ser tan tardía que los síntomas nunca se notan. Con recuentos de repeticiones muy grandes, la HD tiene una penetrancia total y puede producirse antes de los 20 años, donde se la denomina HD juvenil, HD variante de Westphal o acinética rígida. Esto representa alrededor de 7 % de los portadores de HD.

Ataxia telangiectasia. La ataxia telangiectasia (AT o A-T), también conocida como síndrome de ataxia telangiectasia o síndrome de Louis-Bar, es una enfermedad autosómica recesiva neurodegenerativa rara, que provoca una discapacidad grave. La ataxia se refiere a desde falta de coordinación y telangiectasia hasta dilatación de los vasos sanguíneos pequeños, las cuales son distintivos de la enfermedad.

La A-T afecta muchas partes del cuerpo. Afecta determinadas áreas del cerebro, que incluyen el cerebelo, lo que provoca dificultades con el movimiento y la coordinación. Se debilita el sistema inmunitario, lo que provoca una predisposición a las infecciones. Previene la reparación del ADN interrumpido, lo que aumenta el riesgo de cáncer.

Los síntomas casi siempre aparecen por primera vez en la primera infancia (la etapa de niño pequeño) cuando los niños comienzan a caminar. Aunque generalmente comienzan a caminar a una edad normal, se tambalean o se balancean cuando caminan, permanecen quietos o sentados, y

puede parecer casi como si estuvieran borrachos. En la etapa preescolar tardía y en la edad escolar temprana, desarrollan dificultades para mover sus ojos de manera natural de un lugar a otro (apraxia oculomotora). Desarrollan el habla confusa o distorsionada, y tienen problemas para tragar. Algunos tienen una mayor cantidad de infecciones del tracto respiratorio (infecciones de oído, sinusitis, bronquitis y neumonía). Debido a que no todos los niños se desarrollan de la misma manera o al mismo ritmo, es posible que pasen algunos años antes de que se diagnostique adecuadamente la A-T. La mayoría de los niños con A-T tienen síntomas neurológicos estables durante los primeros 4-5 años de vida, pero comienzan a mostrar problemas crecientes en los primeros años escolares.

La A-T es causada por un defecto en el gen ATM, que es responsable de administrar la respuesta de la célula a múltiples formas de estrés, las que incluyen interrupciones de cadena doble en el ADN. En términos simples, la proteína producida por el gen ATM reconoce que hay una interrupción en el ADN, capta otras proteínas para corregir la interrupción y evita que la célula genere ADN nuevo hasta que se complete la reparación.

Existe una variabilidad sustancial en la gravedad de las características de la A-T entre las personas afectadas y en diferentes edades. Los siguientes síntomas o problemas son características comunes o importantes de la A-T:

Ataxia (dificultad con el control del movimiento) que se manifiesta de forma temprana, pero empeora en los años escolares o de preadolescencia.

Apraxia oculomotora (dificultad para coordinar el movimiento de la cabeza y los ojos al cambiar la mirada de un lugar a otro).

Movimientos involuntarios.

Telangiectasia (vasos sanguíneos dilatados) sobre la parte blanca (esclerótica) de los ojos, lo que hace que parezcan inyectados con sangre. Estos no son evidentes en la infancia y pueden aparecer por primera vez a los 5-8 años de edad. La telangiectasia también puede aparecer en áreas de la piel expuestas al sol.

Problemas con infecciones, especialmente de los oídos, senos nasales y pulmones.

Aumento de la incidencia del cáncer (principalmente, pero no exclusivamente, linfomas y leucemias).

Inicio tardío o desarrollo puberal incompleto, y menopausia muy temprana.

Ralentización de la velocidad de crecimiento (peso y/o altura).

Babeo, particularmente, en los niños pequeños cuando están cansados o concentrados en las actividades.

Disartria (sonidos del habla confusos, lentos o distorsionados).

Diabetes en la adolescencia o después.

Cambios prematuros en el cabello y la piel.

Muchos niños son inicialmente diagnosticados erróneamente con parálisis cerebral atáxica. Es posible que el diagnóstico de A-T no se haga hasta los años preescolares cuando aparecen o se empeoran los síntomas neurológicos del andar alterado, la coordinación de las manos, el habla y el movimiento ocular aparecen o empeoran, y aparece por primera vez la telangiectasia. Debido a que la A-T es tan poco frecuente, es posible que los médicos no estén familiarizados con los síntomas o los métodos para hacer un diagnóstico. La aparición tardía de telangiectasia puede ser una barrera para el diagnóstico. Puede tomar algún tiempo antes de que los médicos consideren la A-T como una posibilidad debido a la estabilidad temprana de los síntomas y signos.

La A-T es causada por mutaciones en el gen ATM (mutación de ATM serina/treonina quinasa o ataxia-telangiectasia), que se clonó en 1995. El ATM se encuentra en el cromosoma humano 11 (11q22.3) y está formado por 69 exones distribuidos en 150 kb del ADN genómico.

El modo de herencia para la A-T es autosómico recesivo. Cada padre es un portador, lo que significa que tienen una copia normal del gen de A-T (ATM) y una copia mutada. La A-T se produce si un niño hereda el gen de A-T mutado de cada padre, por lo que en una familia con dos padres portadores, hay 1 posibilidad en 4 de que un niño nacido de los padres tenga el trastorno. El diagnóstico prenatal (y la detección del portador) puede realizarse en las familias si se han identificado los errores (mutación) en los dos genes ATM de un niño afectado. El proceso para lograrlo puede ser complicado y, como requiere tiempo, debe organizarse antes de la concepción.

La búsqueda de mutaciones en el gen ATM de una persona no relacionada (por ejemplo, el cónyuge de un portador de A-T conocido) presenta desafíos significativos. Los genes a menudo tienen variantes de manifestación (polimorfismos) que no afectan la función. En un gen tan grande como el ATM, es probable que se produzcan este tipo de manifestaciones y los médicos no siempre pueden predecir si una variante específica causará o no una enfermedad. La consulta genética puede ayudar a los miembros de la familia de un paciente con A-T a comprender qué se puede o no evaluar y cómo deben interpretarse los resultados de la prueba.

Los portadores de A-T, como los padres de una persona con A-T, tienen una copia mutada del gen ATM y una copia normal. En general, son saludables, pero existe un riesgo mayor de cáncer de mama en las mujeres. Este hallazgo se ha confirmado de varias formas diferentes y se está investigando actualmente. Se recomienda la vigilancia estándar (incluidos los autoexámenes mensuales de mamas y la mamografía a la edad habitual), a menos que se indiquen pruebas adicionales porque la persona tiene otros factores de riesgo (p.ej., antecedentes familiares de cáncer de mama).

Neurofibromatosis tipo 1 y 2. La neurofibromatosis (NF) es un grupo de tres afecciones en las cuales crecen tumores en el sistema nervioso. Los tres tipos son neurofibromatosis tipo 1 (NF1),

neurofibromatosis tipo 2 (NF2) y schwannomatosis. En la NF1, los síntomas incluyen manchas marrones claras en la piel, pecas en las axilas y la ingle, pequeñas protuberancias en los nervios y escoliosis. En la NF2, puede haber pérdida de audición, cataratas a una edad temprana, problemas de equilibrio, colgajos de piel de color carne y atrofia muscular. Los tumores son generalmente no cancerosos.

La causa es una mutación genética en determinados genes. En la mitad de los casos, estas son heredadas de los padres de una persona, mientras que en el resto se producen durante el desarrollo temprano. Los tumores implican células de apoyo en el sistema nervioso en lugar de las neuronas. En la NF1, los tumores son neurofibromas (tumores de los nervios periféricos), mientras que en la NF2 y schwannomatosis son más comunes los tumores de células de Schwann. El diagnóstico generalmente se basa en los signos y síntomas y, en ocasiones, se respalda con pruebas genéticas.

No hay prevención o cura conocida. Se puede realizar una cirugía para extirpar los tumores que causan problemas o que se han vuelto cancerosos. La radiación y la quimioterapia también pueden usarse si se produce cáncer. Un implante coclear o un implante auditivo del tronco encefálico puede ayudar a algunas personas con pérdida de audición.

En los Estados Unidos, alrededor de 1 de cada 3500 personas tienen NF1 y 1 de cada 25.000 tiene NF2. Los hombres y las mujeres se ven afectados con la misma frecuencia. En la NF1, los síntomas a menudo se presentan al nacer y se desarrollan antes de los 10 años de edad. Mientras que la afección generalmente empeora con el tiempo, la mayoría de las personas con NF1 tienen una expectativa de vida normal. En la NF2, es posible que los síntomas no aparezcan hasta la edad adulta temprana. La NF2 aumenta el riesgo de muerte prematura. Las descripciones de la afección se remontan al siglo 1.

La neurofibromatosis (NF1) en la vida temprana puede causar problemas de aprendizaje y de conducta: alrededor de 60 % de los niños que tienen NF1 tienen una dificultad leve en la escuela. En cuanto a los signos que podría tener una persona son los siguientes: seis o más manchas dermatológicas de color marrón claro («manchas de color café con leche»), al menos dos neurofibromas, al menos dos crecimientos en el iris del ojo y un crecimiento anormal de la columna vertebral (escoliosis).

La neurofibromatosis es un trastorno autosómico dominante, lo que significa que solo se necesita una copia del gen afectado para que se desarrolle el trastorno. Por lo tanto, si solo uno de los padres tiene neurofibromatosis, sus hijos también tienen 50 % de probabilidad de desarrollar la afección. El niño afectado podría tener una NF1 leve, aunque sea heredada de un padre con una forma grave del trastorno. Hay dos tipos de neurofibromatosis. La neurofibromatosis tipo I se caracteriza por el crecimiento de tejido nervioso en tumores (neurofibromas) que pueden ser benignos y pueden causar

daños graves al comprimir los nervios y otros tejidos. La neurofibromatosis tipo II muestra neuromas acústicos bilaterales (tumores del nervio vestibulococlear o del nervio craneal 8 (CN VIII), también conocidos como schwannoma), que a menudo producen una pérdida de la audición.

Schwannomatosis, en la cual se desarrollan schwannomas dolorosos en los nervios espinales y periféricos.

Mutación CEP290 en amaurosis congénita de Leber. La proteína centrosómica de 290 kDa es una proteína que está codificada en humanos por el gen de *CEP290*. CEP290se encuentra en el brazo Q del cromosoma 12. El gen CEP290 es una proteína centrosómica que desempeña un papel importante en el desarrollo de centrosomas y cilios. Este gen es vital en la formación del cilio primario, una pequeña proyección similar a una antena de la membrana celular que desempeña un papel importante en los fotorreceptores de la parte posterior de la retina (que detectan luz y color) y en el riñón, el cerebro. y muchos otros órganos del cuerpo. La reducción de los niveles de la transcripción del gen CEP290 dio lugar a una supresión drástica de la ciliogénesis en las células epiteliales del pigmento de la retina en el cultivo, lo que demuestra cuán importante es el CEP290 para la formación de cilios.

A nivel molecular, se ha demostrado que el CEP290 desempeña un papel regulador y estructural crucial en la formación del cilio primario. Estudios recientes han implicado al CEP290 como un microtúbulo y una proteína de unión a la membrana que podría servir como un enlace estructural entre el núcleo del microtúbulo de cilio y la membrana ciliar superpuesta. Se ha demostrado que la interrupción del dominio de unión a los microtúbulos de CEP290 en el modelo de ratón rd16 de la enfermedad de CEP290 produce una degeneración rápida y drástica de la retina, lo que demuestra la importancia de la unión de los microtúbulos de CEP290 en la enfermedad. El papel de CEP290 en la promoción de la ciliogénesis está inhibido tanto mediante los dominios de autorregulación que se encuentran en cada extremo de la proteína CEP290 como a través de la interacción de CEP290 con la proteína inhibidora CP110.

El descubrimiento del gen CEP290 ha llevado a los investigadores a encontrar otro gen crucial en la función de la retina, LCA5. Los ensayos clínicos que involucran el reemplazo genético de estos dos genes comenzaron en Filadelfia, donde los investigadores tienen la esperanza de que la amaurosis congénita de Leber pueda curarse algún día.

Este gen codifica una proteína con 13 dominios putativos de bobina enrollada, una región con homología a las ATPasas de segregación del cromosoma SMC, seis motivos KID, tres dominios de homología de tropomiosina y un motivo A del sitio de unión a ATP/GTP. La proteína se encuentra en el centrosoma y los cilios y tiene sitios para la N-glicosilación, sulfatación de tirosina, fosforilación, N-miristoilación y amidación.

Las mutaciones en este gen se han asociado con el síndrome de Joubert y la nefronafisis, y recientemente con una forma frecuente de amaurosis congénita de Leber, llamada LCA10. La presencia de anticuerpos contra esta proteína está asociada con varias formas de cáncer.

Una mutación en este gen produce ceguera en bebés y niños, una enfermedad conocida como amaurosis congénita de Leber. En la actualidad, 35 mutaciones diferentes en el CEP290 son responsables de causar LCA. También se han identificado otras mutaciones en el CEP290 que causan el síndrome de Meckel y el síndrome de Joubert, unos pocas entre muchos síndromes. Un gen CEP290 defectuoso suele ser la causa de estos trastornos debido a cilios anormales. Se desconoce cómo una mutación en un gen puede causar tantos tipos diferentes de síndromes, en particular, muchos de los cuales afectan al sistema nervioso central.

III. Sistemas de CRISPR

A. CRISPR

Las CRISPR (repeticiones palindrómicas cortas agrupadas y regularmente espaciadas) son locus de ADN que contienen repeticiones cortas de secuencias de bases. Cada repetición es seguida por segmentos cortos de «ADN espaciador» de exposiciones previas a un virus. Las CRISPR se encuentran en aproximadamente 40 % de los genomas de eubacterias secuenciadas y en 90 % de las arqueas secuenciadas. Las CRISPR se asocian a menudo con C como genes que codifican proteínas relacionadas con CRISPR. El sistema de CRISPR/Cas es un sistema inmunitario procariota que confiere resistencia a elementos genéticos extraños, como plásmidos y fagos, y proporciona una forma de inmunidad adquirida. Los espaciadores de CRISPR reconocen y silencian estos elementos genéticos exógenos como el ARNi en organismos eucariotas.

El tamaño de las repeticiones CRISPR varía de 24 a 48 pares de bases. Por lo general, muestran determinada simetría de díadas, lo que implica la formación de una estructura secundaria, tal como una horquilla, pero no son verdaderamente palindrómicas. Las repeticiones están separadas por separadores de longitud similar. Algunas secuencias espaciadoras de CRISPR coinciden exactamente con secuencias de plásmidos y fagos, aunque algunos espaciadores coinciden con el genoma procariota (espaciadores autodirigidos). Se pueden agregar rápidamente espaciadores nuevos en respuesta a la infección por fagos.

B. Nucleasas Cas

Los genes asociados a CRISPR (*cas*) a menudo se asocian con conjuntos de repeticiones-espaciadores de CRISPR. Hasta 2013, se habían descrito más de cuarenta familias de la proteína

Cas diferentes. De esas familias de proteínas, Cas1 parece ser ubicua entre distintos sistemas de CRISPR/Cas. Se han utilizado combinaciones particulares de genes *cas* y estructuras de repetición para definir 8 subtipos de CRISPR (Ecoli, Ypest, Nmeni, Dvulg, Tneap, Hmari, Apern y Mtube), algunos de los cuales se asocian con un módulo génico adicional que codifica proteínas misteriosas asociadas con la repetición (RAMP, por sus siglas en inglés). Más de un subtipo de CRISPR puede producirse en un único genoma. La distribución esporádica de los subtipos de CRISPR/Cas sugiere que el sistema está sujeto a transferencia génica horizontal durante la evolución microbiana.

Aparentemente, el ADN exógeno es procesado por proteínas codificadas por los genes Cas en elementos pequeños (~30 pares de bases de longitud), que luego se insertan de algún modo en el locus de CRISPR cerca de la secuencia líder. Los ARN de los locus de CRISPR se expresan de forma constitutiva y son procesados por proteínas Cas en ARN pequeños compuestos por elementos de secuencia individuales, derivados de forma exógena con una secuencia de repetición flanqueante. Los ARN guían otras proteínas Cas para silenciar los elementos genéticos exógenos a nivel de ARN o ADN. La evidencia sugiere diversidad funcional entre los subtipos de CRISPR. Las proteínas Cse (Cas subtipo *E. coli*) (denominadas CasA-E en *E. coli*) forman un complejo funcional, Cascade, que procesa las transcripciones del ARN de CRISPR en unidades de repetición-espaciador retenidas por Cascade. En otros procariotas, Cas6 procesa las transcripciones de CRISPR. Curiosamente, la inactivación de fagos basada en CRISPR en *E. coli* requiere Cascade y Cas3, pero no Cas1 y Cas2. Las proteínas Cmr (módulo Cas RAMP) encontradas en *Pyrococcus furiosus* y otros procariotas forman un complejo funcional con ARN de CRISPR pequeños que reconocen y escinden los ARN diana complementarios. Las enzimas de CRISPR guiadas por ARN se clasifican como enzimas de restricción tipo V.

Cas9 es una nucleasa, una enzima especializada para cortar el ADN, con dos sitios de corte activos, uno para cada cadena de la doble hélice. El equipo demostró que se podía deshabilitar uno o ambos sitios mientras que se conservaba la capacidad de Cas9 para localizar su ADN diana. Jinek et ál. (2012) combinaron ARNtracr y ARN espaciador en una molécula de «ARN de una sola guía» que, mezclada con Cas9, puede encontrar y cortar las dianas de ADN correctas y dichos ARN guía sintéticos se utilizan para la edición génica.

Las proteínas Cas9 están altamente enriquecidas con bacterias patógenas y comensales. La regulación génica mediada por CRISPR/Cas puede contribuir a la regulación de los genes bacterianos endógenos, particularmente, durante la interacción bacteriana con hospedadores eucariotas. Por ejemplo, la proteína Cas, Cas9, de *Francisella novicida* usa un único ARN asociado a CRISPR/Cas pequeño (ARNacp) para reprimir una transcripción endógena que codifica una lipoproteína bacteriana que es crucial para que *F. novicida* disminuya la respuesta del hospedador y

promueva la virulencia. Wang et ál. (2013) demostraron que la inyección conjunta de ARNm de Cas9 y ARNgs en la línea germinal (cigotos) generó ratones con mutaciones. También se contempla el suministro de secuencias de ADN de Cas9.

Los sistemas de CRISPR/Cas se separan en tres clases. La clase 1 usa varias proteínas Cas junto con los ARN de CRISPR (ARNcr) para construir una endonucleasa funcional. Los sistemas de CRISPR de clase 2 utilizan una única proteína Cas con un ARNcr. Cpf1 ha sido identificado recientemente como un sistema de CRISPR/Cas Tipo V Clase II que contiene una proteína de 1300 aminoácidos. Véase también la publicación de patente estadounidense n.° 2014/0068797, la que se incorpora en su totalidad mediante referencia.

En algunas modalidades, las composiciones de la descripción incluyen una versión pequeña de un Cas9 de la bacteria *Staphylococcus aureus* (n.º de acceso UniProt J7RUA5). La versión pequeña de Cas9 proporciona ventajas con respecto a Cas9 de tipo salvaje o de longitud completa. En algunas modalidades, el Cas9 esun spCas9 (AddGene).

C. Nucleasas Cpf1

Las repeticiones palindrómicas cortas agrupadas y regularmente espaciadas de *Prevotella* y *Francisella* 1 o CRISPR/Cpf1 son una tecnología de edición del ADN que comparten algunas similitudes con el sistema de CRISPR/Cas9. Cpf1 es una endonucleasa guiada por ARN de un sistema CRISPR/Cas de clase II. Este mecanismo inmunitario adquirido se encuentra en las bacterias *Prevotella* y *Francisella* Previene el daño genético de los virus. Los genes Cpf1 se asocian con el locus de CRISPR, que codifica una endonucleasa que usa un ARN guía para encontrar y escindir el ADN viral. Cpf1 es una endonucleasa más pequeña y simple que Cas9, que supera algunas de las limitaciones del sistema CRISPR/Cas9.

Cpf1 aparece en muchas especies bacterianas. La última endonucleasa Cpf1 que se desarrolló como una herramienta para la edición genómica se tomó de una de las primeras 16 especies conocidas que la albergan.

En algunas modalidades, la Cpf1 es una enzima de Cpf1 de *Acidaminococcus* (especie BV3L6, n.º de acceso UniProt U2UMQ6; SEQ ID NO: 870), que tiene la secuencia que se presenta a continuación:

1 MTQFEGFTNL YQVSKTLRFE LIPQGKTLKH IQEQGFIEED KARNDHYKEL KPIIDRIYKT
61 YADQCLQLVQ LDWENLSAAI DSYRKEKTEE TRNALIEEQA TYRNAIHDYF IGRTDNLTDA
121 INKRHAEIYK GLFKAELFNG KVLKQLGTVT TTEHENALLR SFDKFTTYFS GFYENRKNVF
181 SAEDISTAIP HRIVQDNFPK FKENCHIFTR LITAVPSLRE HFENVKKAIG IFVSTSIEEV
241 FSFPFYNQLL TQTQIDLYNQ LLGGISREAG TEKIKGLNEV LNLAIQKNDE TAHIIASLPH
301 RFIPLFKQIL SDRNTLSFIL EEFKSDEEVI QSFCKYKTLL RNENVLETAE ALFNELNSID

361 LTHIFISHKK LETISSALCD HWDTLRNALY ERRISELTGK ITKSAKEKVQ RSLKHEDINL
421 QEIISAAGKE LSEAFKQKTS EILSHAHAAL DQPLPTTLKK QEEKEILKSQ LDSLLGLYHL
481 LDWFAVDESN EVDPEFSARL TGIKLEMEPS LSFYNKARNY ATKKPYSVEK FKLNFQMPTL
541 ASGWDVNKEK NNGAILFVKN GLYYLGIMPK QKGRYKALSF EPTEKTSEGF DKMYYDYFPD
601 AAKMIPKCST QLKAVTAHFQ THTTPILLSN NFIEPLEITK EIYDLNNPEK EPKKFQTAYA
661 KKTGDQKGYR EALCKWIDFT RDFLSKYTKT TSIDLSSLRP SSQYKDLGEY YAELNPLLYH
721 ISFQRIAEKE IMDAVETGKL YLFQIYNKDF AKGHHGKPNL HTLYWTGLFS PENLAKTSIK
781 LNGQAELFYR PKSRMKRMAH RLGEKMLNKK LKDQKTPIPD TLYQELYDYV NHRLSHDLSD
841 EARALLPNVI TKEVSHEIIK DRRFTSDKFF FHVPITLNYQ AANSPSKFNQ RVNAYLKEHP
901 ETPIIGIDRG ERNLIYITVI DSTGKILEQR SLNTIQQFDY QKKLDNREKE RVAARQAWSV
961 VGTIKDLKQG YLSQVIHEIV DLMIHYQAVV VLENLNFGFK SKRTGIAEKA VYQQFEKMLI
1021 DKLNCLVLKD YPAEKVGGVL NPYQLTDQFT SFAKMGTQSG FLFYVPAPYT SKIDPLTGFV
1081 DPFVWKTIKN HESRKHFLEG FDFLHYDVKT GDFILHFKMN RNLSFQRGLP GFMPAWDIVF
1141 EKNETQFDAK GTPFIAGKRI VPVIENHRFT GRYRDLYPAN ELIALLEEKG IVFRDGSNIL
1201 PKLLENDDSH AIDTMVALIR SVLQMRNSNA ATGEDYINSP VRDLNGVCFD SRFQNPEWPM
1261 DADANGAYHI ALKGQLLLNH LKESKDLKLQ NGISNQDWLA YIQELRN

En algunas modalidades, Cpf1 es una enzima Cpf1 de *Lachnospiraceae* (especie ND2006, n.º de acceso UniProt A0A182DWE3; SEQ ID NO: 871), que tiene la secuencia que se presenta a continuación:

1 AASKLEKFTN CYSLSKTLRF KAIPVGKTQE NIDNKRLLVE DEKRAEDYKG VKKLLDRYYL
61 SFINDVLHSI KLKNLNNYIS LFRKKTRTEK ENKELENLEI NLRKEIAKAF KGAAGYKSLF
121 KKDIIETILP EAADDKDEIA LVNSFNGFTT AFTGFFDNRE NMFSEEAKST SIAFRCINEN
181 LTRYISNMDI FEKVDAIFDK HEVQEIKEKI LNSDYDVEDF FEGEFFNFVL TQEGIDVYNA
241 IIGGFVTESG EKIKGLNEYI NLYNAKTKQA LPKFKPLYKQ VLSDRESLSF YGEGYTSDEE
301 VLEVFRNTLN KNSEIFSSIK KLEKLFKNFD EYSSAGIFVK NGPAISTISK DIFGEWNLIR
361 DKWNAEYDDI HLKKKAVVTE KYEDDRRKSF KKIGSFSLEQ LQEYADADLS VVEKLKEIII
421 QKVDEIYKVY GSSEKLFDAD FVLEKSLKKN DAVVAIMKDL LDSVKSFENY IKAFFGEGKE
481 TNRDESFYGD FVLAYDILLK VDHIYDAIRN YVTQKPYSKD KFKLYFQNPQ FMGGWDKDKE
541 TDYRATILRY GSKYYLAIMD KKYAKCLQKI DKDDVNGNYE KINYKLLPGP NKMLPKVFFS
601 KKWMAYYNPS EDIQKIYKNG TFKKGDMFNL NDCHKLIDFF KDSISRYPKW SNAYDFNFSE
661 TEKYKDIAGF YREVEEQGYK VSFESASKKE VDKLVEEGKL YMFQIYNKDF SDKSHGTPNL
721 HTMYFKLLFD ENNHGQIRLS GGAELFMRRA SLKKEELVVH PANSPIANKN PDNPKKTTTL
781 SYDVYKDKRF SEDQYELHIP IAINKCPKNI FKINTEVRVL LKHDDNPYVI GIDRGERNLL

841 YIVVVDGKGN IVEQYSLNEI INNFNGIRIK TDYHSLLDKK EKERFEARQN WTSIENIKEL
901 KAGYISQVVH KICELVEKYD AVIALEDLNS GFKNSRVKVE KQVYQKFEKM LIDKLNYMVD
961 KKSNPCATGG ALKGYQITNK FESFKSMSTQ NGFIFYIPAW LTSKIDPSTG FVNLLKTKYT
1021 SIADSKKFIS SFDRIMYVPE EDLFEFALDY KNFSRTDADY IKKWKLYSYG NRIRIFAAAK
1081 KNNVFAWEEV CLTSAYKELF NKYGINYQQG DIRALLCEQS DKAFYSSFMA LMSLMLQMRN
1141 SITGRTDVDF LISPVKNSDG IFYDSRNYEA QENAILPKNA DANGAYNIAR KVLWAIGQFK
1201 KAEDEKLDKV KIAISNKEWL EYAQTSVK

En algunas modalidades, la Cpf1 está optimizada con codones para la expresión en células de mamíferos. En algunas modalidades, la Cpf1 está optimizada con codones para la expresión en células humanas o células de ratón.

El locus de Cpf1 contiene un dominio mixto alfa/beta, un RuvC-I seguido por una región helicoidal, un RuvC-II y un dominio similar a un dedo de zinc. La proteína Cpf1 tiene un dominio de endonucleasa similar a RuvC que es similar al dominio RuvC de Cas9. Además, la Cpf1 no tiene un dominio de endonucleasa HNH, y el extremo N de Cpf1 no tiene el lóbulo de reconocimiento alfa-helicoidal de Cas9.

La arquitectura del dominio CRISPR-Cas de Cpf1 muestra que Cpf1 es funcionalmente única, al estar clasificada como un sistema de CRISPR tipo V de clase 2. Los locus de Cpf1 codifican las proteínas Cas1, Cas2 y Cas4 más similares a los sistemas tipo I y III que tipo II. Las búsquedas en la base de datos sugieren la abundancia de proteínas de la familia Cpf1 en muchas especies bacterianas.

La Cpf1 funcional no requiere un ARNtracr, por lo tanto, solo se requiere el ARNcr. Esto beneficia la edición genómica dado que Cpf1 no solo es más pequeña que Cas9, sino que también tiene una molécula de ARNgs más pequeña (aproximadamente la mitad de los nucleótidos que Cas9).

El complejo de Cpf1-ARNcr escinde el ADN o el ARN diana mediante la identificación de un motivo adyacente al protoespaciador 5'-YTN-3' (donde «Y» es una pirimidina y «N» es cualquier nucleobase) o 5'-TTN-3', en contraste con el PAM rico en G al que se dirige Cas9. Después de la identificación de PAM, Cpf1 introduce una interrupción de cadena doble de ADN tipo extremo pegajoso de 4 o 5 nucleótidos excedentes.

El sistema de CRISPR/Cpf1 consiste en una enzima Cpf1 y un ARN guía que encuentra y coloca el complejo en el lugar correcto en la hélice doble para escindir el ADN diana. La actividad de los sistemas de CRISPR/Cpf1 tiene tres etapas:

Adaptación, durante la cual las proteínas Cas1 y Cas2 facilitan la adaptación de pequeños fragmentos de ADN en la matriz CRISPR;

Formación de ARNcr: procesamiento de pre-ARNcr que producen ARNcr maduros para guiar la

proteína Cas; e

Interferencia, en la que Cpf1 se une a un ARNcr para formar un complejo binario para identificar y escindir una secuencia de ADN diana.

D. ARNg

Como una proteína guiada por ARN, Cas9 requiere un ARN corto para dirigir el reconocimiento de las dianas de ADN. Aunque Cas9 interroga preferentemente a las secuencias de ADN que contienen una secuencia PAM NGG, puede unirse aquí sin una diana protoespaciadora. Sin embargo, el complejo Cas9-ARNg requiere una coincidencia cercana al ARNg para crear una interrupción de cadena doble. Las secuencias de CRISPR en bacterias se expresan en múltiples ARN y luego se procesan para crear cadenas guía para el ARN. Debido a que los sistemas eucariotas carecen de algunas de las proteínas requeridas para procesar los ARN de CRISPR, se creó el ARNg de construcción sintética para combinar las piezas esenciales de ARN para el direccionamiento a Cas9 en un ARN simple expresado con el promotor tipo III de ARN polimerasa U6. Los ARNg sintéticos tienen un poco más de 100 pb en la longitud mínima y contienen una parte que se dirige a los 20 nucleótidos protoespaciadores que preceden inmediatamente a la secuencia PAM NGG; los ARNg no contienen una secuencia PAM.

En algunas modalidades, el ARNg se dirige a un sitio dentro de un gen de distrofina de tipo salvaje. En algunas modalidades, el ARNg se dirige a un sitio dentro de un gen de distrofina mutante. En algunas modalidades, el ARNg se dirige a un intrón de distrofina. En algunas modalidades, el ARNg se dirige a un exón de distrofina. En algunas modalidades, el ARNg se dirige a un sitio en un exón de distrofina que se expresa y está presente en una o más de las isoformas de distrofina que se muestran en la Tabla 1. En algunas modalidades, el ARNg se dirige a un sitio de corte y empalme de distrofina. En algunas modalidades, el ARNg se dirige a un sitio donante de corte y empalme en el gen de distrofina. En algunas modalidades, el ARNg se dirige a un sitio aceptor de corte y empalme en el gen de distrofina.

En algunas modalidades, el ARN guía se dirige a un exón de DMD mutante. En algunas modalidades, el exón mutante es el exón 23 o 51. En algunas modalidades, el ARN guía se dirige al menos a uno de los exones 1, 23, 41, 44, 46, 47, 48, 49, 50, 51, 52, 53, 54 o 55 del gen de distrofina. En algunas modalidades, el ARN guía se dirige al menos a uno de los intrones 44, 45, 50, 51, 52, 53, 54 o 55 del gen de distrofina. En modalidades preferidas, los ARN guía están diseñados para inducir la omisión del exón 51 o el exón 23. En algunas modalidades, el ARNg se dirige a un sitio aceptor de corte y empalme del exón 51 o el exón 23.

Los ARNg adecuados para uso en diversas composiciones y métodos que se describen en la

presente se proporcionan como las SEQ ID NO. 383-705, 709-711, 715-717, 790-862, 864. (Tablas 7, 9, 11, 13 y 15). En modalidades preferidas, el ARNg se selecciona de cualquiera de la SEQ ID NO: 790 a la SEQ ID NO: 862.

En algunas modalidades, los ARNg de la descripción comprenden una secuencia que es complementaria a una secuencia diana dentro de una secuencia codificante o una secuencia no codificante correspondiente al gen *DMD* y, por lo tanto, se hibrida con la secuencia diana. En algunas modalidades, los ARNg para Cpf1 comprenden un único ARNcr que contiene una secuencia de andamiaje de repetición directa seguida por 24 nucleótidos de la secuencia guía. En algunas modalidades, una secuencia «guía» del ARNcr comprende una secuencia del ARNg que es complementaria a una secuencia diana. En algunas modalidades, el ARNcr de la descripción comprende una secuencia del ARNg que no es complementaria a una secuencia diana. Las secuencias de «andamiaje» de la descripción enlazan el ARNg al polipéptido Cpf1. Las secuencias de «andamiaje» de la descripción no son equivalentes a una secuencia de ARNtracr de una construcción de ARNg-Cas9.

En algunas modalidades, un ácido nucleico puede comprender una o más secuencias que codifican un ARNg. En algunas modalidades, un ácido nucleico puede comprender 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 secuencias que codifican un ARNg. En algunas modalidades, todas las secuencias codifican el mismo ARNg. En algunas modalidades, todas las secuencias codifican ARNg diferentes. En algunas modalidades, al menos 2 de las secuencias codifican el mismo ARNg, por ejemplo, al menos 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, o 20 de las secuencias codifican el mismo ARNg.

E. Cas9 *versus* Cpf1

Cas9 requiere dos moléculas de ARN para cortar el ADN, mientras que Cpf1 necesita una. Las proteínas también cortan el ADN en diferentes lugares, ofreciendo a los investigadores más opciones al seleccionar un sitio de edición. Cas9 corta ambas cadenas en una molécula de ADN en la misma posición, dejando atrás los extremos «romos». Cpf1 deja una cadena más larga que la otra, creando extremos «pegajosos» con los que es más fácil trabajar. Cpf1 parece ser más capaz de insertar secuencias nuevas en el sitio de corte, en comparación con Cas9. Aunque el sistema CRISPR/Cas9 puede inhabilitar los genes de manera eficaz, es difícil insertar genes o generar una expresión. Cpf1 carece de ARNtracr, utiliza un PAM rico en T y escinde el ADN a través de un DSB de ADN escalonado.

En resumen, las diferencias importantes entre los sistemas de Cpf1 y Cas9 son que Cpf1 reconoce diferentes PAM, permitiendo nuevas posibilidades de direccionamiento, crea extremos pegajosos de

4-5 nt de largo, en lugar de los extremos romos producidos por Cas9, lo que mejora la eficacia de las inserciones genéticas y la especificidad durante NHEJ o HDR, y corta el ADN diana lejos del PAM, lejos del sitio de corte de Cas9, lo que permite nuevas posibilidades para escindir el ADN.

Tabla 3: Diferencias entre Cas9 y Cpf1

Características	**Cas9**	**Cpf1**
Estructura	Se requieren dos ARN (o 1 transcripción de fusión (ARNcr+ ARNtracr=ARNg))	Se requiere un ARN
Mecanismo de corte	Cortes de extremo romo	Cortes de extremo escalonados
Sitio de corte	Proximal al sitio de reconocimiento	Distal del sitio de reconocimiento
Sitios diana	PAM rico en G	PAM rico en T

F. Edición génica mediada por CRISPR

La primera etapa para editar el gen DMD mediante el uso de CRISPR/Cpf1 o CRISPR/Cas9 es identificar la secuencia diana genómica. La diana genómica para los ARNg de la descripción puede ser cualquier secuencia de ADN de ~24 nucleótidos, siempre que la secuencia sea única en comparación con el resto del genoma. En algunas modalidades, la secuencia diana genómica corresponde a una secuencia dentro del exón 51, el exón 45, el exón 44, el exón 53, el exón 46, el exón 52, el exón 50, el exón 43, el exón 6, el exón 7, el exón 8 y/o el exón 55 del gen de la distrofina humana. En algunas modalidades, la secuencia diana genómica es un sitio de corte y empalme 5' o 3' del exón 51, el exón 45, el exón 44, el exón 53, el exón 46, el exón 52, el exón 50, el exón 43, el exón 6, el exón 7, el exón 8 y/o el exón 55 del gen de la distrofina humana. En algunas modalidades, la secuencia diana genómica corresponde a una secuencia dentro de un intrón inmediatamente corriente arriba o corriente abajo del exón 51, el exón 45, el exón 44, el exón 53, el exón 46, el exón 52, el exón 50, el exón 43, el exón 6, el exón 7, exón 8 y/o el exón 55 del gen de la distrofina humana. Las secuencias diana genómicas ilustrativas se pueden encontrar en las Tablas 6, 8, 10, 12 y 14.

La siguiente etapa para editar el gen DMD es identificar todas las secuencias de motivo adyacente a protoespaciador (PAM) dentro de la región genética a la que se va a dirigir. La secuencia diana debe estar inmediatamente corriente arriba de un PAM. Una vez que se hayan identificado todas las secuencias de PAM posibles y los sitios diana posibles, la siguiente etapa es elegir qué sitio es probable que resulte en la escisión más eficiente dentro de la diana. La secuencia de

direccionamiento de ARNg debe coincidir con la secuencia diana, y la secuencia de direccionamiento de ARNg no debe coincidir con sitios adicionales dentro del genoma. En modalidades preferidas, la secuencia de direccionamiento de ARNg tiene una homología perfecta con la diana sin homología en ninguna otra parte del genoma. En algunas modalidades, una secuencia de direccionamiento de ARNg dada tendrá sitios adicionales en todo el genoma donde existe una homología parcial. Estos sitios se denominan «fuera de la diana» y deben considerarse al diseñar un ARNg. En general, los sitios fuera de la diana no se escinden tan eficientemente cuando se producen errores de emparejamiento cerca de la secuencia de PAM, por lo que los ARNg sin homología o aquellos con errores de emparejamiento cerca de la secuencia de PAM tendrán la mayor especificidad. Además de la «actividad fuera de la diana», se deben considerar los factores que maximizan la escisión de la secuencia diana deseada («actividad dentro de la diana»). Los expertos en la técnica saben que dos secuencias de direccionamiento de ARNg, cada una de ellas con 100 % de homología con el ADN diana, pueden no resultar en una eficiencia de escisión equivalente. De hecho, la eficiencia de la escisión puede aumentar o disminuir dependiendo de los nucleótidos específicos dentro de la secuencia diana seleccionada. Es necesario realizar un examen detallado de la actividad prevista dentro de la diana y fuera de la diana de cada secuencia de direccionamiento de ARNg posible para diseñar el mejor ARNg. Se han desarrollado varios programas de diseño de ARNg que son capaces de localizar PAM y secuencias diana posibles y clasificar los ARNg asociados en función de su actividad prevista dentro y fuera de la diana (por ejemplo, CRISPRdirecto, disponible en www.crispr.dbcls.jp).

La siguiente etapa es sintetizar y clonar los ARNg deseados. Los oligos de direccionamiento pueden sintetizarse, hibridarse e insertarse en plásmidos que contienen el andamiaje de ARNg mediante el uso de clonación de ligación-restricción estándar. Sin embargo, la estrategia de clonación exacta dependerá del vector de ARNg que se elija. Los ARNg para Cpf1 son notablemente más simples que los ARNg para Cas9, y solo consisten en un ARNcr simple que contiene una secuencia de andamioajes de repetición directa seguida por ~24 nucleótidos de la secuencia guía.

Cada ARNg debe validarse en una o más líneas celulares diana. Por ejemplo, después de que Cas9 o Cpf1 y el ARNg se suministran a la célula, la región diana genómica puede amplificarse mediante el uso de PCR y secuenciarse de acuerdo con los métodos conocidos por los expertos en la técnica.

En algunas modalidades, la edición génica puede realizarse in vitro o ex vivo. En algunas modalidades, las células se ponen en contacto in vitro o ex vivo con Cas9 o Cpf1 y un ARNg que se dirige a un sitio de corte y empalme de distrofina. En algunas modalidades, las células se ponen en contacto con uno o más ácidos nucleicos que codifican Cas9 o Cpf1 y el ARN guía. En algunas modalidades, los uno o más ácidos nucleicos se introducen en las células, por ejemplo, mediante el

uso de lipofección o electroporación. La edición génica también se puede realizar en cigotos. En algunas modalidades, los cigotos se pueden inyectar con uno o más ácidos nucleicos que codifican Cas9 o Cpf1 y un ARNg que se dirige a un sitio de corte y empalme de distrofina. Los cigotos se pueden inyectar posteriormente en un hospedador.

En algunas modalidades, Cas9 o Cpf1 se proporciona en un vector. En algunas modalidades, el vector contiene Cas9 derivado de S. *pyogenes* (SpCas9, SEQ ID NO. 872). En algunas modalidades, el vector contiene Cas9 derivado de S. *aureus* (SaCas9, SEQ ID NO. 873). En algunas modalidades, el vector contiene una secuencia de Cpf1 derivada de una bacteria *Lachnospiraceae*. Véase, por ejemplo, n.º de acceso Uniprot A0A182DWE3; SEQ ID NO. 871. En algunas modalidades, el vector contiene una secuencia de Cpf1 derivada de una bacteria *Acidaminococcus*. Véase, por ejemplo, n.º de Acceso Uniprot U2UMQ6; SEQ ID NO. 870. En algunas modalidades, la secuencia de Cas9 o Cpf1 está optimizada con codones para la expresión en células humanas o células de ratón. En algunas modalidades, el vector contiene, además, una secuencia que codifica una proteína fluorescente, tal como GFP, que permite que las células que expresan Cas 9 o Cpf1 se clasifiquen mediante el uso de la clasificación de células activadas por fluorescencia (FACS). En algunas modalidades, el vector es un vector viral tal como un vector viral adenoasociado.

En algunas modalidades, el ARNg se proporciona en un vector. En algunas modalidades, el vector es un vector viral tal como un vector viral adenoasociado. En algunas modalidades, Cas9 o Cpf1 y el ARN guía se proporcionan en el mismo vector. En algunas modalidades, Cas9 o Cpf1 y el ARN guía se proporcionan en vectores diferentes.

En algunas modalidades, las células se ponen en contacto adicionalmente con un oligonucleótido de DMD de cadena simple para efectuar la reparación dirigida por homología. En algunas modalidades, INDEL pequeños restauran el marco de lectura de proteínas de la distrofina (estrategia de «reestructuración de marco»). Cuando se usa la estrategia de reestructuración de marco, las células pueden ponerse en contacto con un ARNg simple. En algunas modalidades, se interrumpe un sitio donante de corte y empalme o aceptor de corte y empalme, lo que da como resultado la omisión de exones y la restauración del marco de lectura de proteínas (estrategia de «omisión de exones»). Cuando se usa la estrategia de omisión de exones, las células pueden ponerse en contacto con dos o más ARNg.

La eficacia de la escisión de ADN mediada por Cas9 o Cpf1 in vitro o ex vivo puede evaluarse mediante el uso de técnicas conocidas por los expertos en la técnica, tal como el ensayo T7 E1. La restauración de la expresión de DMD se puede confirmar mediante el uso de técnicas conocidas por los expertos en la técnica, tales como RT-PCR, transferencia Western e inmunocitoquímica.

En algunas modalidades, la edición génica in vitro o ex vivo se realiza en una célula muscular o

satélite. En algunas modalidades, la edición génica se realiza en células iPSC o iCM. En algunas modalidades, las células iPSC se diferencian después de la edición génica. Por ejemplo, las células iPSC pueden diferenciarse en una célula muscular o una célula satélite después de la edición. En algunas modalidades, las células iPSC se diferencian en células musculares cardíacas, células musculares esqueléticas o células musculares lisas. En algunas modalidades, las células iPSC se diferencian en cardiomiocitos. Las células iPSC pueden inducirse para diferenciarse de acuerdo con métodos conocidos por los expertos en la técnica.

En algunas modalidades, el contacto de la célula con Cas9 o Cpf1 y el ARNg restaura la expresión de distrofina. En algunas modalidades, las células que se han editado in vitro o ex vivo, o las células derivadas de ellas, muestran niveles de la proteína distrofina que son comparables a los de las células de tipo salvaje. En algunas modalidades, las células editadas, o células derivadas de ellas, expresan distrofina en un nivel 50 %, 60 %, 70 %, 80 %, 90 %, 95 % o cualquier porcentaje intermedio de los niveles de expresión de distrofina de tipo salvaje. En algunas modalidades, las células que se han editado in vitro o ex vivo, o las células derivadas de ellas, tienen una cantidad de mitocondrias que es comparable con el de las células de tipo salvaje. En algunas modalidades, las células editadas, o células derivadas de ellas, tienen 50 %, 60 %, 70 %, 80 %, 90 %, 95 % o cualquier porcentaje intermedio de las mitocondrias en las células de tipo salvaje. En algunas modalidades, las células editadas, o células derivadas de ellas, muestran un aumento en la tasa de consumo de oxígeno (OCR) en comparación con las células no editadas de referencia.

G. ARN Pol III y promotores de Pol III

En las eucariotas, la ARN polimerasa III (también denominada Pol III) transcribe el ADN para sintetizar ARNr 5S ribosómico, ARNt y otros ARN pequeños. Los genes transcritos por ARN Pol III se encuentran en la categoría de genes «de mantenimiento» cuya expresión es necesaria en todos los tipos de células y en la mayoría de las condiciones ambientales. Por lo tanto, la regulación de la transcripción de Pol III está ligada principalmente a la regulación del crecimiento celular y el ciclo celular, por lo que requieren menos proteínas reguladoras que la ARN polimerasa II. Sin embargo, en condiciones de estrés, la proteína Maf1 reprime la actividad de Pol III.

En el proceso de transcripción (por parte de cualquier polimerasa) hay tres etapas principales: (i) inicio, que requiere la construcción del complejo de ARN polimerasa en el promotor del gen; (ii) alargamiento, la síntesis de la transcripción de ARN; y (iii) terminación, finalización de la transcripción de ARN y desmontaje del complejo de ARN polimerasa.

Los promotores bajo el control de la ARN Pol III incluyen aquellos para el ARNr 5S ribosómico, ARNt y otros pocos ARN pequeños tales como ARN de espliceosoma U6, ARN de RNasa P y RNasa MRP,

ARN de 7SL (el componente ARN de las partículas de reconocimiento de señal), ARN de bóveda, ARN Y, SINE (elementos repetitivos interespaciados cortos), ARN 7SK, dos microARN, varios ARN nucleolares pequeños y unos pocos ARN antisentido reguladores.

IV. Suministro de ácido nucleico

Como se describió anteriormente, en determinadas modalidades, se emplean casetes de expresión para expresar un producto de factor de transcripción, ya sea para la purificación posterior y el suministro a una célula/sujeto, o para su uso directamente en un enfoque de suministro basado en la genética. En la presente se proporcionan vectores de expresión que contienen uno o más ácidos nucleicos que codifican Cas9 o Cpf1 y al menos un ARN guía de DMD que se dirige a un sitio de corte y empalme de distrofina. En algunas modalidades, un ácido nucleico que codifica Cas9 o Cpf1 y un ácido nucleico que codifica al menos un ARN guía se proporcionan en el mismo vector. En algunas modalidades adicionales, un ácido nucleico que codifica Cas9 o Cpf1 y un ácido nucleico que codifica al menos un ARN guía se proporcionan en vectores separados.

La expresión requiere que se proporcionen señales apropiadas en los vectores, e incluyen varios elementos reguladores tales como potenciadores/promotores de fuentes virales y de mamíferos que dirigen la expresión de los genes de interés en las células. También se definen los elementos diseñados para optimizar la estabilidad y la traducibilidad del ARN mensajero en las células hospedadoras. También se proporcionan las condiciones para el uso de varios marcadores de selección de fármacos dominantes para establecer clones de células estables permanentes que expresan los productos, ya que es un elemento que vincula la expresión de los marcadores de selección de fármacos con la expresión del polipéptido.

A. Elementos reguladores

A lo largo de esta solicitud, se pretende que el término «casete de expresión» incluya cualquier tipo de construcción genética que contenga un ácido nucleico que codifique un producto génico en el que una parte o la totalidad de la secuencia que codifica el ácido nucleico pueda transcribirse y traducirse, es decir, esté bajo el control de un promotor. Un «promotor» se refiere a una secuencia de ADN reconocida por la maquinaria sintética de la célula, o la maquinaria sintética introducida, necesaria para iniciar la transcripción específica de un gen. La expresión «bajo control transcripcional» significa que el promotor se encuentra en la ubicación y la orientación correctas con relación al ácido nucleico para controlar el inicio de la ARN polimerasa y la expresión del gen. Se pretende que un «vector de expresión» incluya casetes de expresión comprendidos en una construcción genética que sea capaz de replicarse y, por lo tanto, incluya uno o más orígenes de replicación, señales de terminación de la

transcripción, regiones poli-A, marcadores seleccionables y sitios de clonación multipropósito.

El término promotor se usará en la presente para hacer referencia a un grupo de módulos de control de la transcripción que se agrupan alrededor del sitio de inicio para la ARN polimerasa II. Gran parte del pensamiento acerca de cómo se organizan los promotores deriva de los análisis de varios promotores virales, incluidos los de la timidina quinasa de VHS (*tk*) y unidades de transcripción temprana SV40. Estos estudios, complementados por trabajos más recientes, han demostrado que los promotores están compuestos por módulos funcionales discretos, cada uno de los cuales consiste en aproximadamente 7-20 pb de ADN y contienen uno o más sitios de reconocimiento para las proteínas activadoras o represoras de la transcripción.

Al menos un módulo en cada promotor funciona para colocar el sitio de inicio para la síntesis de ARN. El mejor ejemplo conocido de esto es la caja TATA, pero en algunos promotores que carecen de una caja TATA, como el promotor del gen de la desoxinucleotidil transferasa terminal de mamíferos y el promotor de los genes tardíos de SV40, un elemento discreto superpuesto al sitio de inicio ayuda a fijar el lugar de inicio.

En algunas modalidades, las construcciones Cas9 o Cpf1 de la descripción se expresan mediante un promotor específico de células musculares. Este promotor específico de células musculares puede ser constitutivamente activo o puede ser un promotor inducible.

Los elementos promotores adicionales regulan la frecuencia de inicio de la transcripción Comúnmente, estos se encuentran ubicados en la región 30-110 pb corriente arriba del sitio de inicio, si bien recientemente se ha demostrado que una cantidad de promotores también contienen elementos funcionales corriente abajo del sitio de inicio. El espacio entre los elementos promotores con frecuencia es flexible, de manera que se conserve la función del promotor cuando los elementos se invierten o mueven unos con respecto a los otros. En el promotor tk, el espacio entre los elementos promotores puede aumentar a 50 bp de separación antes de que comience a decaer la actividad. Dependiendo del promotor, parece que los elementos individuales pueden funcionar ya sea de forma cooperativa o independiente para activar la transcripción.

En determinadas modalidades, pueden usarse promotores virales tales como el promotor génico temprano inmediato del citomegalovirus (CMV) humano, el promotor temprano de SV40, la repetición terminal larga del virus del sarcoma de Rous, el promotor de insulina de rata y la gliceraldehído-3-fosfato deshidrogenasa para obtener un alto nivel expresión de la secuencia codificante de interés. También se contempla el uso de otros promotores de fagos bacterianos o de células de mamíferos o virus que son conocidos en la técnica para lograr la expresión de una secuencia codificante de interés, siempre que los niveles de expresión sean suficientes para un propósito determinado. Al emplear un promotor con propiedades conocidas, se puede optimizar el nivel y el patrón de expresión

de la proteína de interés después de la transfección o transformación. Además, la selección de un promotor que está regulado en respuesta a señales fisiológicas específicas puede permitir la expresión inducible del producto génico.

Los potenciadores son elementos genéticos que aumentan la transcripción de un promotor ubicado en una posición distante en la misma molécula de ADN. Los potenciadores se organizan de manera muy parecida a los promotores. Es decir, están compuestos por muchos elementos individuales, cada uno de los cuales se une a una o más proteínas transcripcionales. La distinción básica entre potenciadores y promotores es operativa. Una región potenciadora como un todo debe ser capaz de estimular la transcripción a una distancia; esto no tiene por qué ser cierto para una región promotora o sus elementos componentes. Por otro lado, un promotor debe tener uno o más elementos que dirijan el inicio de la síntesis de ARN en un sitio particular y en una orientación particular, mientras que los potenciadores carecen de estas especificidades. Los promotores y potenciadores a menudo se superponen y son contiguos, a menudo parecen tener una organización modular muy similar.

A continuación, se muestra una lista de promotores/potenciadores y promotores/potenciadores inducibles que podrían usarse en combinación con el ácido nucleico que codifica un gen de interés en una construcción de expresión. Además, también podría usarse cualquier combinación de promotor/potenciador (según la base de datos de promotores eucariotas EPDB) para dirigir la expresión del gen. Las células eucariotas pueden soportar la transcripción citoplásmica de ciertos promotores bacterianos si se proporciona la polimerasa bacteriana apropiada, ya sea como parte del complejo de suministro o como una construcción de expresión genética adicional.

El promotor y/o potenciador pueden ser, por ejemplo, una cadena ligera de inmunoglobulina, cadena pesada de inmunoglobulina, receptor de linfocitos-T, HLA DQ a y/o DQ β, β-interferón, interleucina-2, receptor de interleucina-2, MHC clase II 5, MHC clase II HLA-Dra, β-Actina, creatina quinasa muscular (MCK), prealbúmina (transtiretina), elastasa I, metalotioneína (MTII), colagenasa, albúmina, α-fetoproteína, t-globina, β-globina, c-fos, c-HA-*ras*, insulina, molécula de adhesión de células neurales (NCAM), α_1-antitripsina, histona H2B (TH2B), colágeno de ratón y/o tipo I, proteínas reguladas por glucosa (GRP94 y GRP78), hormona de crecimiento de rata, amiloide de suero humano A (SAA), troponina I (TN I), factor de crecimiento derivado de plaquetas (PDGF), distrofia muscular de Duchenne, SV40, polioma, retrovirus, virus del papiloma, virus de la hepatitis B, virus de la inmunodeficiencia humana, citomegalovirus (CMV) y virus de la leucemia del mono gibón.

En algunas modalidades, pueden usarse elementos inducibles. En algunas modalidades, el elemento inducible es, por ejemplo, MTII, MMTV (virus de tumor mamario de ratón), β-interferón, adenovirus 5 E2, colagenasa, estromelisina, SV40, gen murino MX, gen GRP78, α-2-macroglobulina, vimentina, gen de MHC clase I H-2κb, HSP70, proliferina, factor de necrosis tumoral y/o gen α de la hormona

estimulante de la tiroides. En algunas modalidades, el inductor es éster de forbol (TFA), metales pesados, glucocorticoides, poli(rI)x, poli(rc), ElA, éster de forbol (TPA), interferón, virus de la enfermedad de Newcastle, A23187, IL-6, suero, interferón, antígeno T grande de SV40, PMA y/o hormona tiroidea. Cualquiera de los elementos inducibles descritos en la presente puede usarse con cualquiera de los inductores descritos en la presente.

Los promotores específicos de los músculos son de particular interés. Estos incluyen el promotor de la cadena ligera de la miosina-2, el promotor de la α-actina, el promotor de la troponina 1; el promotor intercambiador de Na^{+}/Ca^{2+}, el promotor de la distrofina, el promotor de la integrina α7, el promotor del péptido natriurético cerebral y el promotor de la proteína de choque térmico pequeña/cristalina αB, el promotor de la cadena pesada de la α-miosina y el promotor de ANF. En algunas modalidades, el promotor específico de los músculos es el promotor CK8. El promotor CK8 tiene la siguiente secuencia (SEQ ID NO. 874):

1 CTAGACTAGC ATGCTGCCCA TGTAAGGAGG CAAGGCCTGG GGACACCCGA GATGCCTGGT

61 TATAATTAAC CCAGACATGT GGCTGCCCCC CCCCCCCCAA CACCTGCTGC CTCTAAAAAT

121 AACCCTGCAT GCCATGTTCC CGGCGAAGGG CCAGCTGTCC CCCGCCAGCT AGACTCAGCA

181 CTTAGTTTAG GAACCAGTGA GCAAGTCAGC CCTTGGGGCA GCCCATACAA GGCCATGGGG

241 CTGGGCAAGC TGCACGCCTG GGTCCGGGGT GGGCACGGTG CCCGGGCAAC GAGCTGAAAG

301 CTCATCTGCT CTCAGGGGCC CCTCCCTGGG GACAGCCCCT CCTGGCTAGT CACACCCTGT

361 AGGCTCCTCT ATATAACCCA GGGGCACAGG GGCTGCCCTC ATTCTACCAC CACCTCCACA

421 GCACAGACAG ACACTCAGGA GCCAGCCAGC

En algunas modalidades, el promotor específico de los músculos es una variante del promotor de CK8, denominado CK8e. El promotor CK8e tiene la siguiente secuencia (SEQ ID NO. 875):

1 TGCCCATGTA AGGAGGCAAG GCCTGGGGAC ACCCGAGATG CCTGGTTATA ATTAACCCAG

61 ACATGTGGCT GCCCCCCCCC CCCCAACACC TGCTGCCTCT AAAAATAACC CTGCATGCCA

121 TGTTCCCGGC GAAGGGCCAG CTGTCCCCCG CCAGCTAGAC TCAGCACTTA GTTTAGGAAC

181 CAGTGAGCAA GTCAGCCCTT GGGGCAGCCC ATACAAGGCC ATGGGGCTGG

GCAAGCTGCA

241 CGCCTGGGTC CGGGGTGGGC ACGGTGCCCG GGCAACGAGC TGAAAGCTCA TCTGCTCTCA

301 GGGGCCCCTC CCTGGGGACA GCCCCTCCTG GCTAGTCACA CCCTGTAGGC TCCTCTATAT

361 AACCCAGGGG CACAGGGGCT GCCCTCATTC TACCACCACC TCCACAGCAC AGACAGACAC

421 TCAGGAGCCA GCCAGC

Cuando se emplea un inserto de ADNc, se deseará típicamente incluir una señal de poliadenilación para efectuar la poliadenilación apropiada de la transcripción del gen. Se puede emplear cualquier secuencia de poliadenilación, tal como la hormona de crecimiento humana y las señales de poliadenilación de SV40. Un terminador también se contempla como un elemento del casete de expresión. Estos elementos pueden servir para mejorar los niveles de los mensajes y para minimizar la lectura del casete en otras secuencias.

B. Péptido 2A

En algunas modalidades, se usa un dominio de autoescisión similar a 2A del virus de insecto *Thosea asigna* (Péptido TaV 2A) (SEQ ID NO. 876, EGRGSLLTCGDVEENPGP). Se ha demostrado que estos dominios similares a 2A funcionan a través de eucariotas y hacen que la escisión de los aminoácidos se produzca de forma cotraduccional dentro del dominio peptídico similar a 2A. Por lo tanto, la inclusión del péptido TaV 2A permite la expresión de múltiples proteínas a partir de una única transcripción de ARNm. Es importante destacar que el dominio de TaV cuando se analizó en sistemas eucariotas ha mostrado más de 99 % de actividad de escisión. Otros péptidos similares a 2A aceptables incluyen, de modo no taxativo, péptido del virus 2A de rinitis equina A (ERAV) (SEQ ID NO. 877; QCTNYALLKLAGDVESNPGP), péptido 2A de teschovirus porcino-1 (PTV1)(SEQ ID NO. 878; ATNFSLLKQAGDVEENPGP) y péptido 2A del virus de la fiebre aftosa (FMDV) (SEQ ID NO. 879; PVKQLLNFDLLKLAGDVESNPGP) o versiones modificadas de estos.

En algunas modalidades, el péptido 2A se usa para expresar un indicador y Cas9 o Cpf1 simultáneamente. El indicador puede ser, por ejemplo, GFP.

Otros péptidos de autoescisión que pueden usarse incluyen, de modo no taxativo, una proteasa de proteínas de inclusión nuclear a (Nia), una proteasa P1, una proteasa 3C, una proteasa L, una proteasa similar a 3C o versiones modificadas de estas.

C. Suministro de vectores de expresión

Hay varias formas en que los vectores de expresión pueden introducirse en las células. En determinadas modalidades, la construcción de expresión comprende un virus o construcción modificada genéticamente derivada de un genoma viral. La capacidad de determinados virus para ingresar a las células a través de endocitosis mediada por receptor para integrarse en el genoma de la célula hospedadora y expresar genes virales de manera estable y eficiente los ha convertido en candidatos atractivos para la transferencia de genes extraños a las células de mamíferos. Estos tienen una capacidad relativamente baja para secuencias de ADN extrañas y tienen un espectro de hospedadores restringido. Además, su potencial oncogénico y los efectos citopáticos en las células permisivas plantean problemas de seguridad. Solo pueden alojar hasta 8 kB de material genético extraño, pero pueden introducirse fácilmente en una variedad de líneas celulares y animales de laboratorio.

Uno de los métodos preferidos para el suministro *in vivo* implica el uso de un vector de expresión de adenovirus. Se pretende que el «vector de expresión de adenovirus» incluya las construcciones que contienen secuencias de adenovirus suficientes para (a) soportar el empaquetamiento de la construcción y (b) expresar un polinucleótido antisentido clonado en este. En este contexto, la expresión no requiere que el producto genético se sintetice.

El vector de expresión comprende una forma modificada genéticamente de adenovirus. El conocimiento de la organización genética del adenovirus, un virus de ADN de cadena doble lineal de 36 kB, permite la sustitución de grandes fragmentos de ADN adenoviral con secuencias extrañas de hasta 7 kB. A diferencia del retrovirus, la infección adenoviral de las células hospedadoras no produce integración cromosómica porque el ADN adenoviral puede replicarse de manera episomal sin genotoxicidad potencial. Además, los adenovirus son estructuralmente estables, y no se ha detectado un reordenamiento del genoma después de una amplificación extensa. El adenovirus puede infectar virtualmente a todas las células epiteliales independientemente de su etapa de ciclo celular. Hasta ahora, la infección por adenovirus parece estar relacionada solo con una enfermedad leve como la enfermedad respiratoria aguda en humanos.

El adenovirus es particularmente adecuado para su uso como vector de transferencia de genes debido a su genoma de tamaño mediano, facilidad de manipulación, alta titulación, amplio rango de células diana y alta infectividad. Ambos extremos del genoma viral contienen 100-200 pares de repeticiones invertidas (ITR), que son elementos *cis* necesarios para la replicación y empaquetamiento del ADN viral. Las regiones temprana (E) y tardía (L) del genoma contienen unidades de transcripción diferentes que se dividen al inicio de la replicación del ADN viral. La región E1 (E1A y E1B) codifica proteínas responsables de la regulación de la transcripción del genoma viral

y algunos genes celulares. La expresión de la región E2 (E2A y E2B) da como resultado la síntesis de las proteínas para la replicación del ADN viral. Estas proteínas están involucradas en la replicación del ADN, la expresión génica tardía y la interrupción de la célula hospedadora. Los productos de los genes tardíos, que incluyen la mayoría de las proteínas de la cápside viral, se expresan solo después del procesamiento significativo de una única transcripción primaria emitida por el promotor tardío principal (MLP). El MLP (ubicado a 16,8 m.u.) es particularmente eficiente durante la fase tardía de la infección, y todos los ARNm emitidos por este promotor poseen una secuencia líder tripartita (TPL) de 5' que los convierte en los ARNm preferidos para la traducción. En un sistema, el adenovirus recombinante se genera a partir de la recombinación homóloga entre el vector transportador y el vector proviral. Debido a la posible recombinación entre dos vectores provirales, se puede generar adenovirus de tipo salvaje a partir de este proceso. Por lo tanto, es muy importante aislar un clon simple de virus de una placa individual y examinar su estructura genómica.

La generación y propagación de los vectores de adenovirus actuales, con deficiencia en la replicación, dependen de una única línea celular auxiliar, denominada 293, que se transformó a partir de células de riñón embrionario humano mediante fragmentos de ADN Ad5 y expresa de forma constitutiva las proteínas E1. Dado que el genoma de adenovirus puede prescindir de la región E3, los vectores de adenovirus actuales, con la ayuda de células 293, transportan ADN extraño en E1, D3 o ambas regiones. En la naturaleza, el adenovirus puede empaquetar aproximadamente 105 % del genoma de tipo salvaje, lo que proporciona capacidad para alrededor de 2 kb adicionales de ADN. En combinación con aproximadamente 5,5 kb de ADN que se pueden reemplazar en las regiones E1 y E3, la capacidad máxima del vector de adenovirus actual es inferior a 7,5 kb, o aproximadamente 15 % de la longitud total del vector. Más de 80 % del genoma viral del adenovirus permanece en la estructura principal del vector y es la fuente de citotoxicidad transmitida por el vector. Además, la deficiencia de replicación del virus con eliminación de E1 es incompleta.

Las líneas celulares auxiliares pueden derivar de células humanas tales como células renales embrionarias humanas, células musculares, células hematopoyéticas u otras células mesenquimales o epiteliales embrionarias humanas. Alternativamente, las células auxiliares pueden derivar de las células de otras especies de mamíferos que son permisivas para el adenovirus humano. Tales células incluyen, por ejemplo, células Vero u otras células mesenquimales o epiteliales embrionarias de mono. Tal como se indicó anteriormente, la línea celular auxiliar preferida es 293.

Los métodos mejorados para cultivar células 293 y propagar adenovirus son conocidos en la técnica. En un formato, los agregados de células naturales se cultivan mediante la inoculación de células individuales en matraces de 1 litro de silicona (Techne, Cambridge, Reino Unido) que contienen 100-200 ml de medio. Después de agitar a 40 rpm, se estima la viabilidad celular con azul de tripano. En

otro formato, se emplean microportadores Fibra-Cel (Bibby Sterlin, Stone, Reino Unido) (5 g/l) de la siguiente manera. Se agrega un inóculo celular, resuspendido en 5 ml de medio, al portador (50 ml) en un matraz Erlenmeyer de 250 ml y se deja en reposo, con agitación ocasional, durante 1 a 4 h. El medio se reemplaza luego con 50 ml de medio fresco y se inicia la agitación. Para la producción de virus, se permite que las células crezcan hasta alrededor de 80 % de confluencia, después de lo cual el medio se reemplaza (hasta 25 % del volumen final) y se agrega adenovirus a una MOI de 0,05. Los cultivos se dejan en reposo durante la noche, después de lo cual el volumen se incrementa al 100 % y se inicia la agitación durante otras 72 h.

Los adenovirus de la descripción tienen replicación defectuosa, o al menos condicionalmente replicación defectuosa. El adenovirus puede ser de cualquiera de los 42 serotipos o subgrupos de F-A diferentes conocidos. El adenovirus tipo 5 del subgrupo C es el material de partida preferido para obtener el vector de adenovirus con replicación defectuosa condicional para uso en la presente descripción.

Como se indicó anteriormente, el vector típico de acuerdo con la presente descripción es defectuoso en la replicación y no tendrá una región E1 de adenovirus. Por lo tanto, será más conveniente introducir el polinucleótido que codifica el gen de interés en la posición de la que se han eliminado las secuencias codificantes de E1. Sin embargo, la posición de inserción de la construcción dentro de las secuencias de adenovirus no es crucial. El polinucleótido que codifica el gen de interés también puede insertarse en lugar de la región E3 eliminada en vectores de reemplazo E3, o en la región E4 donde una línea celular auxiliar o virus auxiliar complementa el defecto de E4.

El adenovirus es fácil de cultivar y manipular y presenta una amplia gama de hospedadores *in vitro* e *in vivo*. Este grupo de virus se puede obtener en titulaciones altas, p.ej., 10^9-10^{12} unidades formadoras de placa por ml, y son altamente infecciosas. El ciclo de vida del adenovirus no requiere integración en el genoma de la célula hospedadora. Los genes extraños suministrados por los vectores de adenovirus son episomales y, por lo tanto, tienen una genotoxicidad baja para las células hospedadoras. No se han informado efectos secundarios en estudios de vacunación con adenovirus de tipo salvaje, lo que demuestra su seguridad y potencial terapéutico como vectores de transferencia de genes *in vivo*.

Los vectores de adenovirus se han utilizado en la expresión de genes eucariotas y en el desarrollo de vacunas. Los estudios en animales sugirieron que el adenovirus recombinante podría usarse para la terapia génica. Los estudios sobre la administración de adenovirus recombinante a diferentes tejidos incluyen instilación de tráquea, inyección muscular, inyecciones intravenosas periféricas e inoculación estereotáctica en el cerebro.

Los retrovirus son un grupo de virus de ARN de cadena simple caracterizados por la capacidad de

convertir su ARN en ADN de cadena doble en células infectadas mediante un proceso de transcripción inversa. El ADN resultante luego se integra de manera estable en los cromosomas celulares como un provirus y dirige la síntesis de proteínas virales. La integración da como resultado la retención de las secuencias de genes virales en la célula receptora y sus descendientes. El genoma retroviral contiene tres genes, gag, pol y env que codifican proteínas de la cápside, enzima polimerasa y componentes de la envoltura, respectivamente. Una secuencia que se encuentra corriente arriba del gen gag contiene una señal para empaquetar el genoma en viriones. Dos secuencias largas de repetición terminal (LTR) están presentes en los extremos 5' y 3' del genoma viral. Estos contienen secuencias promotoras y potenciadoras fuertes y también se requieren para la integración en el genoma de la célula hospedadora.

Para construir un vector retroviral, se inserta un ácido nucleico que codifica un gen de interés en el genoma viral en el lugar de determinadas secuencias virales para producir un virus con deficiencia de replicación. Para producir viriones, se construye una línea celular de empaquetamiento que contiene los genes gag, pol y env, pero sin los componentes LTR y de empaquetamiento. Cuando se introduce un plásmido recombinante que contiene un ADNc junto con las secuencias de empaquetamiento y LTR retroviral en esta línea celular (mediante precipitación con fosfato de calcio), la secuencia de empaquetamiento permite que la transcripción de ARN del plásmido recombinante sea empaquetada en partículas de virus, que luego se secretan en los medios de cultivo. Los medios que contienen los retrovirus recombinantes se recolectan, opcionalmente se concentran y se usan para la transferencia de genes. Los vectores retrovirales pueden infectar una amplia variedad de tipos de células. Sin embargo, la integración y la expresión estable requieren la división de las células hospedadoras.

Recientemente, se desarrolló un nuevo enfoque diseñado para permitir el direccionamiento específico de vectores de retrovirus en función de la modificación química de un retrovirus mediante la adición química de residuos de lactosa a la envoltura viral. Esta modificación podría permitir la infección específica de hepatocitos mediante receptores de sialoglicoproteínas.

Puede usarse un enfoque diferente para el direccionamiento de retrovirus recombinantes, en el que se usan anticuerpos biotinilados contra una proteína de envoltura retroviral y contra un receptor celular específico. Los anticuerpos se acoplan a través de los componentes de biotina mediante el uso de estreptavidina. Mediante el uso de anticuerpos contra los antígenos de clase I y clase II del complejo de histocompatibilidad principal, se ha demostrado la infección de una variedad de células humanas que portaban esos antígenos de superficie con un virus ecotrópico *in vitro* (Roux et ál., 1989).

Existen determinadas limitaciones para el uso de vectores de retrovirus en todos los aspectos de la presente descripción. Por ejemplo, los vectores de retrovirus generalmente se integran en sitios

aleatorios en el genoma celular. Esto puede conducir a mutagénesis de inserción a través de la interrupción de los genes del hospedador o a través de la inserción de secuencias reguladoras virales que pueden interferir con la función de los genes flanqueantes. Otro problema del uso de vectores de retrovirus defectuosos es la posible aparición de virus competentes para la replicación de tipo salvaje en las células de empaquetamiento. Esto puede producirse a partir de eventos de recombinación en los que la secuencia intacta del virus recombinante se inserta corriente arriba de la secuencia de gag, pol, env, integrada en el genoma de la célula hospedadora. Sin embargo, en la actualidad se encuentran disponibles líneas celulares nuevas de empaquetamiento que deberían disminuir considerablemente la probabilidad de recombinación (véase, por ejemplo, Markowitz et ál. 1988; Hersdorffer et ál. 1990).

Otros vectores virales pueden emplearse como construcciones de expresión en la presente descripción. Pueden emplearse vectores derivados de virus, como el virus adenoasociado del virus de la vacuna (AAV) y los herpesvirus. Estos ofrecen varias características atractivas para varias células de mamíferos.

En algunas modalidades, el vector AAV tiene defectos en la replicación o tiene defectos condicionales en la replicación. En algunas modalidades, el vector AAV es un vector AAV recombinante. En algunas modalidades, el vector AAV comprende una secuencia aislada o derivada de un vactor AAV del serotipo AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 o cualquier combinación de estos.

En algunas modalidades, se usa un único vector viral para administrar un ácido nucleico que codifica Cas9 o Cpf1 y al menos un ARNg a una célula. En algunas modalidades, se proporciona Cas9 o Cpf1 a una célula mediante el uso de un primer vector viral y se proporciona al menos un ARNg a la célula mediante el uso de un segundo vector viral.

En algunas modalidades, se usa un único vector viral para administrar un ácido nucleico que codifica Cas9 o Cpf1 y al menos un ARNg a una célula. En algunas modalidades, se proporciona Cas9 o Cpf1 a una célula mediante el uso de un primer vector viral y se proporciona al menos un ARNg a la célula mediante el uso de un segundo vector viral. Para efectuar la expresión de construcciones génicas sentido o antisentido, la construcción de expresión debe ser administrada a una célula. La célula puede ser una célula muscular, una célula satélite, un mesangioblasto, una célula derivada de la médula ósea, una célula estromal o una célula madre mesenquimal. En algunas modalidades, la célula es una célula muscular cardíaca, una célula muscular esquelética o una célula muscular lisa. En algunas modalidades, la célula es una célula en el tibial anterior, cuadríceps, sóleo, diafragma o corazón. En algunas modalidades, la célula es una célula madre pluripotente inducida (iPSC) o célula de masa celular interna (iCM). En modalidades adicionales, la célula es una iPSC humana o una iCM

humana. En algunas modalidades, las iPSC humanas o las iCM humanas de la descripción pueden derivar de una línea de células madre cultivadas, una célula madre adulta, una célula madre placentaria o de otra fuente de células madre adultas o embrionarias que no requieren la destrucción de un embrión humano. El suministro a una célula puede realizarse *in vitro*, como en los procedimientos de laboratorio para transformar líneas celulares, o *in vivo* o *ex vivo*, como en el tratamiento de determinados estados patológicos. Un mecanismo para la administración es a través de una infección viral donde la construcción de expresión está encapsidada en una partícula viral infecciosa.

La presente descripción contempla varios métodos no virales para la transferencia de construcciones de expresión en células de mamíferos cultivadas. Estos incluyen precipitación con fosfato de calcio, DEAE-dextrano, electroporación, microinyección directa, liposomas cargados de ADN y complejos de lipofectamina-ADN, sonicación celular, bombardeo de genes mediante el uso de microproyectiles de alta velocidad y transfección mediada por receptores. Algunas de estas técnicas pueden ser adaptadas exitosamente para el uso *in vivo* o *ex vivo*.

Una vez que la construcción de expresión se haya administrado a la célula, el ácido nucleico que codifica el gen de interés puede posicionarse y expresarse en diferentes sitios. En determinadas modalidades, el ácido nucleico que codifica el gen puede integrarse de manera estable en el genoma de la célula. Esta integración puede estar en la orientación y la ubicación cognada a través de la recombinación homóloga (reemplazo de genes) o puede integrarse en una ubicación aleatoria, no específica (aumento de genes). En otras modalidades adicionales, el ácido nucleico puede mantenerse de manera estable en la célula como un segmento de ADN episomal separado. Dichos segmentos de ácido nucleico o «episomas» codifican secuencias suficientes para permitir el mantenimiento y la replicación independientemente de, o en sincronización con, el ciclo de la célula hospedadora. La forma en que se suministra la construcción de expresión a una célula y en qué parte de la célula permanece el ácido nucleico depende del tipo de construcción de expresión empleada.

En aun otra modalidad, la construcción de expresión puede consistir simplemente en ADN recombinante sin tratamiento o plásmidos. La transferencia de la construcción puede realizarse por cualquiera de los métodos mencionados anteriormente que permeabilizan física o químicamente la membrana celular. Esto es particularmente aplicable para la transferencia *in vitro*, pero también puede aplicarse al uso *in vivo*. Dubensky et ál. (1984) inyectaron con éxito ADN de poliomavirus en forma de precipitados de fosfato de calcio en el hígado y el bazo de ratones adultos y recién nacidos, lo que demostró una replicación viral activa y una infección aguda. Benvenisty y Neshif (1986) también demostraron que la inyección intraperitoneal directa de plásmidos precipitados con fosfato de calcio da como resultado la expresión de los genes transfectados. El ADN que codifica un gen de

interés también puede transferirse de manera similar *in vivo* y expresar el producto génico.

En incluso otra modalidad, la transferencia de una construcción de expresión de ADN sin tratamiento a células puede implicar un bombardeo de partículas. Este método depende de la capacidad de acelerar los microproyectiles recubiertos de ADN hasta una alta velocidad que les permita perforar las membranas celulares y entrar a las células sin destruirlas. Se han desarrollado varios dispositivos para acelerar partículas pequeñas. Uno de estos dispositivos se basa en una descarga de alto voltaje para generar una corriente eléctrica, que a su vez proporciona la fuerza motriz. Los microproyectiles utilizados han consistido en sustancias biológicamente inertes, tales como microesferas de tungsteno o de oro.

En algunas modalidades, la construcción de expresión se administra directamente al hígado, la piel y/o el tejido muscular de un sujeto. Esto puede requerir la exposición quirúrgica del tejido o las células, para eliminar cualquier tejido intermedio entre la pistola y el órgano diana, es decir, tratamiento *ex vivo*. Nuevamente, el ADN que codifica un gen particular puede administrarse a través de este método y aún puede incorporarse en la presente descripción.

En una modalidad adicional, la construcción de expresión puede estar atrapada en un liposoma. Los liposomas son estructuras vesiculares caracterizadas por una membrana de bicapa de fosfolípidos y un medio acuoso interno. Los liposomas multilamelares tienen múltiples capas de lípidos separadas por un medio acuoso. Se forman de manera espontánea cuando los fosfolípidos se suspenden en un exceso de solución acuosa. Los componentes lipídicos son sometidos a una autorreorganización antes de la formación de estructuras cerradas y retienen agua y solutos disueltos entre las bicapas lipídicas. También se contemplan complejos de lipofectamina-ADN.

La liberación de ácido nucleico mediada por liposomas y expresión de ADN extraño *in vitro* ha sido muy exitosa. Un reactivo conocido como lipofectamina 2000™ es ampliamente utilizado y se encuentra comercialmente disponible.

En determinadas modalidades, el liposoma puede formar un complejo con un virus hemaglutinante (HVJ) para facilitar la fusión con la membrana celular y promover la entrada en las células del ADN encapsulado en liposomas. En otras modalidades, el liposoma puede formar un complejo o emplearse junto con proteínas cromosómicas no histonas nucleares (HMG-1). En otras modalidades adicionales, el liposoma puede formar un complejo o emplearse junto con HVJ y HMG-1. En el sentido de que tales construcciones de expresión se han empleado con éxito en la transferencia y expresión de ácido nucleico *in vitro* e *in vivo*, estas pueden aplicarse en la presente descripción. Cuando se emplea un promotor bacteriano en la construcción de ADN, también será conveniente incluir dentro del liposoma una polimerasa bacteriana apropiada.

Otras construcciones de expresión que pueden emplearse para administrar un ácido nucleico que

codifica un gen particular en las células son los vehículos de administración mediados por receptor. Estos aprovechan la captación selectiva de macromoléculas por endocitosis mediada por receptores en casi todas las células eucariotas. Debido a la distribución específica del tipo de célula de varios receptores, la administración puede ser altamente específica.

Los vehículos de direccionamiento de genes mediado por receptores generalmente consisten en dos componentes: un ligando específico para el receptor celular y un agente de unión al ADN. Varios ligandos se han utilizado para la transferencia de genes mediada por receptores. Los ligandos más ampliamente caracterizados son asialoorosomucoide (ASOR) y transferrina. Se ha utilizado una neoglicoproteína sintética, que reconoce el mismo receptor que ASOR como vehículo de suministro de genes y también se ha utilizado el factor de crecimiento epidérmico (EGF) para transmitir genes a células de carcinoma escamoso.

D. Vectores de AAV-Cas9

En algunas modalidades, Cas9 se puede empaquetar en un vector AAV. En algunas modalidades, el vector AAV es un vector AAV de tipo salvaje. En algunas modalidades, el vector AAV contiene una o más mutaciones. En algunas modalidades, el vector AAV se aísla o deriva de un vector AAV del serotipo AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 o cualquier combinación de estos.

Los vectores AAV-Cas9 ilustrativos contienen dos secuencias ITR (repetición terminal invertida) que flanquean una región de secuencia central que comprende la secuencia Cas9. En algunas modalidades, las ITR se aíslan o derivan de un vector AAV del seriotipo AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 o cualquier combinación de estos. En algunas modalidades, las ITR comprenden o consisten en secuencias de longitud completa y/o de tipo salvaje para un serotipo de AAV. En algunas modalidades, las ITR comprenden o consisten en secuencias truncadas para un serotipo de AAV. En algunas modalidades, las ITR comprenden o consisten en secuencias alargadas para un serotipo de AAV. En algunas modalidades, las ITR comprenden o consisten en secuencias que comprenden una variación de secuencia en comparación con una secuencia de tipo salvaje para el mismo serotipo de AAV. En algunas modalidades, la variación de secuencia comprende una o más de una sustitución, eliminación, inserción, inversión o transposición. En algunas modalidades, las ITR comprenden o consisten en al menos 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149 o 150 pares de bases. En algunas modalidades, las ITR comprenden o consisten en al menos 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116,

117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149 o 150 pares de bases. En algunas modalidades, las ITR tienen una longitud de 110 ± 10 pares de bases. En algunas modalidades, las ITR tienen una longitud de 120 ± 10 pares de bases. En algunas modalidades, las ITR tienen una longitud de 130 ± 10 pares de bases. En algunas modalidades, las ITR tienen una longitud de 140 ± 10 pares de bases. En algunas modalidades, las ITR tienen una longitud de 150 ± 10 pares de bases. En algunas modalidades, las ITR tienen una longitud de 115, 145 o 141 pares de bases. En algunas modalidades, las ITR tienen una secuencia que se selecciona de la SEQ. ID. NO: 880, la SEQ ID NO: 881, la SEQ ID NO; 882, la SEQ ID NO: 883 y la SEQ ID. NO: 946.

En algunas modalidades, el vector AAV-Cas9 puede contener una o más señales de localización nuclear (NLS). En algunas modalidades, el vector AAV-Cas9 contiene 1, 2, 3, 4 o 5 señales de localización nuclear. Los NLS ilustrativos incluyen el NLS c-myc (SEQ ID NO: 884), el SV40 NLS (SEQ ID NO: 885), el hnRNPAI M9 NLS (SEQ ID NO: 886), la nucleoplasmina NLS (SEQ ID NO: 887), la secuencia RMRKFKNKGKDTAELRRRRVEVSVELRKAKKDEQILKRRNV (SEQ ID NO: 888) del dominio IBB de importina-alfa, las secuencias VSRKRPRP (SEQ ID NO: 889) y PPKKARED (SEQ ID NO: 890) de la proteína T del mioma, la secuencia PQPKKKPL (SEQ ID NO: 891) de p53 humana, la secuencia SALIKKKKKMAP (SEQ ID NO: 892) de ratón c-abl IV, las secuencias DRLRR (SEQ ID NO: 893) y PKQKKRK (SEQ ID NO: 894) del virus de la influenza NS1, la secuencia RKLKKKIKKL (SEQ ID NO: 895) del antígeno del virus de la hepatitis delta y la secuencia REKKKFLKRR (SEQ ID NO: 896) de la proteína Mx1 de ratón. Otras señales de localización nuclear aceptables incluyen secuencias de localización nuclear bipartitas, como la secuencia KRKGDEVDGVDEVAKKKSKK (SEQ ID NO: 897) de la poli(ADP-ribosa) polimerasa humana o la secuencia RKCLQAGMNLEARKTKK (SEQ ID NO: 898) de los receptores de hormonas esteroides (humanos), glucocorticoides.

En algunas modalidades, el vector AAV-Cas9 puede comprender elementos adicionales para facilitar el empaquetamiento del vector y la expresión de Cas9. En algunas modalidades, el vector AAV-Cas9 puede comprender una secuencia de poliA. En algunas modalidades, la secuencia de poliA puede ser una secuencia de poliA mini. En algunas modalidades, el vector AAV-CAs9 puede comprender un elemento transponible. En algunas modalidades, el vector AAV-Cas9 puede comprender un elemento regulador. En algunas modalidades, el elemento regulador es un activador o un represor.

En algunas modalidades, el vector AAV -Cas9 puede contener uno o más promotores. En algunas modalidades, el uno o más promotores dirigen la expresión de Cas9. En algunas modalidades, el uno o más promotores son promotores específicos de los músculos. Los promotores específicos de los músculos incluyen el promotor de la cadena ligera de la miosina-2, el promotor de la α-actina, el

promotor de la troponina 1, el promotor intercambiador de Na+/Ca2+, el promotor de la distrofina, el promotor de la integrina α7, el promotor del péptido natriurético cerebral, el promotor de la proteína de choque térmico pequeña/cristalina αB, el promotor de la cadena pesada de la α-miosina, el promotor de ANF, el promotor CK8 y el promotor CK8e.

En algunas modalidades, el vector AAV-Cas9 puede optimizarse para la producción en levaduras, bacterias, células de insectos o células de mamíferos. En algunas modalidades, el vector AAV-Cas9 puede optimizarse para la expresión en células humanas. En algunas modalidades, el vector AAV-Cas9 puede optimizarse para la expresión en un sistema de expresión de bacculovirus.

En algunas modalidades, el vector AAV-Cas9 comprende una secuencia que se selecciona de la SEQ ID NO: 899, la SEQ ID NO: 900, la SEQ ID NO: 901 o la SEQ ID NO: 902, tal como se muestra en la Tabla 4.

Tabla 4: Construcciones de edición génica ilustrativas (de ITR a ITR para la administración a través del vector AAV)

La SEQ ID NO:	Secuencia
899	GGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCT TTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCC TTGTAGTTAATGATTAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGATTAATTAATGCCCATGTAAGG AGGCAAGGCCTGGGGACACCCGAGATGCCTGGTTATAATTAACCCAGACATGTGGCTGCCCCCCCCCCCCCA ACACCTGCTGCCTCTAAAAATAACCCTGCATGCCATGTTCCCGGCGAAGGGCCAGCTGTCCCCCGCCAGCTA GACTCAGCACTTAGTTTAGGAACCAGTGAGCAAGTCAGCCCTTGGGGCAGCCCATACAAGGCCATGGGGCTG GGCAAGCTGCACGCCTGGGTCCGGGGTGGGCACGGTGCCCGGGCAACGAGCTGAAAGCTCATCTGCTCTCA GGGGCCCCTCCCTGGGGACAGCCCCTCCTGGCTAGTCACACCCTGTAGGCTCCTCTATATAACCCAGGGGCA CAGGGGCTGCCCTCATTCTACCACCACCTCCACAGCACAGACAGACACTCAGGAGCCAGCCAGCGCTAGCGC CACCATGATGGCCCCAAAGAAGAAGCGGAAGGTCGGTATCCACGGAGTCCCAGCAGCCGACAAGAAGTACAG CATCGGCCTGGACATCGGCACCAACTCTGTGGGCTGGGCCGTGATCACCGACGAGTACAAGGTGCCCAGCAA GAAATTCAAGGTGCTGGGCAACACCGACCGGCACAGCATCAAGAAGAACCTGATCGGAGCCCTGCTGTTCGA CAGCGGCGAAACAGCCGAGGCCACCCGGCTGAAGAGAACCGCCAGAAGAAGATACACCAGACGGAAGAACC GGATCTGCTATCTGCAAGAGATCTTCAGCAACGAGATGGCCAAGGTGGACGACAGCTTCTTCCACAGACTGGA AGAGTCCTTCCTGGTGGAAGAGGATAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGACGAGGT GGCCTACCACGAGAAGTACCCCACCATCTACCACCTGAGAAAGAAACTGGTGGACAGCACCGACAAGGCCGA CCTGCGGCTGATCTATCTGGCCCTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGAGGGCGACCT GAACCCCGACAACAGCGACGTGGACAAGCTGTTCATCCAGCTGGTGCAGACCTACAACCAGCTGTTCGAGGA AAACCCCATCAACGCCAGCGGCGTGGACGCCAAGGCCATCCTGTCTGCCAGACTGAGCAAGAGCAGACGGCT GGAAAATCTGATCGCCCAGCTGCCCGGCGAGAAGAAGAATGGCCTGTTCGGCAACCTGATTGCCCTGAGCCT

	GGGCCTGACCCCCAACTTCAAGAGCAACTTCGACCTGGCCGAGGATGCCAAACTGCAGCTGAGCAAGGACAC
	CTACGACGACGACCTGGACAACCTGCTGGCCCAGATCGGCGACCAGTACGCCGACCTGTTTCTGGCCGCCAA
	GAACCTGTCCGACGCCATCCTGCTGAGCGACATCCTGAGAGTGAACACCGAGATCACCAAGGCCCCCCTGAG
	CGCCTCTATGATCAAGAGATACGACGAGCACCACCAGGACCTGACCCTGCTGAAAGCTCTCGTGCGGCAGCA
	GCTGCCTGAGAAGTACAAAGAGATTTTCTTCGACCAGAGCAAGAACGGCTACGCCGGCTACATTGACGGCGG
	AGCCAGCCAGGAAGAGTTCTACAAGTTCATCAAGCCCATCCTGGAAAAGATGGACGGCACCGAGGAACTGCT
	CGTGAAGCTGAACAGAGAGGACCTGCTGCGGAAGCAGCGGACCTTCGACAACGGCAGCATCCCCCACCAGAT
	CCACCTGGGAGAGCTGCACGCCATTCTGCGGCGGCAGGAAGATTTTTACCCATTCCTGAAGGACAACCGGGA
	AAAGATCGAGAAGATCCTGACCTTCCGCATCCCCTACTACGTGGGCCCTCTGGCCAGGGGAAACAGCAGATTC
	GCCTGGATGACCAGAAAGAGCGAGGAAACCATCACCCCCTGGAACTTCGAGGAAGTGGTGGACAAGGGCGCT
	TCCGCCCAGAGCTTCATCGAGCGGATGACCAACTTCGATAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAG
	CACAGCCTGCTGTACGAGTACTTCACCGTGTATAACGAGCTGACCAAAGTGAAATACGTGACCGAGGGAATGA
	GAAAGCCCGCCTTCCTGAGCGGCGAGCAGAAAAAGGCCATCGTGGACCTGCTGTTCAAGACCAACCGGAAAG
	TGACCGTGAAGCAGCTGAAAGAGGACTACTTCAAGAAAATCGAGTGCTTCGACTCCGTGGAAATCTCCGGCGT
	GGAAGATCGGTTCAACGCCTCCCTGGGCACATACCACGATCTGCTGAAAATTATCAAGGACAAGGACTTCCTG
	GACAATGAGGAAAACGAGGACATTCTGGAAGATATCGTGCTGACCCTGACACTGTTTGAGGACAGAGAGATGA
	TCGAGGAACGGCTGAAAACCTATGCCCACCTGTTCGACGACAAAGTGATGAAGCAGCTGAAGCGGCGGAGAT
	ACACCGGCTGGGGCAGGCTGAGCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGTCCGGCAAGACAATC
	CTGGATTTCCTGAAGTCCGACGGCTTCGCCAACAGAAACTTCATGCAGCTGATCCACGACGACAGCCTGACCT
	TTAAAGAGGACATCCAGAAAGCCCAGGTGTCCGGCCAGGGCGATAGCCTGCACGAGCACATTGCCAATCTGG
	CCGGCAGCCCCGCCATTAAGAAGGGCATCCTGCAGACAGTGAAGGTGGTGGACGAGCTCGTGAAAGTGATGG
	GCCGGCACAAGCCCGAGAACATCGTGATCGAAATGGCCAGAGAGAACCAGACCACCCAGAAGGGACAGAAGA
	ACAGCCGCGAGAGAATGAAGCGGATCGAAGAGGGCATCAAAGAGCTGGGCAGCCAGATCCTGAAAGAACACC
	CCGTGGAAAACACCCAGCTGCAGAACGAGAAGCTGTACCTGTACTACCTGCAGAATGGGCGGGATATGTACG
	TGGACCAGGAACTGGACATCAACCGGCTGTCCGACTACGATGTGGACCATATCGTGCCTCAGAGCTTTCTGAA
	GGACGACTCCATCGACAACAAGGTGCTGACCAGAAGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCCTC
	CGAAGAGGTCGTGAAGAAGATGAAGAACTACTGGCGGCAGCTGCTGAACGCCAAGCTGATTACCCAGAGAAA
	GTTCGACAATCTGACCAAGGCCGAGAGAGGCGGCCTGAGCGAACTGGATAAGGCCGGCTTCATCAAGAGACA
	GCTGGTGGAAACCCGGCAGATCACAAAGCACGTGGCACAGATCCTGGACTCCCGGATGAACACTAAGTACGA
	CGAGAATGACAAGCTGATCCGGGAAGTGAAAGTGATCACCCTGAAGTCCAAGCTGGTGTCCGATTTCCGGAAG
	GATTTCCAGTTTTACAAAGTGCGCGAGATCAACAACTACCACCACGCCCACGACGCCTACCTGAACGCCGTCG
	TGGGAACCGCCCTGATCAAAAAGTACCCTAAGCTGGAAAGCGAGTTCGTGTACGGCGACTACAAGGTGTACGA
	CGTGCGGAAGATGATCGCCAAGAGCGAGCAGGAAATCGGCAAGGCTACCGCCAAGTACTTCTTCTACAGCAA
	CATCATGAACTTTTTCAAGACCGAGATTACCCTGGCCAACGGCGAGATCCGGAAGCGGCCTCTGATCGAGACA
	AACGGCGAAACCGGGGAGATCGTGTGGGATAAGGGCCGGGATTTTGCCACCGTGCGGAAAGTGCTGAGCAT
	GCCCCAAGTGAATATCGTGAAAAAGACCGAGGTGCAGACAGGCGGCTTCAGCAAAGAGTCTATCCTGCCCAA
	GAGGAACAGCGATAAGCTGATCGCCAGAAAGAAGGACTGGGACCCTAAGAAGTACGGCGGCTTCGACAGCCC
	CACCGTGGCCTATTCTGTGCTGGTGGTGGCCAAAGTGGAAAAGGGCAAGTCCAAGAAACTGAAGAGTGTGAA
	AGAGCTGCTGGGGATCACCATCATGGAAAGAAGCAGCTTCGAGAAGAATCCCATCGACTTTCTGGAAGCCAAG
	GGCTACAAAGAAGTGAAAAAGGACCTGATCATCAAGCTGCCTAAGTACTCCCTGTTCGAGCTGGAAAACGGCC
	GGAAGAGAATGCTGGCCTCTGCCGGCGAACTGCAGAAGGGAAACGAACTGGCCCTGCCCTCCAAATATGTGA

	ACTTCCTGTACCTGGCCAGCCACTATGAGAAGCTGAAGGGCTCCCCCGAGGATAATGAGCAGAAACAGCTGTT TGTGGAACAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCAGCGAGTTCTCCAAGAGAGTGATCCTG GCCGACGCTAATCTGGACAAAGTGCTGTCCGCCTACAACAAGCACCGGGATAAGCCCATCAGAGAGCAGGCC GAGAATATCATCCACCTGTTTACCCTGACCAATCTGGGAGCCCCTGCCGCCTTCAAGTACTTTGACACCACCAT CGACCGGAAGAGGTACACCAGCACCAAAGAGGTGCTGGACGCCACCCTGATCCACCAGAGCATCACCGGCCT GTACGAGACACGGATCGACCTGTCTCAGCTGGGAGGCGACAAGCGTCCTGCTGCTACTAAGAAAGCTGGTCA AGCTAAGAAAAAGAAATGAATCGATTAGCAATAAAGGATCGTTTATTTTCATTGGAAGCGTGTGTTGGTTTTTTG ATCAGGCGCGGGTACCAGGTCGCGGCCGCTCTAGAGCATGGCTACGTAGATAAGTAGCATGGCGGGTTAATC ATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCG GGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGA GGGA
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	CAGGACAGAAATGCCTCGACTTCGCTGCTGCCCAAGGTTGCCGGGTGACGCACACCGTGGAAACGGATGAAG GCACGAACCCAGTTGACATAAGCCTGTTCGGTTCGTAAACTGTAATGCAAGTAGCGTATGCGCTCACGCAACT GGTCCAGAACCTTGACCGAACGCAGCGGTGGTAACGGCGCAGTGGCGGTTTTCATGGCTTGTTATGACTGTTT TTTTGTACAGTCTATGCCTCGGGCATCCAAGCAGCAAGCGCGTTACGCCGTGGGTCGATGTTTGATGTTATGG AGCAGCAACGATGTTACGCAGCAGCAACGATGTTACGCAGCAGGGCAGTCGCCCTAAAACAAAGTTAGGTGG CTCAAGTATGGGCATCATTCGCACATGTAGGCTCGGCCCTGACCAAGTCAAATCCATGCGGGCTGCTCTTGAT CTTTTCGGTCGTGAGTTCGGAGACGTAGCCACCTACTCCCAACATCAGCCGGACTCCGATTACCTCGGGAACT TGCTCCGTAGTAAGACATTCATCGCGCTTGCTGCCTTCGACCAAGAAGCGGTTGTTGGCGCTCTCGCGGCTTA CGTTCTGCCCAAGTTTGAGCAGCCGCGTAGTGAGATCTATATCTATGATCTCGCAGTCTCCGGCGAGCACCGG AGGCAGGGCATTGCCACCGCGCTCATCAATCTCCTCAAGCATGAGGCCAACGCGCTTGGTGCTTATGTGATCT ACGTGCAAGCAGATTACGGTGACGATCCCGCAGTGGCTCTCTATACAAAGTTGGGCATACGGGAAGAAGTGAT GCACTTTGATATCGACCCAAGTACCGCCACCTAACAATTCGTTCAAGCCGAGATCGGCTTCCCGGCCGCGGAG TTGTTCGGTAAATTGTCACAACGCCGCGAATATAGTCTTTACCATGCCCTTGGCCACGCCCCTCTTTAATACGA CGGGCAATTTGCACTTCAGAAAATGAAGAGTTTGCTTTAGCCATAACAAAAGTCCAGTATGCTTTTTCACAGCAT AACTGGACTGATTTCAGTTTACAACTATTCTGTCTAGTTTAAGACTTTATTGTCATAGTTTAGATCTATTTTGTTCA GTTTAAGACTTTATTGTCCGCCCACACCCGCTTACGC
902	AAGATGACGGTTTGTCACATGGAGTTGGCAGGATGTTTGATTAAAAACATAACAGGAAGAAAAATGCCCCGCTG TGGGCGGACAAAATAGTTGGGAACTGGGAGGGGTGGAAATGGAGTTTTTAAGGATTATTTAGGGAAGAGTGAC AAAATAGATGGGAACTGGGTGTAGCGTCGTAAGCTAATACGAAAATTAAAAATGACAAAATAGTTTGGAACTAG ATTTCACTTATCTGGTTCGGATCTCCTAGGCGATATCAGTGATCAcggatctcgaccaattgacattattgaagcaACTAGTAT CGATtttatcagggttattgtctcagaGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGT CGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAAC TCCATCACTAGGGGTTCCTTGTAGTTAATGATTAACCCGCCATGCTACTTATCTACGTAGCCATGCTCTAGATTA ATTAATGCCCATGTAAGGAGGCAAGGCCTGGGGACACCCGAGATGCCTGGTTATAATTAACCCAGACATGTGG CTGCCCCCCCCCCCCCCAACACCTGCTGCCTCTAAAAATAACCCTGCATGCCATGTTCCCGGCGAAGGGCCAG CTGTCCCCCGCCAGCTAGACTCAGCACTTAGTTTAGGAACCAGTGAGCAAGTCAGCCCTTGGGGCAGCCCATA CAAGGCCATGGGGCTGGGCAAGCTGCACGCCTGGGTCCGGGGTGGGCACGGTGCCCGGGCAACGAGCTGA AAGCTCATCTGCTCTCAGGGGCCCCTCCCTGGGGACAGCCCCTCCTGGCTAGTCACACCCTGTAGGCTCCTC TATATAACCCAGGGGCACAGGGGCTGCCCTCATTCTACCACCACCTCCACAGCACAGACAGACACTCAGGAG CCAGCCAGCGCTAGCGCCACCATGATGGCCCCAAAGAAGAAGCGGAAGGTCGGTATCCACGGAGTCCCAGC AGCCGACAAGAAGTACAGCATCGGCCTGGACATCGGCACCAACTCTGTGGGCTGGGCCGTGATCACCGACGA GTACAAGGTGCCCAGCAAGAAATTCAAGGTGCTGGGCAACACCGACCGGCACAGCATCAAGAAGAACCTGAT CGGAGCCCTGCTGTTCGACAGCGGCGAAACAGCCGAGGCCACCCGGCTGAAGAGAACCGCCAGAAGAAGAT ACACCAGACGGAAGAACCGGATCTGCTATCTGCAAGAGATCTTCAGCAACGAGATGGCCAAGGTGGACGACA GCTTCTTCCACAGACTGGAAGAGTCCTTCCTGGTGGAAGAGGATAAGAAGCACGAGCGGCACCCCATCTTCG GCAACATCGTGGACGAGGTGGCCTACCACGAGAAGTACCCCACCATCTACCACCTGAGAAAGAAACTGGTGG ACAGCACCGACAAGGCCGACCTGCGGCTGATCTATCTGGCCCTGGCCCACATGATCAAGTTCCGGGGCCACT TCCTGATCGAGGGCGACCTGAACCCCGACAACAGCGACGTGGACAAGCTGTTCATCCAGCTGGTGCAGACCT ACAACCAGCTGTTCGAGGAAAACCCCATCAACGCCAGCGGCGTGGACGCCAAGGCCATCCTGTCTGCCAGAC TGAGCAAGAGCAGACGGCTGGAAAATCTGATCGCCCAGCTGCCCGGCGAGAAGAAGAATGGCCTGTTCGGCA

	ACCTGATTGCCCTGAGCCTGGGCCTGACCCCCAACTTCAAGAGCAACTTCGACCTGGCCGAGGATGCCAAAC TGCAGCTGAGCAAGGACACCTACGACGACGACCTGGACAACCTGCTGGCCCAGATCGGCGACCAGTACGCC GACCTGTTTCTGGCCGCCAAGAACCTGTCCGACGCCATCCTGCTGAGCGACATCCTGAGAGTGAACACCGAG ATCACCAAGGCCCCCCTGAGCGCCTCTATGATCAAGAGATACGACGAGCACCACCAGGACCTGACCCTGCTG AAAGCTCTCGTGCGGCAGCAGCTGCCTGAGAAGTACAAAGAGATTTTCTTCGACCAGAGCAAGAACGGCTACG CCGGCTACATTGACGGCGGAGCCAGCCAGGAAGAGTTCTACAAGTTCATCAAGCCCATCCTGGAAAAGATGG ACGGCACCGAGGAACTGCTCGTGAAGCTGAACAGAGAGGACCTGCTGCGGAAGCAGCGGACCTTCGACAAC GGCAGCATCCCCCACCAGATCCACCTGGGAGAGCTGCACGCCATTCTGCGGCGGCAGGAAGATTTTTACCCA TTCCTGAAGGACAACCGGGAAAAGATCGAGAAGATCCTGACCTTCCGCATCCCCTACTACGTGGGCCCTCTGG CCAGGGGAAACAGCAGATTCGCCTGGATGACCAGAAAGAGCGAGGAAACCATCACCCCCTGGAACTTCGAGG AAGTGGTGGACAAGGGCGCTTCCGCCCAGAGCTTCATCGAGCGGATGACCAACTTCGATAAGAACCTGCCCA ACGAGAAGGTGCTGCCCAAGCACAGCCTGCTGTACGAGTACTTCACCGTGTATAACGAGCTGACCAAAGTGAA ATACGTGACCGAGGGAATGAGAAAGCCCGCCTTCCTGAGCGGCGAGCAGAAAAAGGCCATCGTGGACCTGCT GTTCAAGACCAACCGGAAAGTGACCGTGAAGCAGCTGAAAGAGGACTACTTCAAGAAAATCGAGTGCTTCGAC TCCGTGGAAATCTCCGGCGTGGAAGATCGGTTCAACGCCTCCCTGGGCACATACCACGATCTGCTGAAAATTA TCAAGGACAAGGACTTCCTGGACAATGAGGAAAACGAGGACATTCTGGAAGATATCGTGCTGACCCTGACACT GTTTGAGGACAGAGAGATGATCGAGGAACGGCTGAAAACCTATGCCCACCTGTTCGACGACAAAGTGATGAAG CAGCTGAAGCGGCGGAGATACACCGGCTGGGGCAGGCTGAGCCGGAAGCTGATCAACGGCATCCGGGACAA GCAGTCCGGCAAGACAATCCTGGATTTCCTGAAGTCCGACGGCTTCGCCAACAGAAACTTCATGCAGCTGATC CACGACGACAGCCTGACCTTTAAAGAGGACATCCAGAAAGCCCAGGTGTCCGGCCAGGGCGATAGCCTGCAC GAGCACATTGCCAATCTGGCCGGCAGCCCCGCCATTAAGAAGGGCATCCTGCAGACAGTGAAGGTGGTGGAC GAGCTCGTGAAAGTGATGGGCCGGCACAAGCCCGAGAACATCGTGATCGAAATGGCCAGAGAGAACCAGACC ACCCAGAAGGGACAGAAGAACAGCCGCGAGAGAATGAAGCGGATCGAAGAGGGCATCAAAGAGCTGGGCAG CCAGATCCTGAAAGAACACCCCGTGGAAAACACCCAGCTGCAGAACGAGAAGCTGTACCTGTACTACCTGCAG AATGGGCGGGATATGTACGTGGACCAGGAACTGGACATCAACCGGCTGTCCGACTACGATGTGGACCATATC GTGCCTCAGAGCTTTCTGAAGGACGACTCCATCGACAACAAGGTGCTGACCAGAAGCGACAAGAACCGGGGC AAGAGCGACAACGTGCCCTCCGAAGAGGTCGTGAAGAAGATGAAGAACTACTGGCGGCAGCTGCTGAACGCC AAGCTGATTACCCAGAGAAAGTTCGACAATCTGACCAAGGCCGAGAGAGGCGGCCTGAGCGAACTGGATAAG GCCGGCTTCATCAAGAGACAGCTGGTGGAAACCCGGCAGATCACAAAGCACGTGGCACAGATCCTGGACTCC CGGATGAACACTAAGTACGACGAGAATGACAAGCTGATCCGGGAAGTGAAAGTGATCACCCTGAAGTCCAAGC TGGTGTCCGATTTCCGGAAGGATTTCCAGTTTTACAAAGTGCGCGAGATCAACAACTACCACCACGCCCACGA CGCCTACCTGAACGCCGTCGTGGGAACCGCCCTGATCAAAAAGTACCCTAAGCTGGAAAGCGAGTTCGTGTA CGGCGACTACAAGGTGTACGACGTGCGGAAGATGATCGCCAAGAGCGAGCAGGAAATCGGCAAGGCTACCG CCAAGTACTTCTTCTACAGCAACATCATGAACTTTTTCAAGACCGAGATTACCCTGGCCAACGGCGAGATCCGG AAGCGGCCTCTGATCGAGACAAACGGCGAAACCGGGGAGATCGTGTGGGATAAGGGCCGGGATTTTGCCACC GTGCGGAAAGTGCTGAGCATGCCCCAAGTGAATATCGTGAAAAAGACCGAGGTGCAGACAGGCGGCTTCAGC AAAGAGTCTATCCTGCCCAAGAGGAACAGCGATAAGCTGATCGCCAGAAAGAAGGACTGGGACCCTAAGAAGT ACGGCGGCTTCGACAGCCCCACCGTGGCCTATTCTGTGCTGGTGGTGGCCAAAGTGGAAAAGGGCAAGTCCA AGAAACTGAAGAGTGTGAAAGAGCTGCTGGGGATCACCATCATGGAAAGAAGCAGCTTCGAGAAGAATCCCAT CGACTTTCTGGAAGCCAAGGGCTACAAAGAAGTGAAAAAGGACCTGATCATCAAGCTGCCTAAGTACTCCCTG TTCGAGCTGGAAAACGGCCGGAAGAGAATGCTGGCCTCTGCCGGCGAACTGCAGAAGGGAAACGAACTGGC

	CCTGCCCTCCAAATATGTGAACTTCCTGTACCTGGCCAGCCACTATGAGAAGCTGAAGGGCTCCCCCGAGGAT AATGAGCAGAAACAGCTGTTTGTGGAACAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCAGCGAGT TCTCCAAGAGAGTGATCCTGGCCGACGCTAATCTGGACAAAGTGCTGTCCGCCTACAACAAGCACCGGGATAA GCCCATCAGAGAGCAGGCCGAGAATATCATCCACCTGTTTACCCTGACCAATCTGGGAGCCCCTGCCGCCTTC AAGTACTTTGACACCACCATCGACCGGAAGAGGTACACCAGCACCAAAGAGGTGCTGGACGCCACCCTGATC CACCAGAGCATCACCGGCCTGTACGAGACACGGATCGACCTGTCTCAGCTGGGAGGCGACAAGCGTCCTGCT GCTACTAAGAAAGCTGGTCAAGCTAAGAAAAAGAAATGAATCGATTAGCAATAAAGGATCGTTTATTTTCATTGG AAGCGTGTGTTGGTTTTTTGATCAGGCGCGGGTACCAGGTCGCGGCCGCTCTAGAGCATGGCTACGTAGATAA GTAGCATGGCGGGTTAATCATTAACTACAAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCT CGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAG CGAGCGAGCGCGCAGAGAGGGACATGCAAGCTGTAGCCAACCACTAGAACTATAGCTAGAGTCCTGGGCGAA CAAACGATGCTCGCCTTCCAGAAAACCGAGGATGCGAACCACTTCATCCGGGGTCAGCACCACCGGCAAGCG CCGCGACGGCCGAGGTCTTCCGATCTCCTGAAGCCAGGGCAGATCCGTGCACAGCACCTTGCCGTAGAAGAA CAGCAAGGCCGCCAATGCCTGACGATGCGTGGAGACCGAAACCTTGCGCTCGTTCGCCAGCCAGGACAGAAA TGCCTCGACTTCGCTGCTGCCCAAGGTTGCCGGGTGACGCACACCGTGGAAACGGATGAAGGCACGAACCCA GTTGACATAAGCCTGTTCGGTTCGTAAACTGTAATGCAAGTAGCGTATGCGCTCACGCAACTGGTCCAGAACC TTGACCGAACGCAGCGGTGGTAACGGCGCAGTGGCGGTTTTCATGGCTTGTTATGACTGTTTTTTTGTACAGT CTATGCCTCGGGCATCCAAGCAGCAAGCGCGTTACGCCGTGGGTCGATGTTTGATGTTATGGAGCAGCAACG ATGTTACGCAGCAGCAACGATGTTACGCAGCAGGGCAGTCGCCCTAAAACAAAGTTAGGTGGCTCAAGTATGG GCATCATTCGCACATGTAGGCTCGGCCCTGACCAAGTCAAATCCATGCGGGCTGCTCTTGATCTTTTCGGTCG TGAGTTCGGAGACGTAGCCACCTACTCCCAACATCAGCCGGACTCCGATTACCTCGGGAACTTGCTCCGTAGT AAGACATTCATCGCGCTTGCTGCCTTCGACCAAGAAGCGGTTGTTGGCGCTCTCGCGGCTTACGTTCTGCCCA AGTTTGAGCAGCCGCGTAGTGAGATCTATATCTATGATCTCGCAGTCTCCGGCGAGCACCGGAGGCAGGGCA TTGCCACCGCGCTCATCAATCTCCTCAAGCATGAGGCCAACGCGCTTGGTGCTTATGTGATCTACGTGCAAGC AGATTACGGTGACGATCCCGCAGTGGCTCTCTATACAAAGTTGGGCATACGGGAAGAAGTGATGCACTTTGAT ATCGACCCAAGTACCGCCACCTAACAATTCGTTCAAGCCGAGATCGGCTTCCCGGCCGCGGAGTTGTTCGGTA AATTGTCACAACGCCGCGAATATAGTCTTTACCATGCCCTTGGCCACGCCCCTCTTTAATACGACGGGCAATTT GCACTTCAGAAAATGAAGAGTTTGCTTTAGCCATAACAAAAGTCCAGTATGCTTTTTCACAGCATAACTGGACTG ATTTCAGTTTACAACTATTCTGTCTAGTTTAAGACTTTATTGTCATAGTTTAGATCTATTTTGTTCAGTTTAAGACT TTATTGTCCGCCCACACCCGCTTACGC

En algunas modalidades de las construcciones de edición génica de la descripción, incluidas aquellas modalidades que abarcan las SEQ ID NO: 899-902, la construcción comprende o consiste en un promotor y una nucleasa. En algunas modalidades, la construcción comprende o consiste en un promotor CK8e y una nucleasa Cas9. En algunas modalidades, la construcción comprende o consiste en un promotor CK8e y una nucleasa Cas9 aislada o derivada de *Staphylococcus pyogenes* («SpCas9»). En algunas modalidades, el promotor CK8e comprende o consiste en una secuencia de nucleótidos de TGCCCATGTAAGGAGGCAAGGCCTGGGGACACCCGAGATGCCTGGTTATAATTAACCCAGACAT GTGGCTGCCCCCCCCCCCCCAACACCTGCTGCCTCTAAAAATAACCCTGCATGCCATGTTCCCG

GCGAAGGGCCAGCTGTCCCCCGCCAGCTAGACTCAGCACTTAGTTTAGGAACCAGTGAGCAAGT
CAGCCCTTGGGGCAGCCCATACAAGGCCATGGGGCTGGGCAAGCTGCACGCCTGGGTCCGGG
GTGGGCACGGTGCCCGGGCAACGAGCTGAAAGCTCATCTGCTCTCAGGGGCCCCTCCCTGGGG
ACAGCCCCTCCTGGCTAGTCACACCCTGTAGGCTCCTCTATATAACCCAGGGGCACAGGGGCTG
CCCTCATTCTACCACCACCTCCACAGCACAGACAGACACTCAGGAGCCAGCCAGC (SEQ ID NO: 875). En algunas modalidades, la nucleasa SpCas9 comprende o consiste en una secuencia de nucleótidos de
GACAAGAAGTACAGCATCGGCCTGGACATCGGCACCAACTCTGTGGGCTGGGCCGTGATCACC
GACGAGTACAAGGTGCCCAGCAAGAAATTCAAGGTGCTGGGCAACACCGACCGGCACAGCATCA
AGAAGAACCTGATCGGAGCCCTGCTGTTCGACAGCGGCGAAACAGCCGAGGCCACCCGGCTGA
AGAGAACCGCCAGAAGAAGATACACCAGACGGAAGAACCGGATCTGCTATCTGCAAGAGATCTT
CAGCAACGAGATGGCCAAGGTGGACGACAGCTTCTTCCACAGACTGGAAGAGTCCTTCCTGGTG
GAAGAGGATAAGAAGCACGAGCGGCACCCCATCTTCGGCAACATCGTGGACGAGGTGGCCTAC
CACGAGAAGTACCCCACCATCTACCACCTGAGAAAGAAACTGGTGGACAGCACCGACAAGGCCG
ACCTGCGGCTGATCTATCTGGCCCTGGCCCACATGATCAAGTTCCGGGGCCACTTCCTGATCGA
GGGCGACCTGAACCCCGACAACAGCGACGTGGACAAGCTGTTCATCCAGCTGGTGCAGACCTA
CAACCAGCTGTTCGAGGAAAACCCCATCAACGCCAGCGGCGTGGACGCCAAGGCCATCCTGTCT
GCCAGACTGAGCAAGAGCAGACGGCTGGAAAATCTGATCGCCCAGCTGCCCGGCGAGAAGAAG
AATGGCCTGTTCGGCAACCTGATTGCCCTGAGCCTGGGCCTGACCCCCAACTTCAAGAGCAACT
TCGACCTGGCCGAGGATGCCAAACTGCAGCTGAGCAAGGACACCTACGACGACGACCTGGACA
ACCTGCTGGCCCAGATCGGCGACCAGTACGCCGACCTGTTTCTGGCCGCCAAGAACCTGTCCGA
CGCCATCCTGCTGAGCGACATCCTGAGAGTGAACACCGAGATCACCAAGGCCCCCCTGAGCGC
CTCTATGATCAAGAGATACGACGAGCACCACCAGGACCTGACCCTGCTGAAAGCTCTCGTGCGG
CAGCAGCTGCCTGAGAAGTACAAAGAGATTTTCTTCGACCAGAGCAAGAACGGCTACGCCGGCT
ACATTGACGGCGGAGCCAGCCAGGAAGAGTTCTACAAGTTCATCAAGCCCATCCTGGAAAAGAT
GGACGGCACCGAGGAACTGCTCGTGAAGCTGAACAGAGAGGACCTGCTGCGGAAGCAGCGGAC
CTTCGACAACGGCAGCATCCCCCACCAGATCCACCTGGGAGAGCTGCACGCCATTCTGCGGCG
GCAGGAAGATTTTTACCCATTCCTGAAGGACAACCGGGAAAAGATCGAGAAGATCCTGACCTTCC
GCATCCCCTACTACGTGGGCCCTCTGGCCAGGGGAAACAGCAGATTCGCCTGGATGACCAGAAA
GAGCGAGGAAACCATCACCCCCTGGAACTTCGAGGAAGTGGTGGACAAGGGCGCTTCCGCCCA
GAGCTTCATCGAGCGGATGACCAACTTCGATAAGAACCTGCCCAACGAGAAGGTGCTGCCCAAG
CACAGCCTGCTGTACGAGTACTTCACCGTGTATAACGAGCTGACCAAAGTGAAATACGTGACCGA
GGGAATGAGAAAGCCCGCCTTCCTGAGCGGCGAGCAGAAAAAGGCCATCGTGGACCTGCTGTT
CAAGACCAACCGGAAAGTGACCGTGAAGCAGCTGAAAGAGGACTACTTCAAGAAAATCGAGTGC

TTCGACTCCGTGGAAATCTCCGGCGTGGAAGATCGGTTCAACGCCTCCCTGGGCACATACCACG
ATCTGCTGAAAATTATCAAGGACAAGGACTTCCTGGACAATGAGGAAAACGAGGACATTCTGGAA
GATATCGTGCTGACCCTGACACTGTTTGAGGACAGAGAGATGATCGAGGAACGGCTGAAAACCT
ATGCCCACCTGTTCGACGACAAAGTGATGAAGCAGCTGAAGCGGCGGAGATACACCGGCTGGG
GCAGGCTGAGCCGGAAGCTGATCAACGGCATCCGGGACAAGCAGTCCGGCAAGACAATCCTGG
ATTTCCTGAAGTCCGACGGCTTCGCCAACAGAAACTTCATGCAGCTGATCCACGACGACAGCCT
GACCTTTAAAGAGGACATCCAGAAAGCCCAGGTGTCCGGCCAGGGCGATAGCCTGCACGAGCA
CATTGCCAATCTGGCCGGCAGCCCCGCCATTAAGAAGGGCATCCTGCAGACAGTGAAGGTGGTG
GACGAGCTCGTGAAAGTGATGGGCCGGCACAAGCCCGAGAACATCGTGATCGAAATGGCCAGA
GAGAACCAGACCACCCAGAAGGGACAGAAGAACAGCCGCGAGAGAATGAAGCGGATCGAAGAG
GGCATCAAAGAGCTGGGCAGCCAGATCCTGAAAGAACACCCCGTGGAAAACACCCAGCTGCAGA
ACGAGAAGCTGTACCTGTACTACCTGCAGAATGGGCGGGATATGTACGTGGACCAGGAACTGGA
CATCAACCGGCTGTCCGACTACGATGTGGACCATATCGTGCCTCAGAGCTTTCTGAAGGACGAC
TCCATCGACAACAAGGTGCTGACCAGAAGCGACAAGAACCGGGGCAAGAGCGACAACGTGCCC
TCCGAAGAGGTCGTGAAGAAGATGAAGAACTACTGGCGGCAGCTGCTGAACGCCAAGCTGATTA
CCCAGAGAAAGTTCGACAATCTGACCAAGGCCGAGAGAGGCGGCCTGAGCGAACTGGATAAGG
CCGGCTTCATCAAGAGACAGCTGGTGGAAACCCGGCAGATCACAAAGCACGTGGCACAGATCCT
GGACTCCCGGATGAACACTAAGTACGACGAGAATGACAAGCTGATCCGGGAAGTGAAAGTGATC
ACCCTGAAGTCCAAGCTGGTGTCCGATTTCCGGAAGGATTTCCAGTTTTACAAAGTGCGCGAGAT
CAACAACTACCACCACGCCCACGACGCCTACCTGAACGCCGTCGTGGGAACCGCCCTGATCAAA
AAGTACCCTAAGCTGGAAAGCGAGTTCGTGTACGGCGACTACAAGGTGTACGACGTGCGGAAGA
TGATCGCCAAGAGCGAGCAGGAAATCGGCAAGGCTACCGCCAAGTACTTCTTCTACAGCAACAT
CATGAACTTTTTCAAGACCGAGATTACCCTGGCCAACGGCGAGATCCGGAAGCGGCCTCTGATC
GAGACAAACGGCGAAACCGGGGAGATCGTGTGGGATAAGGGCCGGGATTTTGCCACCGTGCGG
AAAGTGCTGAGCATGCCCCAAGTGAATATCGTGAAAAAGACCGAGGTGCAGACAGGCGGCTTCA
GCAAAGAGTCTATCCTGCCCAAGAGGAACAGCGATAAGCTGATCGCCAGAAAGAAGGACTGGGA
CCCTAAGAAGTACGGCGGCTTCGACAGCCCCACCGTGGCCTATTCTGTGCTGGTGGTGGCCAAA
GTGGAAAAGGGCAAGTCCAAGAAACTGAAGAGTGTGAAAGAGCTGCTGGGGATCACCATCATGG
AAAGAAGCAGCTTCGAGAAGAATCCCATCGACTTTCTGGAAGCCAAGGGCTACAAAGAAGTGAAA
AAGGACCTGATCATCAAGCTGCCTAAGTACTCCCTGTTCGAGCTGGAAAACGGCCGGAAGAGAA
TGCTGGCCTCTGCCGGCGAACTGCAGAAGGGAAACGAACTGGCCCTGCCCTCCAAATATGTGAA
CTTCCTGTACCTGGCCAGCCACTATGAGAAGCTGAAGGGCTCCCCCGAGGATAATGAGCAGAAA
CAGCTGTTTGTGGAACAGCACAAGCACTACCTGGACGAGATCATCGAGCAGATCAGCGAGTTCT
CCAAGAGAGTGATCCTGGCCGACGCTAATCTGGACAAAGTGCTGTCCGCCTACAACAAGCACCG

GGATAAGCCCATCAGAGAGCAGGCCGAGAATATCATCCACCTGTTTACCCTGACCAATCTGGGA
GCCCCTGCCGCCTTCAAGTACTTTGACACCACCATCGACCGGAAGAGGTACACCAGCACCAAAG
AGGTGCTGGACGCCACCCTGATCCACCAGAGCATCACCGGCCTGTACGAGACACGGATCGACC
TGTCTCAGCTGGGAGGCGAC (SEQ ID NO:872). En algunas modalidades, la construcción que comprende un promotor y una nucleasa comprende además al menos dos secuencias de repetición terminal invertida (ITR). En algunas modalidades, la construcción que comprende un promotor y una nucleasa comprende además al menos dos secuencias ITR de aislados o derivados de un AAV del serotipo 2 (AAV2). En algunas modalidades, la construcción que comprende un promotor y una nucleasa comprende además al menos dos secuencias ITR, en donde cada una comprende o consiste en una secuencia de nucleótidos de GGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACG CCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGA (SEQ ID NO:880). En algunas modalidades, la construcción que comprende un promotor y una nucleasa comprende además al menos dos secuencias ITR, en donde la primera secuencia ITR comprende o consiste en una secuencia de nucleótidos de CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGG GCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTC CATCACTAGGGGTTCCT (SEQ ID NO: 881) y la segunda secuencia de ITR comprende o consiste en una secuencia de nucleótidos de AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCG GGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCG CGCAGCTGCCTGCAGG (SEQ ID NO: 882). En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera ITR, una secuencia que codifica un promotor, una secuencia que codifica una nucleasa y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera ITR de AAV2, una secuencia que codifica un promotor CK8e, una secuencia que codifica una nucleasa SpCas9 y una segunda ITR de AAV2. En algunas modalidades, la construcción que comprende o consiste en, de 5’ a 3’, una primera ITR, una secuencia que codifica un promotor, una secuencia que codifica una nucleasa y una segunda ITR, comprende además una secuencia poliA. En algunas modalidades, la secuencia poliA comprende o consiste en una secuencia poliA mini. Las secuencias poliA mini ilustrativas de la descripción comprenden o consisten en una secuencia de nucleótidos de TAGCAATAAAGGATCGTTTATTTTCATTGGAAGCGTGTGTTGGTTTTTTGATCAGGCGCG (SEQ ID NO: 903). En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera ITR, una secuencia que codifica un promotor, una secuencia que codifica una nucleasa, una

secuencia poli A y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera ITR, una secuencia que codifica un promotor, una secuencia que codifica una nucleasa, una secuencia A de minipoli y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera ITR de AAV2, una secuencia que codifica un promotor CK8e, una secuencia que codifica una nucleasa SpCas9, una secuencia de poliA mini y una segunda ITR de AAV2. En algunas modalidades, la construcción que comprende, de 5’ a 3’, una primera ITR, una secuencia que codifica un promotor, una secuencia que codifica una nucleasa, una secuencia poliA y una segunda ITR, comprende además al menos una señal de localización nuclear. En algunas modalidades, la construcción que comprende, de 5’ a 3’, una primera ITR, una secuencia que codifica un promotor, una secuencia que codifica una nucleasa, una secuencia de poli A y una segunda ITR, comprende además al menos dos señales de localización nuclear. Las señales de localización nuclear ilustrativas de la descripción comprenden o consisten en una secuencia de nucleótidos de AAGCGTCCTGCTGCTACTAAGAAAGCTGGTCAAGCTAAGAAAAAGAAA (SEQ ID NO. 887), o una secuencia de nucleótidos de ATGGCCCCAAAGAAGAAGCGGAAGGTCGGTATCCACGGAGTCCCAGCAGCC (SEQ ID NO. 885). En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera ITR, una secuencia que codifica un promotor, una secuencia que codifica una primera señal de localización nuclear, una secuencia que codifica una nucleasa, una secuencia de poli A y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera ITR, una secuencia que codifica un promotor, una secuencia que codifica una primera señal de localización nuclear, una secuencia que codifica una nucleasa, una secuencia que codifica una segunda señal de localización nuclear, una secuencia poli A y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera ITR de AAV2, una secuencia que codifica un promotor CK8e, una señal de localización nuclear que tiene una secuencia de la SEQ ID NO: 885, una secuencia que codifica una nucleasa SpCas9, una secuencia poli A mini y una segunda ITR de AAV2. En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera ITR de AAV2, una secuencia que codifica un promotor CK8e, una secuencia que codifica una nucleasa SpCas9, una señal de localización nuclear que tiene una secuencia de la SEQ ID NO: 887, una secuencia poli A mini y una segunda ITR de AAV2. En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera ITR de AAV2, una secuencia que codifica un promotor CK8e, una señal de localización nuclear que tiene una secuencia de la SEQ ID NO. 885, una secuencia que codifica una nucleasa SpCas9, una señal de localización nuclear que tiene una secuencia de la SEQ ID NO: 887, una secuencia poli A mini y una segunda ITR de AAV2. En algunas

modalidades, la construcción que comprende, de 5’ a 3’, una primera ITR, una secuencia que codifica un promotor, una secuencia que codifica una primera señal de localización nuclear, una secuencia que codifica una nucleasa, una secuencia que codifica una segunda señal de localización nuclear, una secuencia poli A y una segunda ITR, comprende además un codón de terminación. El codón de terminación puede tener una secuencia de TAG (SEQ ID NO. 904), TAA (SEQ ID NO. 905), o TGA (SEQ ID NO. 906). En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera ITR, una secuencia que codifica un promotor, una secuencia que codifica una primera señal de localización nuclear, una secuencia que codifica una nucleasa, una secuencia que codifica una segunda señal de localización nuclear, un codón de terminación, una secuencia poli A y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera ITR de AAV2, una secuencia que codifica un promotor CK8e, una señal de localización nuclear que tiene una secuencia de la SEQ ID NO: 885, una secuencia que codifica una nucleasa SpCas9, un codón de terminación, una secuencia poli A mini y una segunda ITR de AAV2. En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera ITR de AAV2, una secuencia que codifica un promotor CK8e, una secuencia que codifica una nucleasa SpCas9, una señal de localización nuclear que tiene una secuencia de la SEQ ID NO: 887, un codón de terminación, una secuencia poli A mini y una segunda ITR de AAV2. En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera ITR de AAV2, una secuencia que codifica un promotor CK8e, una señal de localización nuclear que tiene una secuencia de la SEQ ID NO. 885, una secuencia que codifica una nucleasa SpCas9, una señal de localización nuclear que tiene una secuencia de la SEQ ID NO: 887, un codón de terminación, una secuencia poli A mini y una segunda ITR de AAV2. En algunas modalidades, la construcción que comprende o consiste en, de 5’ a 3’, una primera ITR, una secuencia que codifica un promotor, una secuencia que codifica una primera señal de localización nuclear, una secuencia que codifica una nucleasa, una secuencia que codifica una segunda señal de localización nuclear, un codón de terminación, una secuencia poli A y una segunda ITR, comprende además repeticiones invertidas de elementos transponibles. Las repeticiones invertidas de elementos transponibles de la descripción comprenden o consisten en una secuencia de nucleótidos de TGTGGGCGGACAAAATAGTTGGGAACTGGGAGGGGTGGAAATGGAGTTTTTAAGGATTATTTAG GGAAGAGTGACAAAATAGATGGGAACTGGGTGTAGCGTCGTAAGCTAATACGAAAATTAAAAATG ACAAAATAGTTTGGAACTAGATTTCACTTATCTGGTT (SEQ ID NO. 907), y/o una secuencia de nucleótidos de GAATATAGTCTTTACCATGCCCTTGGCCACGCCCCTCTTTAATACGACGGGCAATTTGCACTTCA GAAAATGAAGAGTTTGCTTTAGCCATAACAAAAGTCCAGTATGCTTTTTCACAGCATAACTGGACT

GATTTCAGTTTACAACTATTCTGTCTAGTTTAAGACTTTATTGTCATAGTTTAGATCTATTTTGTTCA
GTTTAAGACTTTATTGTCCGCCCACA (SEQ ID NO. 908). En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera repetición invertida de un elemento transponible, una primera ITR, una secuencia que codifica un promotor, una secuencia que codifica una primera señal de localización nuclear, una secuencia que codifica una nucleasa, una secuencia que codifica una segunda señal de localización nuclear, un codón de terminación, una secuencia poli A, una segunda ITR, y una segunda repetición invertida de un elemento transponible. En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera repetición invertida de un elemento transponible que tiene una secuencia de la SEQ ID NO. 907, una primera ITR de AAV2, una secuencia que codifica un promotor CK8e, una señal de localización nuclear que tiene una secuencia de la SEQ ID NO: 885, una secuencia que codifica una nucleasa SpCas9, una señal de localización nuclear que tiene una secuencia de la SEQ ID NO. 887, un codón de terminación, una secuencia poli A mini, una segunda ITR de AAV2 y una segunda repetición invertida de elemento transponible que tiene una secuencia de SEQ ID NO. 908. En algunas modalidades, la construcción que comprende o consiste en, de 5’ a 3’, una primera repetición invertida de un elemento transponible, una primera ITR, una secuencia que codifica un promotor, una secuencia que codifica una primera señal de localización nuclear, una secuencia que codifica una nucleasa, una secuencia que codifica una segunda señal de localización nuclear, un codón de terminación, una secuencia poli A, una segunda ITR, y una segunda repetición invertida de un elemento transponible, comprende además una secuencia reguladora. Las secuencias reguladoras ilustrativas de la descripción comprenden o consisten en una secuencia de nucleótidos de
CATGCAAGCTGTAGCCAACCACTAGAACTATAGCTAGAGTCCTGGGCGAACAAACGATGCTCGC
CTTCCAGAAAACCGAGGATGCGAACCACTTCATCCGGGGTCAGCACCACCGGCAAGCGCCGCG
ACGGCCGAGGTCTTCCGATCTCCTGAAGCCAGGGCAGATCCGTGCACAGCACCTTGCCGTAGAA
GAACAGCAAGGCCGCCAATGCCTGACGATGCGTGGAGACCGAAACCTTGCGCTCGTTCGCCAG
CCAGGACAGAAATGCCTCGACTTCGCTGCTGCCCAAGGTTGCCGGGTGACGCACACCGTGGAA
ACGGATGAAGGCACGAACCCAGTTGACATAAGCCTGTTCGGTTCGTAAACTGTAATGCAAGTAGC
GTATGCGCTCACGCAACTGGTCCAGAACCTTGACCGAACGCAGCGGTGGTAACGGCGCAGTGG
CGGTTTTCATGGCTTGTTATGACTGTTTTTTTGTACAGTCTATGCCTCGGGCATCCAAGCAGCAAG
CGCGTTACGCCGTGGGTCGATGTTTGATGTTATGGAGCAGCAACGATGTTACGCAGCAGCAACG
ATGTTACGCAGCAGGGCAGTCGCCCTAAAACAAAGTTAGGTGGCTCAAGTATGGGCATCATTCG
CACATGTAGGCTCGGCCCTGACCAAGTCAAATCCATGCGGGCTGCTCTTGATCTTTTCGGTCGTG
AGTTCGGAGACGTAGCCACCTACTCCCAACATCAGCCGGACTCCGATTACCTCGGGAACTTGCT
CCGTAGTAAGACATTCATCGCGCTTGCTGCCTTCGACCAAGAAGCGGTTGTTGGCGCTCTCGCG

GCTTACGTTCTGCCCAAGTTTGAGCAGCCGCGTAGTGAGATCTATATCTATGATCTCGCAGTCTC
CGGCGAGCACCGGAGGCAGGGCATTGCCACCGCGCTCATCAATCTCCTCAAGCATGAGGCCAA
CGCGCTTGGTGCTTATGTGATCTACGTGCAAGCAGATTACGGTGACGATCCCGCAGTGGCTCTC
TATACAAAGTTGGGCATACGGGAAGAAGTGATGCACTTTGATATCGACCCAAGTACCGCCACCTA
ACAATTCGTTCAAGCCGAGATCGGCTTCCCGGCCGCGGAGTTGTTCGGTAAATTGTCACAACGC
CG (SEQ ID NO. 909). En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de un elemento transponible, una primera ITR, una secuencia que codifica un promotor, una secuencia que codifica una primera señal de localización nuclear, una secuencia que codifica una nucleasa, una secuencia que codifica una segunda señal de localización nuclear, un codón de terminación, una secuencia poli A, una segunda ITR, una secuencia reguladora y una segunda repetición invertida de un elemento transponible. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de un elemento transponible que tiene una secuencia de la SEQ ID NO. 907, una primera ITR de AAV2, una secuencia que codifica un promotor CK8e, una señal de localización nuclear que tiene una secuencia de la SEQ ID NO: 885, una secuencia que codifica una nucleasa SpCas9, una señal de localización nuclear que tiene una secuencia de la SEQ ID NO. 887, un codón de terminación, una secuencia poli A mini, una segunda ITR de AAV2, una secuencia reguladora que tiene una secuencia de SEQ ID NO. 909, y una segunda repetición invertida del elemento transponible que tiene una secuencia de la SEQ ID NO. 908. En algunas modalidades, la construcción puede comprender además una o más secuencias espaciadoras. Las secuencias espaciadoras ilustrativas de la descripción tienen una longitud de 1-1500 nucleótidos, incluidos todos los intervalos entre ellos. En algunas modalidades, las secuencias espaciadoras pueden ubicarse de 5' a/o 3' respecto a una ITR, un promotor, una secuencia de localización nuclear, una nucleasa, un codón de terminación, una secuencia de poliA, una repetición invertida de un elemento transponible, y/o un elemento regulador. En algunas modalidades, la construcción puede tener una secuencia que comprende o consiste en la SEQ ID NO: 899, la SEQ ID NO: 900, la SEQ ID NO: 901 o la SEQ ID NO: 902.

E. Vectores AAV-ARNgs

En algunas modalidades, al menos una primera secuencia que codifica un ARNg y una segunda secuencia que codifica un ARNg se pueden empaquetar en un vector AAV. En algunas modalidades, al menos una primera secuencia que codifica un ARNg, una segunda secuencia que codifica un ARNg y una tercera secuencia que codifica un ARNg pueden empaquetarse en un vector AAV. En algunas modalidades, al menos una primera secuencia que codifica un ARNg, una segunda secuencia que codifica un ARNg, una tercera secuencia que codifica un ARNg y una cuarta

secuencia que codifica un ARNg pueden empaquetarse en un vector AAV. En algunas modalidades, al menos una primera secuencia que codifica un ARNg, una segunda secuencia que codifica un ARNg, una tercera secuencia que codifica un ARNg, una cuarta secuencia que codifica un ARNg y una quinta secuencia que codifica un ARNg pueden empaquetarse en un vector AAV. En algunas modalidades, múltiples secuencias que codifican un ARNg se empaquetan en un vector AAV. Por ejemplo, pueden empaquetarse 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 o 20 secuencias que codifican un ARNg en un vector AAV. En algunas modalidades, cada secuencia que codifica un ARNg es diferente. En algunas modalidades, al menos 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 de las secuencias que codifican un ARNg son iguales. En algunas modalidades, todas las secuencias que codifican un ARNg son iguales.

En algunas modalidades, el vector AAV es un vector AAV de tipo salvaje. En algunas modalidades, el vector AAV contiene una o más mutaciones. En algunas modalidades, el vector AAV se aísla o deriva de un vector AAV del serotipo AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 o cualquier combinación de estos.

Los vectores AAV-ARNgs ilustrativos contienen dos secuencias ITR (repetición terminal invertida) que flanquean una región de secuencia central que comprende las secuencias de ARNgs. En algunas modalidades, las ITR se aíslan o derivan de un vector AAV del seriotipo AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 o cualquier combinación de estos. En algunas modalidades, las ITR se aíslan o derivan de un vector AAV de un primer serotipo y una secuencia que codifica una proteína de la cápside del vector AAV-ARNgs se aísla o deriva de un vector AAV de un segundo serotipo. En algunas modalidades, el primer serotipo y el segundo serotipo son iguales. En algunas modalidades, el primer serotipo y el segundo serotipo no son iguales. En algunas modalidades, el primer serotipo es AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10 o AAV11. En algunas modalidades, el segundo serotipo es AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10 o AAV11. En algunas modalidades, el primer serotipo es AAV2 y el segundo serotipo es AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10 o AAV11. En algunas modalidades, el primer serotipo es AAV2 y el segundo serotipo es AAV9.

Los vectores AAV-ARNgs ilustrativos contienen dos secuencias de ITR (repetición terminal invertida) que flanquean una región de secuencia central que comprende las secuencias de ARNgs. En algunas modalidades, las ITR se aíslan o derivan de un vector AAV del seriotipo AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 o cualquier combinación de estos. En algunas modalidades, una primera ITR se aísla o deriva de un vector AAV de un primer serotipo, una segunda ITR se aísla o deriva de un vector AAV de un segundo serotipo y una secuencia que codifica una proteína de la cápside del vector AAV-ARNgs se aísla o deriva de un vector AAV de un tercer

serotipo. En algunas modalidades, el primer serotipo y el segundo serotipo son iguales. En algunas modalidades, el primer serotipo y el segundo serotipo no son iguales. En algunas modalidades, el primer serotipo, el segundo serotipo y el tercer serotipo son iguales. En algunas modalidades, el primer serotipo, el segundo serotipo y el tercer serotipo no son iguales. En algunas modalidades, el primer serotipo es AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10 o AAV11. En algunas modalidades, el segundo serotipo es AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10 o AAV11. En algunas modalidades, el tercer serotipo es AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10 o AAV11. En algunas modalidades, el primer serotipo es AAV2, el segundo serotipo es AAV4 y el tercer serotipo es AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10 o AAV11. En algunas modalidades, el primer serotipo es AAV2, el segundo serotipo es AAV4 y el tercer serotipo es AAV9. Los vectores AAV-ARNgs ilustrativos contienen dos secuencias de ITR (repetición terminal invertida) que flanquean una región de secuencia central que comprende las secuencias de ARNgs. En algunas modalidades, las ITR se aíslan o derivan de un vector AAV del seriotipo AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 o cualquier combinación de estos. En algunas modalidades, las ITR comprenden o consisten en secuencias de longitud completa y/o de tipo salvaje para un serotipo de AAV. En algunas modalidades, las ITR comprenden o consisten en secuencias truncadas para un serotipo de AAV. En algunas modalidades, las ITR comprenden o consisten en secuencias alargadas para un serotipo de AAV. En algunas modalidades, las ITR comprenden o consisten en secuencias que comprenden una variación de secuencia en comparación con una secuencia de tipo salvaje para el mismo serotipo de AAV. En algunas modalidades, la variación de secuencia comprende una o más de una sustitución, eliminación, inserción, inversión o transposición. En algunas modalidades, las ITR comprenden o consisten en al menos 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149 o 150 pares de bases. En algunas modalidades, las ITR comprenden o consisten en al menos 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149 o 150 pares de bases. En algunas modalidades, las ITR tienen una longitud de 110 ± 10 pares de bases. En algunas modalidades, las ITR tienen una longitud de 120 ± 10 pares de bases. En algunas modalidades, las ITR tienen una longitud de 130 ± 10 pares de bases. En algunas modalidades, las ITR tienen una longitud de 140 ± 10 pares de bases. En algunas modalidades, las ITR tienen una longitud de 150 ± 10 pares de bases. En algunas modalidades, las ITR tienen una longitud de 115, 145 o 141 pares de bases. En algunas modalidades, las ITR tienen

una secuencia que se selecciona de la SEQ ID NO: 880, la SEQ ID NO: 881, la SEQ ID NO: 882 o la SEQ ID NO: 883.

En algunas modalidades, el vector AAV-ARNgs puede comprender elementos adicionales para facilitar el empaquetamiento del vector y la expresión del ARNgs. En algunas modalidades, el vector AAV-ARNgs puede comprender un elemento transponible. En algunas modalidades, el vector AAV-ARNgs puede comprender un elemento regulador. En algunas modalidades, el elemento regulador comprende un activador o un represor. En algunas modalidades, la secuencia de AAV-ARNgs puede comprender una secuencia no funcional o «de relleno». Las secuencias de relleno ilustrativas de la descripción pueden tener alguna identidad u homología (un porcentaje no nulo) con una secuencia genómica de un mamífero (incluido un ser humano). Alternativamente, las secuencias de relleno ilustrativas de la descripción pueden no tener identificación u homología con una secuencia genómica de un mamífero (incluido un ser humano). Las secuencias de relleno ilustrativas de la descripción pueden comprender o consistir en secuencias no codificantes de origen natural o que no se transcriben ni se traducen después de la administración del vector AAV a un sujeto.

En algunas modalidades, el vector AAV-ARNgs puede optimizarse para la producción en levaduras, bacterias, células de insectos o células de mamíferos. En algunas modalidades, el vector AAV-ARNgs puede optimizarse para la expresión en células humanas. En algunas modalidades, el vector AAV-Cas9 puede optimizarse para la expresión en un sistema de expresión de bacculovirus.

En algunas modalidades, el vector AAV-ARNgs comprende al menos un promotor. En algunas modalidades, el vector AAV-ARNgs comprende al menos dos promotores. En algunas modalidades, el vector AAV-ARNgs comprende al menos tres promotores. En algunas modalidades, el vector AAV-ARNgs comprende al menos cuatro promotores. En algunas modalidades, el vector AAV-ARNgs comprende al menos cinco promotores. Los promotores ilustrativos incluyen, por ejemplo, cadena ligera de inmunoglobulina, cadena pesada de inmunoglobulina, receptor de linfocitos-T, HLA DQ a y/o DQ β, β-interferón, interleucina-2, receptor de interleucina-2, MHC clase II 5, MHC clase II HLA-Dra, β-Actina, creatina quinasa muscular (MCK), prealbúmina (transtiretina), elastasa I, metalotioneína (MTII), colagenasa, albúmina, α-fetoproteína, t-globina, β-globina, c-fos, c-HA-*ras*, insulina, molécula de adhesión de células neurales (NCAM), α_1-antitripsina, histona H2B (TH2B), colágeno de ratón y/o tipo I, proteínas reguladas por glucosa (GRP94 y GRP78), hormona de crecimiento de rata, amiloide de suero humano A (SAA), troponina I (TN I), factor de crecimiento derivado de plaquetas (PDGF), distrofia muscular de Duchenne, SV40, polioma, retrovirus, virus del papiloma, virus de la hepatitis B, virus de la inmunodeficiencia humana, citomegalovirus (CMV) y virus de la leucemia del mono gibón. Otros promotores ilustrativos incluyen el promotor U6, el promotor H1 y el promotor 7SK.

En algunas modalidades, la secuencia que codifica el ARNg comprende una secuencia que se

selecciona de las SEQ ID NO: 383-705, 709-711, 715-717, 790-862, y 864.

En algunas modalidades, el vector AAV comprende una primera secuencia que codifica un ARNg y una segunda secuencia que codifica un ARNg, un primer promotor dirige la expresión de la primera secuencia que codifica un ARNg y un segundo promotor dirige la expresión de la segunda secuencia que codifica un ARNg. En algunas modalidades, el primer y el segundo promotor son iguales. En algunas modalidades, el primer y segundo promotor son diferentes. En algunas modalidades, el primer y segundo promotor se seleccionan del promotor H1, el promotor U6 y el promotor 7SK. En algunas modalidades, la primera secuencia que codifica un ARNg y la segunda secuencia que codifica un ARNg son idénticas. En algunas modalidades, la primera secuencia que codifica un ARNg y la segunda secuencia que codifica un ARNg no son idénticas.

En algunas modalidades, el vector AAV comprende una primera secuencia que codifica un ARNg, una segunda secuencia que codifica un ARNg y una tercera secuencia que codifica un ARNg, un primer promotor dirige la expresión de la primera secuencia que codifica un ARNg, un segundo promotor dirige la expresión de la segunda secuencia que codifica un ARNg, y un tercer promotor dirige la expresión de una tercera secuencia que codifica un ARNg. En algunas modalidades, al menos dos de los promotores primero, segundo y tercero son iguales. En algunas modalidades, cada uno de los promotores primero, segundo y tercero son diferentes. En algunas modalidades, los promotores primero, segundo y tercero se seleccionan del promotor H1, el promotor U6 y el promotor 7SK. En algunas modalidades, el primer promotor es el promotor U6. En algunas modalidades, el segundo promotor es el promotor H1. En algunas modalidades, el tercer promotor es el promotor 7SK. En algunas modalidades, el primer promotor es el promotor U6, el segundo promotor es el promotor H1, y el tercer promotor es el promotor 7SK. En algunas modalidades, la primera secuencia que codifica un ARNg, la segunda secuencia que codifica un ARNg y la tercera secuencia que codifica un ARNg son idénticas. En algunas modalidades, la primera secuencia que codifica un ARNg, la segunda secuencia que codifica un ARNg y la tercera secuencia que codifica un ARNg no son idénticas.

En algunas modalidades, el vector AAV comprende una primera secuencia que codifica un ARNg, una segunda secuencia que codifica un ARNg, una tercera secuencia que codifica un ARNg y una cuarta secuencia que codifica un ARNg, un primer promotor que dirige la expresión de la primera secuencia que codifica un ARNg, un segundo promotor dirige la expresión de la segunda secuencia que codifica un ARNg, un tercer promotor dirige la expresión de la tercera secuencia que codifica un ARNg y un cuarto promotor dirige la expresión de la cuarta secuencia que codifica un ARNg. En algunas modalidades, al menos dos de los promotores primero, segundo, tercero y cuarto son iguales. En algunas modalidades, al menos dos de los promotores primero, segundo, tercero y cuarto

son diferentes. En algunas modalidades, cada uno de los promotores primero, segundo, tercero y cuarto se selecciona del promotor H1, el promotor U6 y el promotor 7SK. En algunas modalidades, la primera secuencia que codifica un ARNg, la segunda secuencia que codifica un ARNg, la tercera secuencia que codifica un ARNg y la cuarta secuencia que codifica un ARNg son idénticas. En algunas modalidades, la primera secuencia que codifica un ARNg, la segunda secuencia que codifica un ARNg, la tercera secuencia que codifica un ARNg y la cuarta secuencia que codifica un ARNg no son idénticas.

En algunas modalidades, el vector AAV comprende una primera secuencia que codifica un ARNg, una segunda secuencia que codifica un ARNg, una tercera secuencia que codifica un ARNg, una cuarta secuencia que codifica un ARNg y una quinta secuencia que codifica un ARNg, un primer promotor dirige la expresión de la primera secuencia que codifica un ARNg, un segundo promotor dirige la expresión de la segunda secuencia que codifica un ARNg, un tercer promotor dirige la expresión de la tercera secuencia que codifica un ARNg, un cuarto promotor dirige la expresión de la cuarta secuencia que codifica un ARNg y un quinto promotor dirige la expresión de la quinta secuencia que codifica un ARNg. En algunas modalidades, al menos dos de los promotores primero, segundo, tercero, cuarto y quinto son iguales. En algunas modalidades, al menos dos de los promotores primero, segundo, tercero, cuarto y quinto son diferentes. En algunas modalidades, al menos dos de los promotores primero, segundo, tercero y cuarto son diferentes. En algunas modalidades, cada uno de los promotores primero, segundo, tercero, cuarto y quinto se selecciona del promotor H1, el promotor U6 y el promotor 7SK. En algunas modalidades, la primera secuencia que codifica un ARNg, la segunda secuencia que codifica un ARNg, la tercera secuencia que codifica un ARNg, la cuarta secuencia que codifica un ARNg y la quinta secuencia que codifica un ARNg son idénticas. En algunas modalidades, la primera secuencia que codifica un ARNg, la segunda secuencia que codifica un ARNg, la tercera secuencia que codifica un ARNg, la cuarta secuencia que codifica un ARNg y la quinta secuencia que codifica un ARNg no son idénticas.

En algunas modalidades, el vector AAV-ARNgs comprende una secuencia que se selecciona de la SEQ ID NO: 910, la SEQ ID NO: 911, la SEQ ID NO: 912 o la SEQ ID NO: 913. En algunas modalidades, el vector AAV-ARNgs comprende una secuencia que se selecciona de la SEQ ID NO: 914, la SEQ ID NO: 915, la SEQ ID NO: 916 o la SEQ ID NO: 917. En algunas modalidades, el vector AAV-ARNgs comprende una secuencia que se selecciona de la SEQ ID NO: 918, la SEQ ID NO: 919, la SEQ ID NO: 920 o la SEQ ID NO: 921. Los vectores AAV-ARNgs ilustrativos se proporcionan en la Tabla 5.

Tabla 5. Vectores AAV-ARNgs ilustrativos.

SEQ ID NO.	Secuencia
910	CCACTCCCTCTATGCGCGCTCGCTCACTCACTCGGCCCTGGAGACCAAAGGTCTCCAGACTGCCGGCCTCTGG CCGGCAGGGCCGAGTGAGTGAGCGAGCGCGCATAGAGGGAGTGGGTACCTCCATCATCTAGGTTTGCCAGAT CTGATATCGGCGCGCCCCTGGGCGCGCCCGAGTCCAACACCCGTGGGAATCCCATGGGCACCATGGCCCCTC GCTCCAAAAATGCTTTCGCGTCGCGCAGACACTGCTCGGTAGTTTCGGGGATCAGCGTTTGAGTAAGAGCCCG CGTCTGAACCCTCCGCGCCGCCCCGGCCCCAGTGGAAAGACGCGCAGGCAAAACGCACCACGTGACGGAGC GTGACCGCGCGCCGAGCGCGCGCCAAGGTCGGGCAGGAAGAGGGCCTATTTCCCATGATTCCTTCATATTTGC ATATACGATACAAGGCTGTTAGAGAGATAATTAGAATTAATTTGACTGTAAACACAAAGATATTAGTACAAAATAC GTGACGTAGAAAGTAATAATTTCTTGGGTAGTTTGCAGTTTTAAAATTATGTTTTAAAATGGACTATCATATGCTTA CCGTAACTTGAAAGTATTTCGATTTCTTGGCTTTATATATCTTGTGGAAAGGACGAAACACCGCACTAGAGTAAC AGTCTGACGTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAA AGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCGCTCGGCGCGCCCATATTTGCATGTCGCTATGTGTTCTG GGAAATCACCATAAACGTGAAATGTCTTTGGATTTGGGAATCTTATAAGTTCTGTATGAGACCACGGTACACCGC ACTAGAGTAACAGTCTGACGTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTAT CAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCTGACGGCGCGCCCTGCAGTATTTAGCAT GCCCCACCCATCTGCAAGGCATTCTGGATAGTGTCAAAACAGCCGGAAATCAAGTCCGTTTATCTCAAACTTTA GCATTTTGGGAATAAATGATATTTGCTATGCTGGTTAAATTAGATTTTAGTTAAATTTCCTGCTGAAGCTCTAGTA CGATAAGTAACTTGACCTAAGTGTAAAGTTGAGATTTCCTTCAGGTTTATATAGCTTGTGCGCCGCCTGGGTACA CCGCACTAGAGTAACAGTCTGACGTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCC GTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCGCTTGCGGCCGCCTCGAGTGATC AAAAAAACCAACACACGCTTCCAATGAAAATAAACGATCCTTTATTGCTAGCCTTTACTTGTACAGCTCGTCCAT GCCGAGAGTGATCCCGGCGGCGGTCACGAACTCCAGCAGGACCATGTGATCGCGCTTCTCGTTGGGGTCTTT GCTCAGGGCGGACTGGGTGCTCAGGTAGTGGTTGTCGGGCAGCAACACGGGGCCGTCGCCGATGGGGGTGT TCTGCTGGTAGTGGTCGGCGAGCTGCACGCTGCCGTCCTCGATGTTGTGGCGGATCTTGAAGTTCACCTTGAT GCCGTTCTTCTGCTTGTCGGCCATGATATAGACGTTGTGGCTGTTGTAGTTGTACTCCAGCTTGTGCCCCAGGA TGTTGCCGTCCTCCTTGAAGTCGATGCCCTTCAGCTCGATGCGGTTCACCAGGGTGTCGCCCTCGAACTTCAC CTCGGCGCGGGTCTTGTAGTTGCCGTCGTCCTTGAAGAAGATGGTGCGCTCCTGGACGTAGCCTTCGGGCATG GCGGACTTGAAGAAGTCGTGCTGCTTCATGTGGTCGGGGTAGCGGCTGAAGCACTGCACGCCGTAGGTCAGG GTGGTCACGAGGGTGGGCCAGGGCACGGGCAGCTTGCCGGTGGTGCAGATGAACTTCAGGGTCAGCTTGCC GTAGGTGGCATCGCCCTCGCCCTCGCCGGACACGCTGAACTTGTGGCCGTTTACGTCGCCGTCCAGCTCGAC CAGGATGGGCACCACCCCGGTGAACAGCTCCTCGCCCTTGCTCACCATGGTGGCGACCGGTGGATCCCGGGC CCGCGGGGTGGCTTTACCAACAGTACCCGGAATGCCAAGCTTACTTAGATCGCAGTCTCGACGCTGGCTGGCT CCTGAGTGTCTGTCTGTGCTGTGGAGGTGGTGGTAGAATGAGGGCAGCCCCTGTGCCCCTGGGTTATATAGAG GAGCCTACAGGGTGTGACTAGCCAGGAGGGGCTGTCCCCAGGGAGGGGCCCCTGAGAGCAGATGAGCTTTCA GCTCGTTGCCCGGGCACCGTGCCCACCCCGGACCCAGGCGTGCAGCTTGCCCAGCCCCATGGCCTTGTATGG GCTGCCCCAAGGGCTGACTTGCTCACTGGTTCCTAAACTAAGTGCTGAGTCTAGCTGGCGGGGGACAGCTGGC CCTTCGCCGGGAACATGGCATGCAGGGTTATTTTTAGAGGCAGCAGGTGTTGGGGGGGGGGGGGCAGCCACA TGTCTGGGTTAATTATAACCAGGCATCTCGGGTGTCCCCAGGCCTTGCCTCCTTACATGGGCACGTCGACGATA TCAGATCTAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGCC

	CGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGG
918	CCACTCCCTCTATGCGCGCTCGCTCACTCACTCGGCCCTGGAGACCAAAGGTCTCCAGACTGCCGGCCTCTGGCCGGCAGGGCCGAGTGAGTGAGCGAGCGCGCATAGAGGGAGTGGGTACCTCCATCATCTAGGTTTGCCAGATCTGATATCGGCGCGCCCCTGGGCGCGCCCGAGTCCAACACCCGTGGGAATCCCATGGGCACCATGGCCCCTCGCTCCAAAAATGCTTTCGCGTCGCGCAGACACTGCTCGGTAGTTTCGGGGATCAGCGTTTGAGTAAGAGCCCGCGTCTGAACCCTCCGCGCCGCCCCGGCCCCAGTGGAAAGACGCGCAGGCAAAACGCACCACGTGACGGAGCGTGACCGCGCGCCGAGCGCGCGCCAAGGTCGGGCAGGAAGAGGGCCTATTTCCCATGATTCCTTCATATTTGCATATACGATACAAGGCTGTTAGAGAGATAATTAGAATTAATTTGACTGTAAACACAAAGATATTAGTACAAAATACGTGACGTAGAAAGTAATAATTTCTTGGGTAGTTTGCAGTTTTAAAATTATGTTTTAAAATGGACTATCATATGCTTACCGTAACTTGAAAGTATTTCGATTTCTTGGCTTTATATATCTTGTGGAAAGGACGAAACACCGCACCAGAGTAACAGTCTGACGTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCTGACGGCGCGCCCTGCAGTATTTAGCATGCCCCACCCATCTGCAAGGCATTCTGGATAGTGTCAAAACAGCCGGAAATCAAGTCCGTTTATCTCAAACTTTAGCATTTTGGGAATAAATGATATTTGCTATGCTGGTTAAATTAGATTTTAGTTAAATTTCCTGCTGAAGCTCTAGTACGATAAGTAACTTGACCTAAGTGTAAAGTTGAGATTTCCTTCAGGTTTATATAGCTTGTGCGCCGCCTGGGTACACCGCACCAGAGTAACAGTCTGACGTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCGCTGTTTAAACCAACAAAATCAGCAGCTAATGAAGGCAAGTCAGCAGGTCACTCATCATTTTCCACTTCGGCAATGCAGTGGGATTATTCCAACAGAGGTTTTTCACAGCATTCCTTCAGTTAACTGGAGATCGAATCTTGATTTTCACAGATATACTTGGCAAGGTCCGCCCTGTCATCAGCACATTCAAGCAGATCTCCATGGCAGCATTCCGTGTGGACTTAGGTAAGATCTGTCACTAACTTGGAAACTTCTGCAAACTCAGCTTAGGGAAATCTCTGGCTCAGGCGAGCTACTGCCTCAGCTTAGAAAGCTCTTTCTCCAAATTATTGGAGACTGGCACACTTAAGTCCCTGTTAGGCAGACGAAGCCTTCCCTTCATCCCGAAGTTCATCGAGCTTTGGCAACAGGCAGGCAGCTTTATCAGCAGCTTGGCAACATTCTGTAAAAGCAGCTTTATACCTTTAAGCAAAGAAAAGGAGTTCCGGGGCATAAAAGTAAGGATGTCTTCTGGCAATTTATAATAAGTATTTTTTCAAAAATGTCTCTTCATTGTCATGAAAAGCAGTGCATCACACATCAACCTCTGGTCTCACCAATCGGGGGAGGTTTGGGTTGTTTACTTAGTGTTGCAAGAATTATTTTATTCTCTCAGGTTCTTGTTTTGCACAGCAGTCAGCTCATTCACCATAGGTTTCACGAAGAGTTGCTGCGGCCGCCTCGATAATACGACTCACTATAGGGTCGACGATATCAGATCTAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGG
914	CCACTCCCTCTATGCGCGCTCGCTCACTCACTCGGCCCTGGAGACCAAAGGTCTCCAGACTGCCGGCCTCTGGCCGGCAGGGCCGAGTGAGTGAGCGAGCGCGCATAGAGGGAGTGGGTACCTCCATCATCTAGGTTTGCCAGATCTGATATCGGCGCGCCCCTGGGCGCGCCCGAGTCCAACACCCGTGGGAATCCCATGGGCACCATGGCCCCTCGCTCCAAAAATGCTTTCGCGTCGCGCAGACACTGCTCGGTAGTTTCGGGGATCAGCGTTTGAGTAAGAGCCCGCGTCTGAACCCTCCGCGCCGCCCCGGCCCCAGTGGAAAGACGCGCAGGCAAAACGCACCACGTGACGGAGCGTGACCGCGCGCCGAGCGCGCGCCAAGGTCGGGCAGGAAGAGGGCCTATTTCCCATGATTCCTTCATATTTGC

	ATATACGATACAAGGCTGTTAGAGAGATAATTAGAATTAATTTGACTGTAAACACAAAGATATTAGTACAAAATAC GTGACGTAGAAAGTAATAATTTCTTGGGTAGTTTGCAGTTTTAAAATTATGTTTTAAAATGGACTATCATATGCTTA CCGTAACTTGAAAGTATTTCGATTTCTTGGCTTTATATATCTTGTGGAAAGGACGAAACACCGCACCAGAGTAAC AGTCTGAGGTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAA AGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCGCTCGGCGCGCCCATATTTGCATGTCGCTATGTGTTCTG GGAAATCACCATAAACGTGAAATGTCTTTGGATTTGGGAATCTTATAAGTTCTGTATGAGACCACGGTACACCGC ACCAGAGTAACAGTCTGAGGTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTAT CAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCTGACGGCGCGCCCTGCAGTATTTAGCAT GCCCCACCCATCTGCAAGGCATTCTGGATAGTGTCAAAACAGCCGGAAATCAAGTCCGTTTATCTCAAACTTTA GCATTTTGGGAATAAATGATATTTGCTATGCTGGTTAAATTAGATTTTAGTTAAATTTCCTGCTGAAGCTCTAGTA CGATAAGTAACTTGACCTAAGTGTAAAGTTGAGATTTCCTTCAGGTTTATATAGCTTGTGCGCCGCCTGGGTACA CCGCACCAGAGTAACAGTCTGAGGTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCC GTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCGCTGTTTAAACCAACAAAATCAGC AGCTAATGAAGGCAAGTCAGCAGGTCACTCATCATTTTCCACTTCGGCAATGCAGTGGGATTATTCCAACAGAG GTTTTTCACAGCATTCCTTCAGTTAACTGGAGATCGAATCTTGATTTTCACAGATATACTTGGCAAGGTCCGCCC TGTCATCAGCACATTCAAGCAGATCTCCATGGCAGCATTCCGTGTGGACTTAGGTAAGATCTGTCACTAACTTG GAAACTTCTGCAAACTCAGCTTAGGGAAATCTCTGGCTCAGGCGAGCTACTGCCTCAGCTTAGAAAGCTCTTTC TCCAAATTATTGGAGACTGGCACACTTAAGTCCCTGTTAGGCAGACGAAGCCTTCCCTTCATCCCGAAGTTCAT CGAGCTTTGGCAACAGGCAGGCAGCTTTATCAGCAGCTTGGCAACATTCTGTAAAAGCAGCTTTATACCTTTAA GCAAAGAAAAGGAGTTCCGGGGCATAAAAGTAAGGATGTCTTCTGGCAATTTATAATAAGTATTTTTTCAAAAAT GTCTCTTCATTGTCATGAAAAGCAGTGCATCACACATCAACCTCTGGTCTCACCAATCGGGGGAGGTTTGGGTT GTTTACTTAGTGTTGCAAGAATTATTTTATTCTCTCAGGTTCTTGTTTTGCACAGCAGTCAGCTCATTCACCATAG GTTTCACGAAGAGTTGCTGCGGCCGCCTCGATAATACGACTCACTATAGGGTCGACGATATCAGATCTAGGAAC CCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCG GGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGG
911	CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTT GGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTAG ATCTGATATCGGCGCGCCCCTGGGCGCGCCCGAGTCCAACACCCGTGGGAATCCCATGGGCACCATGGCCCC TCGCTCCAAAAATGCTTTCGCGTCGCGCAGACACTGCTCGGTAGTTTCGGGGATCAGCGTTTGAGTAAGAGCC CGCGTCTGAACCCTCCGCGCCGCCCCGGCCCCAGTGGAAAGACGCGCAGGCAAAACGCACCACGTGACGGA GCGTGACCGCGCGCCGAGCGCGCGCCAAGGTCGGGCAGGAAGAGGGCCTATTTCCCATGATTCCTTCATATTT GCATATACGATACAAGGCTGTTAGAGAGATAATTAGAATTAATTTGACTGTAAACACAAAGATATTAGTACAAAAT ACGTGACGTAGAAAGTAATAATTTCTTGGGTAGTTTGCAGTTTTAAAATTATGTTTTAAAATGGACTATCATATGC TTACCGTAACTTGAAAGTATTTCGATTTCTTGGCTTTATATATCTTGTGGAAAGGACGAAACACCGCACTAGAGT AACAGTCTGACGTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGA AAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCGCTCGGCGCGCCCATATTTGCATGTCGCTATGTGTT CTGGGAAATCACCATAAACGTGAAATGTCTTTGGATTTGGGAATCTTATAAGTTCTGTATGAGACCACGGTACAC CGCACTAGAGTAACAGTCTGACGTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCCG TTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCTGACGGCGCGCCCTGCAGTATTTAG CATGCCCCACCCATCTGCAAGGCATTCTGGATAGTGTCAAAACAGCCGGAAATCAAGTCCGTTTATCTCAAACT

	TTAGCATTTTGGGAATAAATGATATTTGCTATGCTGGTTAAATTAGATTTTAGTTAAATTTCCTGCTGAAGCTCTA GTACGATAAGTAACTTGACCTAAGTGTAAAGTTGAGATTTCCTTCAGGTTTATATAGCTTGTGCGCCGCCTGGGT ACACCGCACTAGAGTAACAGTCTGACGTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAATAAGGCTAG TCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCGCTTGCGGCCGCCTCGAGTG ATCAAAAAAACCAACACACGCTTCCAATGAAAATAAACGATCCTTTATTGCTAGCCTTTACTTGTACAGCTCGTCC ATGCCGAGAGTGATCCCGGCGGCGGTCACGAACTCCAGCAGGACCATGTGATCGCGCTTCTCGTTGGGGTCTT TGCTCAGGGCGGACTGGGTGCTCAGGTAGTGGTTGTCGGGCAGCAACACGGGGCCGTCGCCGATGGGGGTG TTCTGCTGGTAGTGGTCGGCGAGCTGCACGCTGCCGTCCTCGATGTTGTGGCGGATCTTGAAGTTCACCTTGA TGCCGTTCTTCTGCTTGTCGGCCATGATATAGACGTTGTGGCTGTTGTAGTTGTACTCCAGCTTGTGCCCCAGG ATGTTGCCGTCCTCCTTGAAGTCGATGCCCTTCAGCTCGATGCGGTTCACCAGGGTGTCGCCCTCGAACTTCAC CTCGGCGCGGGTCTTGTAGTTGCCGTCGTCCTTGAAGAAGATGGTGCGCTCCTGGACGTAGCCTTCGGGCATG GCGGACTTGAAGAAGTCGTGCTGCTTCATGTGGTCGGGGTAGCGGCTGAAGCACTGCACGCCGTAGGTCAGG GTGGTCACGAGGGTGGGCCAGGGCACGGGCAGCTTGCCGGTGGTGCAGATGAACTTCAGGGTCAGCTTGCC GTAGGTGGCATCGCCCTCGCCCTCGCCGGACACGCTGAACTTGTGGCCGTTTACGTCGCCGTCCAGCTCGAC CAGGATGGGCACCACCCCGGTGAACAGCTCCTCGCCCTTGCTCACCATGGTGGCGACCGGTGGATCCCGGGC CCGCGGGGTGGCTTTACCAACAGTACCCGGAATGCCAAGCTTACTTAGATCGCAGTCTCGACGCTGGCTGGCT CCTGAGTGTCTGTCTGTGCTGTGGAGGTGGTGGTAGAATGAGGGCAGCCCCTGTGCCCCTGGGTTATATAGAG GAGCCTACAGGGTGTGACTAGCCAGGAGGGGCTGTCCCCAGGGAGGGGCCCCTGAGAGCAGATGAGCTTTCA GCTCGTTGCCCGGGCACCGTGCCCACCCCGGACCCAGGCGTGCAGCTTGCCCAGCCCCATGGCCTTGTATGG GCTGCCCCAAGGGCTGACTTGCTCACTGGTTCCTAAACTAAGTGCTGAGTCTAGCTGGCGGGGGACAGCTGGC CCTTCGCCGGGAACATGGCATGCAGGGTTATTTTTAGAGGCAGCAGGTGTTGGGGGGGGGGGGGGCAGCCACA TGTCTGGGTTAATTATAACCAGGCATCTCGGGTGTCCCCAGGCCTTGCCTCCTTACATGGGCACGTCGACGATA TCAGATCTAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGG CGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCT GCAGG
919	CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTT GGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTAG ATCTGATATCGGCGCGCCCCTGGGCGCGCCCGAGTCCAACACCCGTGGGAATCCCATGGGCACCATGGCCCC TCGCTCCAAAAATGCTTTCGCGTCGCGCAGACACTGCTCGGTAGTTTCGGGGATCAGCGTTTGAGTAAGAGCC CGCGTCTGAACCCTCCGCGCCGCCCCGGCCCCAGTGGAAAGACGCGCAGGCAAAACGCACCACGTGACGGA GCGTGACCGCGCGCCGAGCGCGCGCCAAGGTCGGGCAGGAAGAGGGCCTATTTCCCATGATTCCTTCATATTT GCATATACGATACAAGGCTGTTAGAGAGATAATTAGAATTAATTTGACTGTAAACACAAAGATATTAGTACAAAAT ACGTGACGTAGAAAGTAATAATTTCTTGGGTAGTTTGCAGTTTTAAAATTATGTTTTAAAATGGACTATCATATGC TTACCGTAACTTGAAAGTATTTCGATTTCTTGGCTTTATATATCTTGTGGAAAGGACGAAACACCGCACCAGAGT AACAGTCTGACGTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGA AAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCGCTCGGCGCGCCCATATTTGCATGTCGCTATGTGTT CTGGGAAATCACCATAAACGTGAAATGTCTTTGGATTTGGGAATCTTATAAGTTCTGTATGAGACCACGGTACAC CGCACCAGAGTAACAGTCTGACGTTTAAGAGCTATGCTGGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCCG TTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCTGACGGCGCGCCCTGCAGTATTTAG CATGCCCCACCCATCTGCAAGGCATTCTGGATAGTGTCAAAACAGCCGGAAATCAAGTCCGTTTATCTCAAACT

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916	AAGATGACGGTTTGTCACATGGAGTTGGCAGGATGTTTGATTAAAAACATAACAGGAAGAAAAATGCCCCGCTG TGGGCGGACAAAATAGTTGGGAACTGGGAGGGGTGGAAATGGAGTTTTTAAGGATTATTTAGGGAAGAGTGAC AAAATAGATGGGAACTGGGTGTAGCGTCGTAAGCTAATACGAAAATTAAAAATGACAAAATAGTTTGGAACTAGA TTTCACTTATCTGGTTCGGATCTCCTAGGCGATATCAGTGATCACGGATCTCGACCAATTGACATTATTGAAGCA ACTAGTATCGATTTTATCAGGGTTATTGTCTCAGACCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCG CCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAG GGAGTGGCCAACTCCATCACTAGGGGTTCCTAGATCTGATATCGGCGCGCCCCTGGGCGCGCCCGAGTCCAA CACCCGTGGGAATCCCATGGGCACCATGGCCCCTCGCTCCAAAAATGCTTTCGCGTCGCGCAGACACTGCTCG GTAGTTTCGGGGATCAGCGTTTGAGTAAGAGCCCGCGTCTGAACCCTCCGCGCCGCCCCGGCCCCAGTGGAA AGACGCGCAGGCAAAACGCACCACGTGACGGAGCGTGACCGCGCGCCGAGCGCGCGCCAAGGTCGGGCAGG AAGAGGGCCTATTTCCCATGATTCCTTCATATTTGCATATACGATACAAGGCTGTTAGAGAGATAATTAGAATTAA TTTGACTGTAAACACAAAGATATTAGTACAAAATACGTGACGTAGAAAGTAATAATTTCTTGGGTAGTTTGCAGTT TTAAAATTATGTTTTAAAATGGACTATCATATGCTTACCGTAACTTGAAAGTATTTCGATTTCTTGGCTTTATATAT CTTGTGGAAAGGACGAAACACCGCACCAGAGTAACAGTCTGAGGTTTAAGAGCTATGCTGGAAACAGCATAGC AAGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCGCT CGGCGCGCCCATATTTGCATGTCGCTATGTGTTCTGGGAAATCACCATAAACGTGAAATGTCTTTGGATTTGGG AATCTTATAAGTTCTGTATGAGACCACGGTACACCGCACCAGAGTAACAGTCTGAGGTTTAAGAGCTATGCTGG AAACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTT GCGGCCGCTGACGGCGCGCCCTGCAGTATTTAGCATGCCCCACCCATCTGCAAGGCATTCTGGATAGTGTCAA AACAGCCGGAAATCAAGTCCGTTTATCTCAAACTTTAGCATTTTGGGAATAAATGATATTTGCTATGCTGGTTAAA TTAGATTTTAGTTAAATTTCCTGCTGAAGCTCTAGTACGATAAGTAACTTGACCTAAGTGTAAAGTTGAGATTTCC TTCAGGTTTATATAGCTTGTGCGCCGCCTGGGTACACCGCACCAGAGTAACAGTCTGAGGTTTAAGAGCTATGC TGGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTT TTTGCGGCCGCGCTGTTTAAACCAACAAAATCAGCAGCTAATGAAGGCAAGTCAGCAGGTCACTCATCATTTTC CACTTCGGCAATGCAGTGGGATTATTCCAACAGAGGTTTTTCACAGCATTCCTTCAGTTAACTGGAGATCGAATC TTGATTTTCACAGATATACTTGGCAAGGTCCGCCCTGTCATCAGCACATTCAAGCAGATCTCCATGGCAGCATTC CGTGTGGACTTAGGTAAGATCTGTCACTAACTTGGAAACTTCTGCAAACTCAGCTTAGGGAAATCTCTGGCTCA GGCGAGCTACTGCCTCAGCTTAGAAAGCTCTTTCTCCAAATTATTGGAGACTGGCACACTTAAGTCCCTGTTAG GCAGACGAAGCCTTCCCTTCATCCCGAAGTTCATCGAGCTTTGGCAACAGGCAGGCAGCTTTATCAGCAGCTTG GCAACATTCTGTAAAAGCAGCTTTATACCTTTAAGCAAAGAAAAGGAGTTCCGGGGCATAAAAGTAAGGATGTCT TCTGGCAATTTATAATAAGTATTTTTTCAAAAATGTCTCTTCATTGTCATGAAAAGCAGTGCATCACACATCAACC TCTGGTCTCACCAATCGGGGGAGGTTTGGGTTGTTTACTTAGTGTTGCAAGAATTATTTTATTCTCTCAGGTTCT TGTTTTGCACAGCAGTCAGCTCATTCACCATAGGTTTCACGAAGAGTTGCTGCGGCCGCCTCGATAATACGACT CACTATAGGGTCGACGATATCAGATCTAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCG CTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCG AGCGAGCGCGCAGCTGCCTGCAGGCATGCAAGCTGTAGCCAACCACTAGAACTATAGCTAGAGTCCTGGGCG

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913	AAGATGACGGTTTGTCACATGGAGTTGGCAGGATGTTTGATTAAAAACATAACAGGAAGAAAAATGCCCCGCTG TGGGCGGACAAAATAGTTGGGAACTGGGAGGGGTGGAAATGGAGTTTTTAAGGATTATTTAGGGAAGAGTGAC AAAATAGATGGGAACTGGGTGTAGCGTCGTAAGCTAATACGAAAATTAAAAATGACAAAATAGTTTGGAACTAGA TTTCACTTATCTGGTTCGGATCTCCTAGGCGATATCAGTGATCACGGATCTCGACCAATTGACATTATTGAAGCA ACTAGTATCGATTTTATCAGGGTTATTGTCTCAGACCACTCCCTCTATGCGCGCTCGCTCACTCACTCGGCCCT GGAGACCAAAGGTCTCCAGACTGCCGGCCTCTGGCCGGCAGGGCCGAGTGAGTGAGCGAGCGCGCATAGAG GGAGTGGGTACCTCCATCATCTAGGTTTGCCAGATCTGATATCGGCGCGCCCCTGGGCGCGCCCGAGTCCAAC ACCCGTGGGAATCCCATGGGCACCATGGCCCCTCGCTCCAAAAATGCTTTCGCGTCGCGCAGACACTGCTCGG TAGTTTCGGGGATCAGCGTTTGAGTAAGAGCCCGCGTCTGAACCCTCCGCGCCGCCCCGGCCCCAGTGGAAA GACGCGCAGGCAAAACGCACCACGTGACGGAGCGTGACCGCGCGCCGAGCGCGCGCCAAGGTCGGGCAGGA AGAGGGCCTATTTCCCATGATTCCTTCATATTTGCATATACGATACAAGGCTGTTAGAGAGATAATTAGAATTAAT TTGACTGTAAACACAAAGATATTAGTACAAAATACGTGACGTAGAAAGTAATAATTTCTTGGGTAGTTTGCAGTTT TAAAATTATGTTTTAAAATGGACTATCATATGCTTACCGTAACTTGAAAGTATTTCGATTTCTTGGCTTTATATATC TTGTGGAAAGGACGAAACACCGCACTAGAGTAACAGTCTGACGTTTAAGAGCTATGCTGGAAACAGCATAGCAA GTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCGCTTC GGCGCGCCCATATTTGCATGTCGCTATGTGTTCTGGGAAATCACCATAAACGTGAAATGTCTTTGGATTTGGGA ATCTTATAAGTTCTGTATGAGACCACGGTACACCGCACTAGAGTAACAGTCTGACGTTTAAGAGCTATGCTGGAA ACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGC GGCCGCTGACGGCGCGCCCTGCAGTATTTAGCATGCCCCACCCATCTGCAAGGCATTCTGGATAGTGTCAAAA CAGCCGGAAATCAAGTCCGTTTATCTCAAACTTTAGCATTTTGGGAATAAATGATATTTGCTATGCTGGTTAAATT AGATTTTAGTTAAATTTCCTGCTGAAGCTCTAGTACGATAAGTAACTTGACCTAAGTGTAAAGTTGAGATTTCCTT

	CAGGTTTATATAGCTTGTGCGCCGCCTGGGTACACCGCACTAGAGTAACAGTCTGACGTTTAAGAGCTATGCTG GAAACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTT TGCGGCCGCGCTGCGGCCGCCTCGAGTGATCAAAAAAACCAACACACGCTTCCAATGAAAATAAACGATCCTTT ATTGCTAGCCTTTACTTGTACAGCTCGTCCATGCCGAGAGTGATCCCGGCGGCGGTCACGAACTCCAGCAGGA CCATGTGATCGCGCTTCTCGTTGGGGTCTTTGCTCAGGGCGGACTGGGTGCTCAGGTAGTGGTTGTCGGGCAG CAACACGGGGCCGTCGCCGATGGGGGTGTTCTGCTGGTAGTGGTCGGCGAGCTGCACGCTGCCGTCCTCGAT GTTGTGGCGGATCTTGAAGTTCACCTTGATGCCGTTCTTCTGCTTGTCGGCCATGATATAGACGTTGTGGCTGT TGTAGTTGTACTCCAGCTTGTGCCCCAGGATGTTGCCGTCCTCCTTGAAGTCGATGCCCTTCAGCTCGATGCGG TTCACCAGGGTGTCGCCCTCGAACTTCACCTCGGCGCGGGTCTTGTAGTTGCCGTCGTCCTTGAAGAAGATGG TGCGCTCCTGGACGTAGCCTTCGGGCATGGCGGACTTGAAGAAGTCGTGCTGCTTCATGTGGTCGGGGTAGC GGCTGAAGCACTGCACGCCGTAGGTCAGGGTGGTCACGAGGGTGGGCCAGGGCACGGGCAGCTTGCCGGTG GTGCAGATGAACTTCAGGGTCAGCTTGCCGTAGGTGGCATCGCCCTCGCCCTCGCCGGACACGCTGAACTTGT GGCCGTTTACGTCGCCGTCCAGCTCGACCAGGATGGGCACCACCCCGGTGAACAGCTCCTCGCCCTTGCTCA CCATGGTGGCGACCGGTGGATCCCGGGCCCGCGGGGTGGCTTTACCAACAGTACCCGGAATGCCAAGCTTAC TTAGATCGCAGTCTCGACGCTGGCTGGCTCCTGAGTGTCTGTCTGTGCTGTGGAGGTGGTGGTAGAATGAGGG CAGCCCCTGTGCCCCTGGGTTATATAGAGGAGCCTACAGGGTGTGACTAGCCAGGAGGGGCTGTCCCCAGGG AGGGGCCCCTGAGAGCAGATGAGCTTTCAGCTCGTTGCCCGGGCACCGTGCCCACCCCGGACCCAGGCGTGC AGCTTGCCCAGCCCCATGGCCTTGTATGGGCTGCCCCAAGGGCTGACTTGCTCACTGGTTCCTAAACTAAGTG CTGAGTCTAGCTGGCGGGGGACAGCTGGCCCTTCGCCGGGAACATGGCATGCAGGGTTATTTTTAGAGGCAG CAGGTGTTGGGGGGGGGGGGGCAGCCACATGTCTGGGTTAATTATAACCAGGCATCTCGGGTGTCCCCAGGC CTTGCCTCCTTACATGGGCACGTCGACGATATCAGATCTAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCT CTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGC CTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCATGCAAGCTGTAGCCAACCACTAGAACTATAGCTAG AGTCCTGGGCGAACAAACGATGCTCGCCTTCCAGAAAACCGAGGATGCGAACCACTTCATCCGGGGTCAGCAC CACCGGCAAGCGCCGCGACGGCCGAGGTCTTCCGATCTCCTGAAGCCAGGGCAGATCCGTGCACAGCACCTT GCCGTAGAAGAACAGCAAGGCCGCCAATGCCTGACGATGCGTGGAGACCGAAACCTTGCGCTCGTTCGCCAG CCAGGACAGAAATGCCTCGACTTCGCTGCTGCCCAAGGTTGCCGGGTGACGCACACCGTGGAAACGGATGAA GGCACGAACCCAGTTGACATAAGCCTGTTCGGTTCGTAAACTGTAATGCAAGTAGCGTATGCGCTCACGCAACT GGTCCAGAACCTTGACCGAACGCAGCGGTGGTAACGGCGCAGTGGCGGTTTTCATGGCTTGTTATGACTGTTT TTTTGTACAGTCTATGCCTCGGGCATCCAAGCAGCAAGCGCGTTACGCCGTGGGTCGATGTTTGATGTTATGGA GCAGCAACGATGTTACGCAGCAGCAACGATGTTACGCAGCAGGGCAGTCGCCCTAAAACAAAGTTAGGTGGCT CAAGTATGGGCATCATTCGCACATGTAGGCTCGGCCCTGACCAAGTCAAATCCATGCGGGCTGCTCTTGATCTT TTCGGTCGTGAGTTCGGAGACGTAGCCACCTACTCCCAACATCAGCCGGACTCCGATTACCTCGGGAACTTGC TCCGTAGTAAGACATTCATCGCGCTTGCTGCCTTCGACCAAGAAGCGGTTGTTGGCGCTCTCGCGGCTTACGTT CTGCCCAAGTTTGAGCAGCCGCGTAGTGAGATCTATATCTATGATCTCGCAGTCTCCGGCGAGCACCGGAGGC AGGGCATTGCCACCGCGCTCATCAATCTCCTCAAGCATGAGGCCAACGCGCTTGGTGCTTATGTGATCTACGT GCAAGCAGATTACGGTGACGATCCCGCAGTGGCTCTCTATACAAAGTTGGGCATACGGGAAGAAGTGATGCAC TTTGATATCGACCCAAGTACCGCCACCTAACAATTCGTTCAAGCCGAGATCGGCTTCCCGGCCGCGGAGTTGTT CGGTAAATTGTCACAACGCCGCGAATATAGTCTTTACCATGCCCTTGGCCACGCCCCTCTTTAATACGACGGGC AATTTGCACTTCAGAAAATGAAGAGTTTGCTTTAGCCATAACAAAAGTCCAGTATGCTTTTTCACAGCATAACTGG ACTGATTTCAGTTTACAACTATTCTGTCTAGTTTAAGACTTTATTGTCATAGTTTAGATCTATTTTGTTCAGTTTAA

	GACTTTATTGTCCGCCCACACCCGCTTACGC
921	AAGATGACGGTTTGTCACATGGAGTTGGCAGGATGTTTGATTAAAAACATAACAGGAAGAAAAATGCCCCGCTG TGGGCGGACAAAATAGTTGGGAACTGGGAGGGGTGGAAATGGAGTTTTTAAGGATTATTTAGGGAAGAGTGAC AAAATAGATGGGAACTGGGTGTAGCGTCGTAAGCTAATACGAAAATTAAAAATGACAAAATAGTTTGGAACTAGA TTTCACTTATCTGGTTCGGATCTCCTAGGCGATATCAGTGATCACGGATCTCGACCAATTGACATTATTGAAGCA ACTAGTATCGATTTTATCAGGGTTATTGTCTCAGACCACTCCCTCTATGCGCGCTCGCTCACTCACTCGGCCCT GGAGACCAAAGGTCTCCAGACTGCCGGCCTCTGGCCGGCAGGGCCGAGTGAGTGAGCGAGCGCGCATAGAG GGAGTGGGTACCTCCATCATCTAGGTTTGCCAGATCTGATATCGGCGCGCCCCTGGGCGCGCCCGAGTCCAAC ACCCGTGGGAATCCCATGGGCACCATGGCCCCTCGCTCCAAAAATGCTTTCGCGTCGCGCAGACACTGCTCGG TAGTTTCGGGGATCAGCGTTTGAGTAAGAGCCCGCGTCTGAACCCTCCGCGCCGCCCCGGCCCCAGTGGAAA GACGCGCAGGCAAAACGCACCACGTGACGGAGCGTGACCGCGCGCCGAGCGCGCGCCAAGGTCGGGCAGGA AGAGGGCCTATTTCCCATGATTCCTTCATATTTGCATATACGATACAAGGCTGTTAGAGAGATAATTAGAATTAAT TTGACTGTAAACACAAAGATATTAGTACAAAATACGTGACGTAGAAAGTAATAATTTCTTGGGTAGTTTGCAGTTT TAAAATTATGTTTTAAAATGGACTATCATATGCTTACCGTAACTTGAAAGTATTTCGATTTCTTGGCTTTATATATC TTGTGGAAAGGACGAAACACCGCACCAGAGTAACAGTCTGACGTTTAAGAGCTATGCTGGAAACAGCATAGCAA GTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCGCTCG GCGCGCCCATATTTGCATGTCGCTATGTGTTCTGGGAAATCACCATAAACGTGAAATGTCTTTGGATTTGGGAAT CTTATAAGTTCTGTATGAGACCACGGTACACCGCACCAGAGTAACAGTCTGACGTTTAAGAGCTATGCTGGAAA CAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGCG GCCGCTGACGGCGCGCCCTGCAGTATTTAGCATGCCCCACCCATCTGCAAGGCATTCTGGATAGTGTCAAAAC AGCCGGAAATCAAGTCCGTTTATCTCAAACTTTAGCATTTTGGGAATAAATGATATTTGCTATGCTGGTTAAATTA GATTTTAGTTAAATTTCCTGCTGAAGCTCTAGTACGATAAGTAACTTGACCTAAGTGTAAAGTTGAGATTTCCTTC AGGTTTATATAGCTTGTGCGCCGCCTGGGTACACCGCACCAGAGTAACAGTCTGACGTTTAAGAGCTATGCTGG AAACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTT GCGGCCGCGCTGTTTAAACCAACAAAATCAGCAGCTAATGAAGGCAAGTCAGCAGGTCACTCATCATTTTCCAC TTCGGCAATGCAGTGGGATTATTCCAACAGAGGTTTTTCACAGCATTCCTTCAGTTAACTGGAGATCGAATCTTG ATTTTCACAGATATACTTGGCAAGGTCCGCCCTGTCATCAGCACATTCAAGCAGATCTCCATGGCAGCATTCCG TGTGGACTTAGGTAAGATCTGTCACTAACTTGGAAACTTCTGCAAACTCAGCTTAGGGAAATCTCTGGCTCAGG CGAGCTACTGCCTCAGCTTAGAAAGCTCTTTCTCCAAATTATTGGAGACTGGCACACTTAAGTCCCTGTTAGGCA GACGAAGCCTTCCCTTCATCCCGAAGTTCATCGAGCTTTGGCAACAGGCAGGCAGCTTTATCAGCAGCTTGGCA ACATTCTGTAAAAGCAGCTTTATACCTTTAAGCAAAGAAAAGGAGTTCCGGGGCATAAAAGTAAGGATGTCTTCT GGCAATTTATAATAAGTATTTTTTCAAAAATGTCTCTTCATTGTCATGAAAAGCAGTGCATCACACATCAACCTCT GGTCTCACCAATCGGGGGAGGTTTGGGTTGTTTACTTAGTGTTGCAAGAATTATTTTATTCTCTCAGGTTCTTGT TTTGCACAGCAGTCAGCTCATTCACCATAGGTTTCACGAAGAGTTGCTGCGGCCGCCTCGATAATACGACTCAC TATAGGGTCGACGATATCAGATCTAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTC GCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGC GAGCGCGCAGAGAGGGAGTGGCATGCAAGCTGTAGCCAACCACTAGAACTATAGCTAGAGTCCTGGGCGAAC AAACGATGCTCGCCTTCCAGAAAACCGAGGATGCGAACCACTTCATCCGGGGTCAGCACCACCGGCAAGCGCC GCGACGGCCGAGGTCTTCCGATCTCCTGAAGCCAGGGCAGATCCGTGCACAGCACCTTGCCGTAGAAGAACA

	GCAAGGCCGCCAATGCCTGACGATGCGTGGAGACCGAAACCTTGCGCTCGTTCGCCAGCCAGGACAGAAATG CCTCGACTTCGCTGCTGCCCAAGGTTGCCGGGTGACGCACACCGTGGAAACGGATGAAGGCACGAACCCAGT TGACATAAGCCTGTTCGGTTCGTAAACTGTAATGCAAGTAGCGTATGCGCTCACGCAACTGGTCCAGAACCTTG ACCGAACGCAGCGGTGGTAACGGCGCAGTGGCGGTTTTCATGGCTTGTTATGACTGTTTTTTTGTACAGTCTAT GCCTCGGGCATCCAAGCAGCAAGCGCGTTACGCCGTGGGTCGATGTTTGATGTTATGGAGCAGCAACGATGTT ACGCAGCAGCAACGATGTTACGCAGCAGGGCAGTCGCCCTAAAACAAAGTTAGGTGGCTCAAGTATGGGCATC ATTCGCACATGTAGGCTCGGCCCTGACCAAGTCAAATCCATGCGGGCTGCTCTTGATCTTTTCGGTCGTGAGTT CGGAGACGTAGCCACCTACTCCCAACATCAGCCGGACTCCGATTACCTCGGGAACTTGCTCCGTAGTAAGACA TTCATCGCGCTTGCTGCCTTCGACCAAGAAGCGGTTGTTGGCGCTCTCGCGGCTTACGTTCTGCCCAAGTTTGA GCAGCCGCGTAGTGAGATCTATATCTATGATCTCGCAGTCTCCGGCGAGCACCGGAGGCAGGGCATTGCCACC GCGCTCATCAATCTCCTCAAGCATGAGGCCAACGCGCTTGGTGCTTATGTGATCTACGTGCAAGCAGATTACGG TGACGATCCCGCAGTGGCTCTCTATACAAAGTTGGGCATACGGGAAGAAGTGATGCACTTTGATATCGACCCAA GTACCGCCACCTAACAATTCGTTCAAGCCGAGATCGGCTTCCCGGCCGCGGAGTTGTTCGGTAAATTGTCACAA CGCCGCGAATATAGTCTTTACCATGCCCTTGGCCACGCCCCTCTTTAATACGACGGGCAATTTGCACTTCAGAA AATGAAGAGTTTGCTTTAGCCATAACAAAAGTCCAGTATGCTTTTTCACAGCATAACTGGACTGATTTCAGTTTAC AACTATTCTGTCTAGTTTAAGACTTTATTGTCATAGTTTAGATCTATTTTGTTCAGTTTAAGACTTTATTGTCCGCC CACACCCGCTTACGC
917	AAGATGACGGTTTGTCACATGGAGTTGGCAGGATGTTTGATTAAAAACATAACAGGAAGAAAAATGCCCCGCTG TGGGCGGACAAAATAGTTGGGAACTGGGAGGGGTGGAAATGGAGTTTTTAAGGATTATTTAGGGAAGAGTGAC AAAATAGATGGGAACTGGGTGTAGCGTCGTAAGCTAATACGAAAATTAAAAATGACAAAATAGTTTGGAACTAGA TTTCACTTATCTGGTTCGGATCTCCTAGGCGATATCAGTGATCACGGATCTCGACCAATTGACATTATTGAAGCA ACTAGTATCGATTTTATCAGGGTTATTGTCTCAGACCACTCCCTCTATGCGCGCTCGCTCACTCACTCGGCCCT GGAGACCAAAGGTCTCCAGACTGCCGGCCTCTGGCCGGCAGGGCCGAGTGAGTGAGCGAGCGCGCATAGAG GGAGTGGGTACCTCCATCATCTAGGTTTGCCAGATCTGATATCGGCGCGCCCCTGGGCGCGCCCGAGTCCAAC ACCCGTGGGAATCCCATGGGCACCATGGCCCCTCGCTCCAAAAATGCTTTCGCGTCGCGCAGACACTGCTCGG TAGTTTCGGGGATCAGCGTTTGAGTAAGAGCCCGCGTCTGAACCCTCCGCGCCGCCCCGGCCCCAGTGGAAA GACGCGCAGGCAAAACGCACCACGTGACGGAGCGTGACCGCGCGCCGAGCGCGCGCCAAGGTCGGGCAGGA AGAGGGCCTATTTCCCATGATTCCTTCATATTTGCATATACGATACAAGGCTGTTAGAGAGATAATTAGAATTAAT TTGACTGTAAACACAAAGATATTAGTACAAAATACGTGACGTAGAAAGTAATAATTTCTTGGGTAGTTTGCAGTTT TAAAATTATGTTTTAAAATGGACTATCATATGCTTACCGTAACTTGAAAGTATTTCGATTTCTTGGCTTTATATATC TTGTGGAAAGGACGAAACACCGCACCAGAGTAACAGTCTGAGGTTTAAGAGCTATGCTGGAAACAGCATAGCA AGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTGCGGCCGCGCTC GGCGCGCCCATATTTGCATGTCGCTATGTGTTCTGGGAAATCACCATAAACGTGAAATGTCTTTGGATTTGGGA ATCTTATAAGTTCTGTATGAGACCACGGTACACCGCACCAGAGTAACAGTCTGAGGTTTAAGAGCTATGCTGGA AACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTTTTG CGGCCGCTGACGGCGCGCCCTGCAGTATTTAGCATGCCCCACCCATCTGCAAGGCATTCTGGATAGTGTCAAA ACAGCCGGAAATCAAGTCCGTTTATCTCAAACTTTAGCATTTTGGGAATAAATGATATTTGCTATGCTGGTTAAAT TAGATTTTAGTTAAATTTCCTGCTGAAGCTCTAGTACGATAAGTAACTTGACCTAAGTGTAAAGTTGAGATTTCCT TCAGGTTTATATAGCTTGTGCGCCGCCTGGGTACACCGCACCAGAGTAACAGTCTGAGGTTTAAGAGCTATGCT GGAAACAGCATAGCAAGTTTAAATAAGGCTAGTCCGTTATCAACTTGAAAAAGTGGCACCGAGTCGGTGCTTTTT

	TTGCGGCCGCGCTGTTTAAACCAACAAAATCAGCAGCTAATGAAGGCAAGTCAGCAGGTCACTCATCATTTTCC ACTTCGGCAATGCAGTGGGATTATTCCAACAGAGGTTTTTCACAGCATTCCTTCAGTTAACTGGAGATCGAATCT TGATTTTCACAGATATACTTGGCAAGGTCCGCCCTGTCATCAGCACATTCAAGCAGATCTCCATGGCAGCATTC CGTGTGGACTTAGGTAAGATCTGTCACTAACTTGGAAACTTCTGCAAACTCAGCTTAGGGAAATCTCTGGCTCA GGCGAGCTACTGCCTCAGCTTAGAAAGCTCTTTCTCCAAATTATTGGAGACTGGCACACTTAAGTCCCTGTTAG GCAGACGAAGCCTTCCCTTCATCCCGAAGTTCATCGAGCTTTGGCAACAGGCAGGCAGCTTTATCAGCAGCTTG GCAACATTCTGTAAAAGCAGCTTTATACCTTTAAGCAAAGAAAAGGAGTTCCGGGGCATAAAAGTAAGGATGTCT TCTGGCAATTTATAATAAGTATTTTTTCAAAAATGTCTCTTCATTGTCATGAAAAGCAGTGCATCACACATCAACC TCTGGTCTCACCAATCGGGGGAGGTTTGGGTTGTTTACTTAGTGTTGCAAGAATTATTTTATTCTCTCAGGTTCT TGTTTTGCACAGCAGTCAGCTCATTCACCATAGGTTTCACGAAGAGTTGCTGCGGCCGCCTCGATAATACGACT CACTATAGGGTCGACGATATCAGATCTAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCG CTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCG AGCGAGCGCGCAGAGAGGGAGTGGCATGCAAGCTGTAGCCAACCACTAGAACTATAGCTAGAGTCCTGGGCG AACAAACGATGCTCGCCTTCCAGAAAACCGAGGATGCGAACCACTTCATCCGGGGTCAGCACCACCGGCAAGC GCCGCGACGGCCGAGGTCTTCCGATCTCCTGAAGCCAGGGCAGATCCGTGCACAGCACCTTGCCGTAGAAGA ACAGCAAGGCCGCCAATGCCTGACGATGCGTGGAGACCGAAACCTTGCGCTCGTTCGCCAGCCAGGACAGAA ATGCCTCGACTTCGCTGCTGCCCAAGGTTGCCGGGTGACGCACACCGTGGAAACGGATGAAGGCACGAACCC AGTTGACATAAGCCTGTTCGGTTCGTAAACTGTAATGCAAGTAGCGTATGCGCTCACGCAACTGGTCCAGAACC TTGACCGAACGCAGCGGTGGTAACGGCGCAGTGGCGGTTTTCATGGCTTGTTATGACTGTTTTTTTGTACAGTC TATGCCTCGGGCATCCAAGCAGCAAGCGCGTTACGCCGTGGGTCGATGTTTGATGTTATGGAGCAGCAACGAT GTTACGCAGCAGCAACGATGTTACGCAGCAGGGCAGTCGCCCTAAAACAAAGTTAGGTGGCTCAAGTATGGGC ATCATTCGCACATGTAGGCTCGGCCCTGACCAAGTCAAATCCATGCGGGCTGCTCTTGATCTTTTCGGTCGTGA GTTCGGAGACGTAGCCACCTACTCCCAACATCAGCCGGACTCCGATTACCTCGGGAACTTGCTCCGTAGTAAG ACATTCATCGCGCTTGCTGCCTTCGACCAAGAAGCGGTTGTTGGCGCTCTCGCGGCTTACGTTCTGCCCAAGTT TGAGCAGCCGCGTAGTGAGATCTATATCTATGATCTCGCAGTCTCCGGCGAGCACCGGAGGCAGGGCATTGCC ACCGCGCTCATCAATCTCCTCAAGCATGAGGCCAACGCGCTTGGTGCTTATGTGATCTACGTGCAAGCAGATTA CGGTGACGATCCCGCAGTGGCTCTCTATACAAAGTTGGGCATACGGGAAGAAGTGATGCACTTTGATATCGAC CCAAGTACCGCCACCTAACAATTCGTTCAAGCCGAGATCGGCTTCCCGGCCGCGGAGTTGTTCGGTAAATTGT CACAACGCCGCGAATATAGTCTTTACCATGCCCTTGGCCACGCCCCTCTTTAATACGACGGGCAATTTGCACTT CAGAAAATGAAGAGTTTGCTTTAGCCATAACAAAAGTCCAGTATGCTTTTTCACAGCATAACTGGACTGATTTCA GTTTACAACTATTCTGTCTAGTTTAAGACTTTATTGTCATAGTTTAGATCTATTTTGTTCAGTTTAAGACTTTATTGT CCGCCCACACCCGCTTACGC

En algunas modalidades de las construcciones de edición génica de la descripción, incluidas aquellas modalidades que abarcan las SEQ ID NO: 910 a 921, la construcción comprende o consiste en un primer promotor, una primera secuencia que codifica un ARNg, un segundo promotor y una segunda secuencia que codifica un ARNg, un tercer promotor y una tercera secuencia que codifica un ARNg. Las secuencias que codifican los ARNg ilustrativas de la descripción son las SEQ ID NO. 383-705, 709-711, 715-717, 790-862, 864. En algunas modalidades, la secuencia que codifica el ARNg es

CACTAGAGTAACAGTCTGAC (SEQ ID NO. 708). En algunas modalidades, la secuencia que codifica el ARNg es CACCAGAGTAACAGTCTGAG (SEQ ID NO. 714). En algunas modalidades, la secuencia que codifica el ARNg es CACCAGAGTAACAGTCTGAC (SEQ ID NO. 863). En algunas modalidades, la construcción comprende, de 5' a 3', un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO. 708, un segundo promotor, una segunda secuencia que codifica un ARNg de la SEQ ID NO. 708, un tercer promotor y una tercera secuencia que codifica un ARNg de la SEQ ID NO. 708. En algunas modalidades, la construcción comprende, de 5' a 3', un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO. 714, un segundo promotor, una segunda secuencia que codifica un ARNg de la SEQ ID NO. 714, un tercer promotor y una tercera secuencia que codifica un ARNg de la SEQ ID NO. 714. En algunas modalidades, la construcción comprende, de 5' a 3', un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO. 863, un segundo promotor, una segunda secuencia que codifica un ARNg de la SEQ ID NO. 863, un tercer promotor y una tercera secuencia que codifica un ARNg de la SEQ ID NO. 863. Los promotores ilustrativos de la descripción incluyen el promotor U6 que tiene una secuencia de CGAGTCCAACACCCGTGGGAATCCCATGGGCACCATGGCCCCTCGCTCCAAAAATGCTTTCGCG TCGCGCAGACACTGCTCGGTAGTTTCGGGGATCAGCGTTTGAGTAAGAGCCCGCGTCTGAACCC TCCGCGCCGCCCCGGCCCCAGTGGAAAGACGCGCAGGCAAAACGCACCACGTGACGGAGCGT GACCGCGCGCCGAGCGCGCGCCAAGGTCGGGCAGGAAGAGGGCCTATTTCCCATGATTCCTTC ATATTTGCATATACGATACAAGGCTGTTAGAGAGATAATTAGAATTAATTTGACTGTAAACACAAAG ATATTAGTACAAAATACGTGACGTAGAAAGTAATAATTTCTTGGGTAGTTTGCAGTTTTAAAATTAT GTTTTAAAATGGACTATCATATGCTTACCGTAACTTGAAAGTATTTCGATTTCTTGGCTTTATATAT CTTGTGGAAAGGACGAAA (SEQ ID NO: 922), el promotor H1 que tiene una secuencia de GCTCGGCGCGCCCATATTTGCATGTCGCTATGTGTTCTGGGAAATCACCATAAACGTGAAATGTC TTTGGATTTGGGAATCTTATAAGTTCTGTATGAGACCACGGTA (SEQ ID. No923), y el promotor 7SK que tiene una secuencia de TGACGGCGCGCCCTGCAGTATTTAGCATGCCCCACCCATCTGCAAGGCATTCTGGATAGTGTCA AAACAGCCGGAAATCAAGTCCGTTTATCTCAAACTTTAGCATTTTGGGAATAAATGATATTTGCTAT GCTGGTTAAATTAGATTTTAGTTAAATTTCCTGCTGAAGCTCTAGTACGATAAGTAACTTGACCTAA GTGTAAAGTTGAGATTTCCTTCAGGTTTATATAGCTTGTGCGCCGCCTGGGTA (SEQ ID NO. 924). En algunas modalidades, los promotores primero, segundo y tercero se seleccionan individualmente del promotor U6 (SEQ ID NO: 922), el promotor H1 (SEQ ID NO: 923) y el promotor 7SK (SEQ ID NO: 924). En algunas modalidades, los promotores primero, segundo y tercero se seleccionan individualmente del promotor U6 (SEQ ID NO: 922) y el promotor H1 (SEQ ID NO: 923). En algunas modalidades, la construcción comprende, de 5' a 3', un promotor U6, una primera secuencia que

codifica un ARNg, un promotor H1, una segunda secuencia que codifica un ARNg, un promotor 7SK, una tercera secuencia que codifica un ARNg. En algunas modalidades, la construcción comprende, de 5' a 3', el promotor U6, la secuencia que codifica un ARNg de la SEQ ID NO: 708, el promotor H1, una segunda secuencia que codifica un ARNg de la SEQ ID NO: 708, el promotor 7SK y una tercera secuencia que codifica un ARNg de la SEQ ID NO: 708. En algunas modalidades, la construcción comprende, de 5' a 3', el promotor U6, la secuencia que codifica un ARNg de la SEQ ID NO: 714, el promotor H1, una segunda secuencia que codifica un ARNg de la SEQ ID NO: 714, el promotor 7SK y una tercera secuencia que codifica un ARNg de la SEQ ID NO: 714. En algunas modalidades, la construcción comprende, de 5' a 3', el promotor U6, la secuencia que codifica un ARNg de la SEQ ID NO: 863, el promotor H1, una segunda secuencia que codifica un ARNg de la SEQ ID NO: 863, el promotor 7SK y una tercera secuencia que codifica un ARNg de la SEQ ID NO: 863. En algunas modalidades, la construcción que comprende un primer promotor, una primera secuencia que codifica un ARNg, un segundo promotor y una segunda secuencia que codifica un ARNg, un tercer promotor y una tercera secuencia que codifica un ARNg, comprende además al menos dos secuencias de repeticiones terminales invertidas (ITR). En algunas modalidades, la construcción que comprende un primer promotor, una primera secuencia que codifica un ARNg, un segundo promotor y una segunda secuencia que codifica un ARNg, un tercer promotor y una tercera secuencia que codifica un ARNg, comprende además al menos dos secuencias ITR aisladas o derivadas de un AAV de serotipo 2 (AAV2). En algunas modalidades, la construcción que comprende un primer promotor, una primera secuencia que codifica un ARNg, un segundo promotor y una segunda secuencia que codifica un ARNg, un tercer promotor y una tercera secuencia que codifica un ARNg, comprende además al menos dos secuencias ITR, en donde la primera secuencia de ITR se aísla o deriva de un AAV de serotipo 4 (AAV4) y la segunda secuencia de ITR se aísla o deriva de un AAV de serotipo 2 (AAV2). Las secuencias de ITR ilustrativas son CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCT (SEQ ID NO: 881), CCACTCCCTCTATGCGCGCTCGCTCACTCACTCGGCCCTGGAGACCAAAGGTCTCCAGACTGCCGGCCTCTGGCCGGCAGGGCCGAGTGAGTGAGCGAGCGCGCATAGAGGGAGTGGGTACCTCCATCATCTAGGTTTGCC (SEQ ID NO. 883), AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGG (SEQ ID NO. 946), y AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCG

GGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCG CGCAGCTGCCTGCAGG (SEQ ID 882). En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, un primer promotor, una primera secuencia que codifica un ARNg, un segundo promotor y una segunda secuencia que codifica un ARNg, un tercer promotor, una tercera secuencia que codifica un ARNg y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, un promotor U6, una primera secuencia que codifica un ARNg, un promotor H1, una segunda secuencia que codifica un ARNg, un promotor 7SK, una tercera secuencia que codifica un ARNg y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, un segundo promotor, y la secuencia que codifica un ARNg de la SEQ ID NO: 708, un tercer promotor y la secuencia que codifica un ARNg de la SEQ ID NO: 708, y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 714, un segundo promotor, y la secuencia que codifica un ARNg de la SEQ ID NO: 714, un tercer promotor y la secuencia que codifica un ARNg de la SEQ ID NO: 714, y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, un segundo promotor, y la secuencia que codifica un ARNg de la SEQ ID NO: 863, un tercer promotor y la secuencia que codifica un ARNg de la SEQ ID NO.: 863, y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, un promotor U6, la secuencia que codifica un ARNg de la SEQ ID NO: 708, un promotor H1, y la secuencia que codifica un ARNg de la SEQ ID NO: 708, un promotor 7SK y la secuencia que codifica un ARNg de la SEQ ID NO: 708, y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, un promotor U6, la secuencia que codifica un ARNg de la SEQ ID NO: 714, un promotor H1, y la secuencia que codifica un ARNg de la SEQ ID NO: 714, un promotor 7SK y la secuencia que codifica un ARNg de la SEQ ID NO: 714, y una segunda ITR. En algunas modalidades, la construcción que comprende, de 5' a 3', una primera ITR, un primer promotor, una primera secuencia que codifica un ARNg, un segundo promotor y una segunda secuencia que codifica un ARNg, un tercer promotor, una tercera secuencia que codifica un ARNg y una segunda ITR, comprende además una secuencia de poli A. En algunas modalidades, la secuencia de poliA comprende o consiste en una secuencia de poliA mini. Las secuencias de poliA mini ilustrativas de la descripción comprenden o consisten en una secuencia de nucleótidos de TAGCAATAAAGGATCGTTTATTTTCATTGGAAGCGTGTGTTGGTTTTTTGATCAGGCGCG (SEQ ID NO: 903). En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera

ITR, un primer promotor, una primera secuencia que codifica un ARNg, un segundo promotor y una segunda secuencia que codifica un ARNg, un tercer promotor, una tercera secuencia que codifica un ARNg, una secuencia de poliA mini y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, el promotor U6, una primera secuencia que codifica un ARNg, el promotor H1, una segunda secuencia que codifica un ARNg, el promotor 7SK, una tercera secuencia que codifica un ARNg, una secuencia de poliA mini y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, una secuencia poliA mini y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 714, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO. 714, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 714, una secuencia poliA mini y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, una secuencia poliA mini y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, el promotor U6, la secuencia que codifica un ARNg de la SEQ ID NO: 708, el promotor H1, la secuencia que codifica un ARNg de la SEQ ID NO: 708, el promotor 7SK, la secuencia que codifica un ARNg de la SEQ ID NO: 708, una secuencia poliA mini y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, el promotor U6, la secuencia que codifica un ARNg de la SEQ ID NO: 714, el promotor H1, la secuencia que codifica un ARNg de la SEQ ID NO: 714, el promotor 7SK, la secuencia que codifica un ARNg de la SEQ ID NO: 714, una secuencia poliA mini y una segunda ITR. En algunas modalidades, la construcción que comprende, de 5' a 3', una primera ITR, un primer promotor, una primera secuencia que codifica un ARNg, un segundo promotor y una segunda secuencia que codifica un ARNg, un tercer promotor, una tercera secuencia que codifica un ARNg, una secuencia de poliA mini y una segunda ITR, comprende además repeticiones invertidas de elementos transponibles. Las repeticiones invertidas de elementos transponibles de la descripción comprenden o consisten en una secuencia de nucleótidos de TGTGGGCGGACAAAATAGTTGGGAACTGGGAGGGGTGGAAATGGAGTTTTTAAGGATTATTTAG GGAAGAGTGACAAAATAGATGGGAACTGGGTGTAGCGTCGTAAGCTAATACGAAAATTAAAAATG ACAAAATAGTTTGGAACTAGATTTCACTTATCTGGTT (SEQ ID NO: 907), y/o una secuencia de

nucleótidos de GAATATAGTCTTTACCATGCCCTTGGCCACGCCCCTCTTTAATACGACGGGCAATTTGCACTTCA GAAAATGAAGAGTTTGCTTTAGCCATAACAAAAGTCCAGTATGCTTTTTCACAGCATAACTGGACT GATTTCAGTTTACAACTATTCTGTCTAGTTTAAGACTTTATTGTCATAGTTTAGATCTATTTTGTTCA GTTTAAGACTTTATTGTCCGCCCACA (SEQ ID NO: 908). En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, un primer promotor, una primera secuencia que codifica un ARNg, un segundo promotor y una segunda secuencia que codifica un ARNg, un tercer promotor, una tercera secuencia que codifica un ARNg, una secuencia de poliA mini, una segunda ITR y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, el promotor U6, una primera secuencia que codifica un ARNg, el promotor H1, una segunda secuencia que codifica un ARNg, el promotor 7SK, una tercera secuencia que codifica un ARNg, una secuencia de poliA mini, una segunda ITR y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, una secuencia de poliA mini, una segunda ITR y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 714, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 714, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 714, una secuencia de poliA mini, una segunda ITR y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, una secuencia de poliA mini, una segunda ITR y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, el promotor U6, la secuencia que codifica un ARNg de la SEQ ID NO: 708, el promotor H1, la secuencia que codifica un ARNg de la SEQ ID NO: 708, el promotor 7SK, la secuencia que codifica un ARNg de la SEQ ID NO: 708, una secuencia de poliA mini, una segunda ITR y una segunda repetición invertida de elementos transponibles. En algunas

modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera repetición invertida de elementos transponibles, una primera ITR, el promotor U6, la secuencia que codifica un ARNg de la SEQ ID NO: 714, el promotor H1, la secuencia que codifica un ARNg de la SEQ ID NO: 714, el promotor 7SK, la secuencia que codifica un ARNg de la SEQ ID NO: 714, una secuencia de poliA mini, una segunda ITR y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción que comprende una primera repetición invertida de elementos transponibles, una primera ITR, un primer promotor, una primera secuencia que codifica un ARNg, un segundo promotor, una segunda secuencia que codifica un ARNg, un tercer promotor, una tercera secuencia que codifica un ARNg, una secuencia de poliA mini, una segunda ITR y una segunda repetición invertida de elementos transponibles, comprende además una secuencia reguladora. Las secuencias reguladoras ilustrativas de la descripción comprenden o consisten en una secuencia de nucleótidos de

CATGCAAGCTGTAGCCAACCACTAGAACTATAGCTAGAGTCCTGGGCGAACAAACGATGCTCGC
CTTCCAGAAAACCGAGGATGCGAACCACTTCATCCGGGGTCAGCACCACCGGCAAGCGCCGCG
ACGGCCGAGGTCTTCCGATCTCCTGAAGCCAGGGCAGATCCGTGCACAGCACCTTGCCGTAGAA
GAACAGCAAGGCCGCCAATGCCTGACGATGCGTGGAGACCGAAACCTTGCGCTCGTTCGCCAG
CCAGGACAGAAATGCCTCGACTTCGCTGCTGCCCAAGGTTGCCGGGTGACGCACACCGTGGAA
ACGGATGAAGGCACGAACCCAGTTGACATAAGCCTGTTCGGTTCGTAAACTGTAATGCAAGTAGC
GTATGCGCTCACGCAACTGGTCCAGAACCTTGACCGAACGCAGCGGTGGTAACGGCGCAGTGG
CGGTTTTCATGGCTTGTTATGACTGTTTTTTTGTACAGTCTATGCCTCGGGCATCCAAGCAGCAAG
CGCGTTACGCCGTGGGTCGATGTTTGATGTTATGGAGCAGCAACGATGTTACGCAGCAGCAACG
ATGTTACGCAGCAGGGCAGTCGCCCTAAAACAAAGTTAGGTGGCTCAAGTATGGGCATCATTCG
CACATGTAGGCTCGGCCCTGACCAAGTCAAATCCATGCGGGCTGCTCTTGATCTTTTCGGTCGTG
AGTTCGGAGACGTAGCCACCTACTCCCAACATCAGCCGGACTCCGATTACCTCGGGAACTTGCT
CCGTAGTAAGACATTCATCGCGCTTGCTGCCTTCGACCAAGAAGCGGTTGTTGGCGCTCTCGCG
GCTTACGTTCTGCCCAAGTTTGAGCAGCCGCGTAGTGAGATCTATATCTATGATCTCGCAGTCTC
CGGCGAGCACCGGAGGCAGGGCATTGCCACCGCGCTCATCAATCTCCTCAAGCATGAGGCCAA
CGCGCTTGGTGCTTATGTGATCTACGTGCAAGCAGATTACGGTGACGATCCCGCAGTGGCTCTC
TATACAAAGTTGGGCATACGGGAAGAAGTGATGCACTTTGATATCGACCCAAGTACCGCCACCTA
ACAATTCGTTCAAGCCGAGATCGGCTTCCCGGCCGCGGAGTTGTTCGGTAAATTGTCACAACGC
CG (SEQ ID NO: 909). En algunas modalidades, la construcción comprende o consiste en, de 5’ a 3’, una primera repetición invertida de elementos transponibles, una primera ITR, un primer promotor, una primera secuencia que codifica un ARNg, un segundo promotor, una segunda secuencia que codifica un ARNg, un tercer promotor, una tercera secuencia que codifica un ARNg, una secuencia de

poliA mini, una segunda ITR, una secuencia reguladora y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, el promotor U6, una primera secuencia que codifica un ARNg, el promotor H1, una segunda secuencia que codifica un ARNg, el promotor 7SK, una tercera secuencia que codifica un ARNg, una secuencia de poliA mini, una segunda ITR, una secuencia reguladora y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, una secuencia de poliA mini, una segunda ITR, una una secuencia reguladora y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 714, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 714, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 714, una secuencia de poliA mini, una segunda ITR, una una secuencia reguladora y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, una secuencia de poliA mini, una segunda ITR, una una secuencia reguladora y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, el promotor U6, la secuencia que codifica un ARNg de la SEQ ID NO: 708, el promotor H1, la secuencia que codifica un ARNg de la SEQ ID NO. 708, el promotor 7SK, la secuencia que codifica un ARNg de la SEQ ID NO: 708, una secuencia de poliA mini, una segunda ITR, una una secuencia reguladora y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, el promotor U6, una secuencia que codifica un ARNg de la SEQ ID NO: 714, el promotor H1 una secuencia que codifica un ARNg de la SEQ ID NO: 714, el promotor 7SK, una secuencia que codifica un ARNg de la SEQ ID NO. 714, una secuencia de poliA mini, una segunda ITR, una una secuencia reguladora y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción que comprende una primera ITR,

un primer promotor, una primera secuencia que codifica un ARNg, un segundo promotor y una segunda secuencia que codifica un ARNg, un tercer promotor, una tercera secuencia que codifica un ARNg, una secuencia de poliA mini y una segunda ITR, comprende además una secuencia de relleno. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, el promotor U6, una primera secuencia que codifica un ARNg, el promotor H1, una segunda secuencia que codifica un ARNg, el promotor 7SK, una tercera secuencia que codifica un ARNg, una secuencia de relleno, una secuencia de poliA mini y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, una secuencia de relleno, una secuencia poliA mini y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 714, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 714, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO. 714, una secuencia de relleno, una secuencia poliA mini y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, una secuencia de relleno, una secuencia poliA mini y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, el promotor U6, la secuencia que codifica un ARNg de la SEQ ID NO: 708, el promotor H1, la secuencia que codifica un ARNg de la SEQ ID NO: 708, el promotor 7SK, la secuencia que codifica un ARNg de la SEQ ID NO: 708, una secuencia de relleno, una secuencia poliA mini y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera ITR, el promotor U6, la secuencia que codifica un ARNg de la SEQ ID NO: 714, el promotor H1, la secuencia que codifica un ARNg de la SEQ ID NO: 714, el promotor 7SK, la secuencia que codifica un ARNg de la SEQ ID NO: 714, una secuencia de relleno, una secuencia poliA mini y una segunda ITR. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, un primer promotor, una primera secuencia que codifica un ARNg, un segundo promotor y una segunda secuencia que codifica un ARNg, un tercer promotor, una tercera secuencia que codifica un ARNg, una secuencia de relleno, una secuencia de poliA mini, una segunda ITR, una secuencia reguladora y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera

ITR, el promotor U6, una primera secuencia que codifica un ARNg, el promotor H1, una segunda secuencia que codifica un ARNg, el promotor 7SK, una tercera secuencia que codifica un ARNg, una secuencia de relleno, una secuencia de poliA mini, una segunda ITR, una secuencia reguladora y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 708, una secuencia de relleno, una secuencia de poliA mini, una segunda ITR, una una secuencia reguladora y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 714, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 714, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 714, una secuencia de relleno, una secuencia de poliA mini, una segunda ITR, una una secuencia reguladora y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, un primer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, un segundo promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, un tercer promotor, la secuencia que codifica un ARNg de la SEQ ID NO: 863, una secuencia de relleno, una secuencia de poliA mini, una segunda ITR, una una secuencia reguladora y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, el promotor U6, la secuencia que codifica un ARNg de la SEQ ID NO: 708, el promotor H1, la secuencia que codifica un ARNg de la SEQ ID NO: 708, el promotor 7SK, la secuencia que codifica un ARNg de la SEQ ID NO: 708, una secuencia de relleno, una secuencia de poliA mini, una segunda ITR, una una secuencia reguladora y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción comprende o consiste en, de 5' a 3', una primera repetición invertida de elementos transponibles, una primera ITR, el promotor U6, una secuencia que codifica un ARNg de la SEQ ID NO: 714, el promotor H1, una secuencia que codifica un ARNg de la SEQ ID NO: 714, el promotor 7SK, una secuencia que codifica un ARNg de la SEQ ID NO. 714, una secuencia de relleno, una secuencia de poliA mini, una segunda ITR, una una secuencia reguladora y una segunda repetición invertida de elementos transponibles. En algunas modalidades, la construcción puede comprender además una o más secuencias espaciadoras. Las secuencias espaciadoras ilustrativas de la descripción tienen una longitud de 1-1500 nucleótidos, incluidos todos los intervalos entre ellos.

En algunas modalidades, las secuencias espaciadoras pueden ubicarse en una posición de 5’ a/o 3’ respecto a una ITR, un promotor, una secuencia que codifica un ARNg, una secuencia poliA, una repetición invertida del elemento transponible, una secuencia de relleno y/o un elemento regulador.

V. Composiciones farmacéuticas y métodos de administración

Para aplicaciones clínicas, las composiciones farmacéuticas se preparan en una forma apropiada para la aplicación prevista. Generalmente, esto implica preparar composiciones que esencialmente no contienen pirógenos, así como otras impurezas que pueden ser dañinas para los humanos o animales.

Se usan sales y amortiguadores apropiados para hacer que los fármacos, las proteínas o los vectores de administración sean estables y permitan la absorción por parte de las células diana. Las composiciones acuosas de la presente descripción comprenden una cantidad eficaz del fármaco, vector o proteínas, disueltas o dispersas en un vehículo o medio acuoso farmacéuticamente aceptable. La expresión «farmacéuticamente o farmacológicamente aceptable» se refiere a entidades moleculares y composiciones que no producen una reacción adversa, alérgica u otra reacción inadecuada cuando se administran a un animal o un ser humano. Tal como se usa en el presente documento, «portador farmacéuticamente aceptable» incluye solventes, amortiguadores, soluciones, medios de dispersión, recubrimientos, agentes antibacterianos y antifúngicos, agentes isotónicos y de retardo de la absorción y similares, aceptables para uso en la formulación de productos farmacéuticos, tales como productos farmacéuticos adecuados para la administración a seres humanos. Es conocido en la técnica el uso de dichos medios y agentes para sustancias farmacéuticamente activas. Se puede usar cualquier medio o agente convencional que no sea incompatible con los ingredientes activos de la presente descripción en composiciones terapéuticas. Los ingredientes activos suplementarios también pueden incorporarse en las composiciones, siempre que no inactiven los vectores o células de las composiciones.

En algunas modalidades, las composiciones activas de la presente descripción pueden incluir preparaciones farmacéuticas clásicas. La administración de estas composiciones de acuerdo con la presente descripción puede ser mediante cualquier vía común, siempre que el tejido objetivo esté disponible por medio de esa vía, pero generalmente incluye la administración sistémica. Esto incluye vía oral, nasal o bucal. De manera alternativa, la administración puede ser por medio de inyección intradérmica, subcutánea, intramuscular, intraperitoneal o intravenosa, o a través de inyección directa en el tejido muscular. Dichas composiciones se administrarán normalmente como composiciones farmacéuticamente aceptables, tal como se describió *supra*.

Los compuestos activos también se pueden administrar por vía parenteral o intraperitoneal. A modo

ilustrativo, las soluciones de los compuestos activos como base libre o sal farmacéuticamente aceptable se pueden preparar en agua mezclada de forma adecuada con un tensioactivo, como hidroxipropilcelulosa. También pueden prepararse dispersiones en glicerol, polietilenglicoles líquidos y mezclas de estos, así como en aceites. En condiciones normales de almacenamiento y uso, estas preparaciones generalmente contienen un conservante para evitar el crecimiento de microorganismos.

Las formas farmacéuticas adecuadas para uso inyectable incluyen, por ejemplo, soluciones o dispersiones acuosas estériles y polvos estériles para la preparación extemporánea de soluciones o dispersiones inyectables estériles. En general, estas preparaciones son estériles y fluidas en la medida en que existe una fácil inyectabilidad. Las preparaciones deben ser estables en las condiciones de fabricación y almacenamiento y se deben conservar contra la acción contaminante de microorganismos, tales como bacterias y hongos. Los solventes o medios de dispersión adecuados pueden contener, por ejemplo, agua, etanol, poliol (por ejemplo, glicerol, propilenglicol y polietilenglicol líquido y similares) mezclas adecuadas de estos y aceites vegetales. La fluidez adecuada se puede mantener, por ejemplo, mediante el uso de un recubrimiento, tal como lecitina, mediante el mantenimiento del tamaño de partícula necesario en caso de dispersión y mediante el uso de tensioactivos. La prevención de la acción de microorganismos puede ocasionarse mediante diversos agentes antibacterianos y antimicóticos, por ejemplo, parabenos, clorobutanol, fenol, ácido sórbico, timerosal y similares. En muchos casos, será preferible incluir agentes isotónicos, por ejemplo, azúcares o cloruro de sodio. La absorción prolongada de las composiciones inyectables puede ocasionarse mediante el uso en las composiciones de agentes que retardan la absorción, por ejemplo, monoestearato de aluminio y gelatina.

Las soluciones inyectables estériles se pueden preparar incorporando el compuesto activo en la cantidad requerida en un solvente adecuado con una o más combinaciones de ingredientes enumerados anteriormente, según se requiere, seguido de esterilización filtrada. Generalmente, las dispersiones se preparan mediante la incorporación de los diversos ingredientes activos esterilizados en un vehículo estéril que contiene un medio de dispersión básico y los demás ingredientes deseados, por ejemplo, los mencionados anteriormente. En el caso de los polvos estériles para la preparación de soluciones inyectables estériles, los métodos de preparación preferidos incluyen las técnicas de secado al vacío y liofilización que proporcionan un polvo del ingrediente activo más cualquier ingrediente adicional deseado a partir de una solución previamente filtrada en condiciones estériles de esta.

En algunas modalidades, las composiciones de la presente descripción se formulan como formas neutras o de sal. Las sales farmacéuticamente aceptables incluyen, por ejemplo, las sales de adición

de ácido (formadas con los grupos amino libres de la proteína) derivadas de ácidos inorgánicos (por ejemplo, ácidos clorhídricos o fosfóricos), o ácidos orgánicos (por ejemplo, acético, oxálico, tartárico, mandélico) y similares. Las sales formadas con los grupos carboxilo libres de la proteína también pueden derivar de bases inorgánicas (p.ej., sodio, potasio, amonio, calcio o hidróxidos férricos) o de bases orgánicas (p.ej., isopropilamina, trimetilamina, histidina, procaína) y similares.

Luego de la formulación, las soluciones preferentemente, se administran de una manera compatible con la formulación de dosificación y en una cantidad que sea terapéuticamente eficaz. Las formulaciones pueden administrarse fácilmente en diversas formas de dosificación, tales como soluciones inyectables, cápsulas de liberación de fármaco y similares. Para la administración parenteral en una solución acuosa, por ejemplo, la solución generalmente se amortigua de manera adecuada y el diluyente líquido primero se hace isotónico, por ejemplo, con una cantidad suficiente de solución salina o glucosa. Dichas soluciones acuosas pueden usarse, por ejemplo, para administración intravenosa, intramuscular, subcutánea e intraperitoneal. Preferentemente, se emplea medio acuoso estéril como conocen los expertos en la técnica, particularmente, en vista de la presente descripción. A modo de ejemplo, una única dosis se puede disolver en 1 ml de solución de NaCl isotónica y se puede agregar a 1000 ml de fluido de hipodermoclisis o se puede inyectar en el sitio propuesto de la infusión (véase, por ejemplo, «Remington's Pharmaceutical Sciences» 15.ª edición, páginas 1035-1038 y 1570-1580). Se puede producir una variación en la dosificación según la afección del sujeto en tratamiento. La persona responsable de la administración puede, en cualquier caso, determinar la dosis adecuada para el sujeto individual. Además, para la administración a seres humanos, las preparaciones deben cumplir con los estándares de esterilidad, pirogenicidad, seguridad general y pureza que requieren los estándares de la Oficina de productos biológicos de la FDA.

En algunas modaliaddes, el Cas9 o Cpf1 y los gRNA descritos en el presente documento pueden entregarse al paciente mediante el uso de la transferencia de células adoptiva (ACT). En la transferencia de células adoptiva, se proporcionan una o más construcciones de expresión ex vivo a las células que se originaron en el paciente (autólogas) o de uno o más personas distintas al paciente (alogénico). Las células se introducen o reintroducen posteriormente en el paciente. Por lo tanto, en algunas modalidades, uno o más ácidos nucleicos que codifican Cas9 o Cpf1 y un ARN guía que se dirige a un sitio de empalme de distrofina se proporcionan a una célula ex vivo antes de que la célula se introduzca o se reintroduzca en un paciente.

Las siguientes tablas proporcionan cebadores y secuencias de direccionamiento genómico ilustrativas para uso en relación con las composiciones y métodos que se describen en la presente.

TABLA 6 - Secuencias genómicas diana

Exón de ARNg dirigido	Guía n.º	Cadena	Secuencia genómica diana*	PAM	SEQ ID NO.
Exón 51 humano	4	1	tctttttcttctttttcctttt	tttt	60
Exón 51 humano	5	1	cttttttcttctttttcctttttG	tttt	61
Exón 51 humano	6	1	ttttttcttctttttcctttttGC	tttc	62
Exón 51 humano	7	1	tcttctttttcctttttGCAAAA	tttt	63
Exón 51 humano	8	1	cttctttttcctttttGCAAAAA	tttt	64
Exón 51 humano	9	1	ttctttttcctttttGCAAAAAC	tttc	65
Exón 51 humano	10	1	ttcctttttGCAAAAACCCAAAAT	tttt	66
Exón 51 humano	11	1	tcctttttGCAAAAACCCAAAATA	tttt	67
Exón 51 humano	12	1	cctttttGCAAAAACCCAAAATAT	tttt	68
Exón 51 humano	13	1	cttttGCAAAAACCCAAAATATT	tttc	69
Exón 51 humano	14	1	tGCAAAAACCCAAAATATTTTAGC	tttt	70
Exón 51 humano	15	1	GCAAAAACCCAAAATATTTTAGCT	tttt	71
Exón 51 humano	16	1	CAAAAACCCAAAATATTTTAGCTC	tttG	72
Exón 51 humano	17	1	AGCTCCTACTCAGACTGTTACTCT	TTTT	73
Exón 51 humano	18	1	GCTCCTACTCAGACTGTTACTCTG	TTTA	74
Exón 51 humano	19	-1	CTTAGTAACCACAGGTTGTGTCAC	TTTC	75
Exón 51 humano	20	-1	GAGATGGCAGTTTCCTTAGTAACC	TTTG	76
Exón 51 humano	21	-1	TAGTTTGGAGATGGCAGTTTCCTT	TTTC	77
Exón 51 humano	22	-1	TTCTCATACCTTCTGCTTGATGAT	TTTT	78
Exón 51 humano	23	-1	TCATTTTTTCTCATACCTTCTGCT	TTTA	79
Exón 51 humano	24	-1	ATCATTTTTTCTCATACCTTCTGC	TTTT	80
Exón 51 humano	25	-1	AAGAAAAACTTCTGCCAACTTTTA	TTTA	81
Exón 51 humano	26	-1	AAAGAAAAACTTCTGCCAACTTTT	TTTT	82
Exón 51 humano	27	1	TCTTTAAAATGAAGATTTTCCACC	TTTT	83
Exón 51 humano	28	1	CTTTAAAATGAAGATTTTCCACCA	TTTT	84
Exón 51 humano	29	1	TTTAAAATGAAGATTTTCCACCAA	TTTC	85
Exón 51 humano	30	1	AAATGAAGATTTTCCACCAATCAC	TTTA	86
Exón 51 humano	31	1	CCACCAATCACTTTACTCTCCTAG	TTTT	87
Exón 51 humano	32	1	CACCAATCACTTTACTCTCCTAGA	TTTC	88
Exón 51 humano	33	1	CTCTCCTAGACCATTTCCCACCAG	TTTA	89
Exón 45 humano	1	-1	agaaaagattaaacagtgtgctac	tttg	90
Exón 45 humano	2	-1	tttgagaaaagattaaacagtgtg	TTTa	91
Exón 45 humano	3	-1	atttgagaaaagattaaacagtgt	TTTT	92
Exón 45 humano	4	-1	Tatttgagaaaagattaaacagtg	TTTT	93
Exón 45 humano	5	1	atcttttctcaaatAAAAAGACAT	ttta	94
Exón 45 humano	6	1	ctcaaatAAAAAGACATGGGGCTT	tttt	95
Exón 45 humano	7	1	tcaaatAAAAAGACATGGGGCTTC	tttc	96

Exón 45 humano	8	1	TGTTTTGCCTTTTTGGTATCTTAC	TTTT	97
Exón 45 humano	9	1	GTTTTGCCTTTTTGGTATCTTACA	TTTT	98
Exón 45 humano	10	1	TTTTGCCTTTTTGGTATCTTACAG	TTTG	99
Exón 45 humano	11	1	GCCTTTTTGGTATCTTACAGGAAC	TTTT	100
Exón 45 humano	12	1	CCTTTTTGGTATCTTACAGGAACT	TTTG	101
Exón 45 humano	13	1	TGGTATCTTACAGGAACTCCAGGA	TTTT	102
Exón 45 humano	14	1	GGTATCTTACAGGAACTCCAGGAT	TTTT	103
Exón 45 humano	15	-1	AGGATTGCTGAATTATTTCTTCCC	TTTG	104
Exón 45 humano	16	-1	GAGGATTGCTGAATTATTTCTTCC	TTTT	105
Exón 45 humano	17	-1	TGAGGATTGCTGAATTATTTCTTC	TTTT	106
Exón 45 humano	18	-1	CTGTAGAATACTGGCATCTGTTTT	TTTC	107
Exón 45 humano	19	-1	CCTGTAGAATACTGGCATCTGTTT	TTTT	108
Exón 45 humano	20	-1	TCCTGTAGAATACTGGCATCTGTT	TTTT	109
Exón 45 humano	21	-1	CAGACCTCCTGCCACCGCAGATTC	TTTG	110
Exón 45 humano	22	-1	TGTCTGACAGCTGTTTGCAGACCT	TTTC	111
Exón 45 humano	23	-1	CTGTCTGACAGCTGTTTGCAGACC	TTTT	112
Exón 45 humano	24	-1	TCTGTCTGACAGCTGTTTGCAGAC	TTTT	113
Exón 45 humano	25	-1	TTCTGTCTGACAGCTGTTTGCAGA	TTTT	114
Exón 45 humano	26	-1	ATTCCTATTAGATCTGTCGCCCTA	TTTC	115
Exón 45 humano	27	-1	CATTCCTATTAGATCTGTCGCCCT	TTTT	116
Exón 45 humano	28	1	AGCAGACTTTTTAAGCTTTCTTTA	TTTT	117
Exón 45 humano	29	1	GCAGACTTTTTAAGCTTTCTTTAG	TTTA	118
Exón 45 humano	30	1	TAAGCTTTCTTTAGAAGAATATTT	TTTT	119
Exón 45 humano	31	1	AAGCTTTCTTTAGAAGAATATTTC	TTTT	120
Exón 45 humano	32	1	AGCTTTCTTTAGAAGAATATTTCA	TTTA	121
Exón 45 humano	33	1	TTTAGAAGAATATTTCATGAGAGA	TTTC	122
Exón 45 humano	34	1	GAAGAATATTTCATGAGAGATTAT	TTTA	123
Exón 44 humano	1	1	TCAGTATAACCAAAAAATATACGC	TTTG	124
Exón 44 humano	2	1	acataatccatctatttttcttga	tttt	125
Exón 44 humano	3	1	cataatccatctatttttcttgat	ttta	126
Exón 44 humano	4	1	tcttgatccatatgcttttACCTG	tttt	127
Exón 44 humano	5	1	cttgatccatatgcttttACCTGC	tttt	128
Exón 44 humano	6	1	ttgatccatatgcttttACCTGCA	tttc	129
Exón 44 humano	7	-1	TCAACAGATCTGTCAAATCGCCTG	TTTC	130
Exón 44 humano	8	1	ACCTGCAGGCGATTTGACAGATCT	tttt	131
Exón 44 humano	9	1	CCTGCAGGCGATTTGACAGATCTG	tttA	132
Exón 44 humano	10	1	ACAGATCTGTTGAGAAATGGCGGC	TTTG	133
Exón 44 humano	11	-1	TATCATAATGAAAACGCCGCCATT	TTTA	134
Exón 44 humano	12	1	CATTATGATATAAAGATATTTAAT	TTTT	135

Exón 44 humano	13	-1	TATTTAGCATGTTCCCAATTCTCA	TTTG	136
Exón 44 humano	14	-1	GAAAAAACAAATCAAAGACTTACC	TTTC	137
Exón 44 humano	15	1	ATTTGTTTTTTCGAAATTGTATTT	TTTG	138
Exón 44 humano	16	1	TTTTTTCGAAATTGTATTTATCTT	TTTG	139
Exón 44 humano	17	1	TTCGAAATTGTATTTATCTTCAGC	TTTT	140
Exón 44 humano	18	1	TCGAAATTGTATTTATCTTCAGCA	TTTT	141
Exón 44 humano	19	1	CGAAATTGTATTTATCTTCAGCAC	TTTT	142
Exón 44 humano	20	1	GAAATTGTATTTATCTTCAGCACA	TTTC	143
Exón 44 humano	21	-1	AGAAGTTAAAGAGTCCAGATGTGC	TTTA	144
Exón 44 humano	22	1	TCTTCAGCACATCTGGACTCTTTA	TTTA	145
Exón 44 humano	23	-1	CATCACCCTTCAGAACCTGATCTT	TTTC	146
Exón 44 humano	24	1	ACTTCTTAAAGATCAGGTTCTGAA	TTTA	147
Exón 44 humano	25	1	GACTGTTGTTGTCATCATTATATT	TTTT	148
Exón 44 humano	26	1	ACTGTTGTTGTCATCATTATATTA	TTTG	149
Exón 53 humano	1	-1	AACTAGAATAAAAGGAAAAATAAA	TTTC	150
Exón 53 humano	2	1	CTACTATATATTTATTTTTCCTTT	TTTA	151
Exón 53 humano	3	1	TTTTTCCTTTTATTCTAGTTGAAA	TTTA	152
Exón 53 humano	4	1	TCCTTTTATTCTAGTTGAAAGAAT	TTTT	153
Exón 53 humano	5	1	CCTTTTATTCTAGTTGAAAGAATT	TTTT	154
Exón 53 humano	6	1	CTTTTATTCTAGTTGAAAGAATTC	TTTC	155
Exón 53 humano	7	1	ATTCTAGTTGAAAGAATTCAGAAT	TTTT	156
Exón 53 humano	8	1	TTCTAGTTGAAAGAATTCAGAATC	TTTA	157
Exón 53 humano	9	-1	ATTCAACTGTTGCCTCCGGTTCTG	TTTC	158
Exón 53 humano	10	-1	ACATTTCATTCAACTGTTGCCTCC	TTTA	159
Exón 53 humano	11	-1	CTTTTGGATTGCATCTACTGTATA	TTTT	160
Exón 53 humano	12	-1	TGTGATTTTCTTTTGGATTGCATC	TTTC	161
Exón 53 humano	13	-1	ATACTAACCTTGGTTTCTGTGATT	TTTG	162
Exón 53 humano	14	-1	AAAAGGTATCTTTGATACTAACCT	TTTA	163
Exón 53 humano	15	-1	AAAAAGGTATCTTTGATACTAACC	TTTT	164
Exón 53 humano	16	-1	TTTTAAAAAGGTATCTTTGATACT	TTTA	165
Exón 53 humano	17	-1	ATTTTAAAAAGGTATCTTTGATAC	TTTT	166
Exón 46 humano	1	-1	TTAATGCAAACTGGGACACAAACA	TTTG	167
Exón 46 humano	2	1	TAAATTGCCATGTTTGTGTCCCAG	TTTT	168
Exón 46 humano	3	1	AAATTGCCATGTTTGTGTCCCAGT	TTTT	169
Exón 46 humano	4	1	AATTGCCATGTTTGTGTCCCAGTT	TTTA	170
Exón 46 humano	5	1	TGTCCCAGTTTGCATTAACAAATA	TTTG	171
Exón 46 humano	6	-1	CAACATAGTTCTCAAACTATTTGT	tttC	172
Exón 46 humano	7	-1	CCAACATAGTTCTCAAACTATTTG	tttt	173
Exón 46 humano	8	-1	tCCAACATAGTTCTCAAACTATTT	tttt	174

Exón 46 humano	9	-1	tttCCAACATAGTTCTCAAACTAT	tttt	175
Exón 46 humano	10	-1	ttttCCAACATAGTTCTCAAACTA	tttt	176
Exón 46 humano	11	-1	tttttCCAACATAGTTCTCAAACT	tttt	177
Exón 46 humano	12	1	CATTAACAAATAGTTTGAGAACTA	TTTG	178
Exón 46 humano	13	1	AGAACTATGTTGGaaaaaaaaaTA	TTTG	179
Exón 46 humano	14	-1	GTTCTTCTAGCCTGGAGAAAGAAG	TTTT	180
Exón 46 humano	15	1	ATTCTTCTTTCTCCAGGCTAGAAG	TTTT	181
Exón 46 humano	16	1	TTCTTCTTTCTCCAGGCTAGAAGA	TTTA	182
Exón 46 humano	17	1	TCCAGGCTAGAAGAACAAAAGAAT	TTTC	183
Exón 46 humano	18	-1	AAATTCTGACAAGATATTCTTTTG	TTTG	184
Exón 46 humano	19	-1	CTTTTAGTTGCTGCTCTTTTCCAG	TTTT	185
Exón 46 humano	20	-1	AGAAAATAAAATTACCTTGACTTG	TTTG	186
Exón 46 humano	21	-1	TGCAAGCAGGCCCTGGGGGATTTG	TTTA	187
Exón 46 humano	22	1	ATTTTCTCAAATCCCCCAGGGCCT	TTTT	188
Exón 46 humano	23	1	TTTTCTCAAATCCCCCAGGGCCTG	TTTA	189
Exón 46 humano	24	1	CTCAAATCCCCCAGGGCCTGCTTG	TTTT	190
Exón 46 humano	25	1	TCAAATCCCCCAGGGCCTGCTTGC	TTTC	191
Exón 46 humano	26	1	TTAATTCAATCATTGGTTTTCTGC	TTTT	192
Exón 46 humano	27	1	TAATTCAATCATTGGTTTTCTGCC	TTTT	193
Exón 46 humano	28	1	AATTCAATCATTGGTTTTCTGCCC	TTTT	194
Exón 46 humano	29	1	ATTCAATCATTGGTTTTCTGCCCA	TTTA	195
Exón 46 humano	30	-1	GCAAGGAACTATGAATAACCTAAT	TTTA	196
Exón 46 humano	31	1	CTGCCCATTAGGTTATTCATAGTT	TTTT	197
Exón 46 humano	32	1	TGCCCATTAGGTTATTCATAGTTC	TTTC	198
Exón 52 humano	1	-1	TAGAAAACAATTTAACAGGAAATA	TTTA	199
Exón 52 humano	2	1	CTGTTAAATTGTTTTCTATAAACC	TTTC	200
Exón 52 humano	3	-1	GAAATAAAAAAGATGTTACTGTAT	TTTA	201
Exón 52 humano	4	-1	AGAAATAAAAAAGATGTTACTGTA	TTTT	202
Exón 52 humano	5	1	CTATAAACCCTTATACAGTAACAT	TTTT	203
Exón 52 humano	6	1	TATAAACCCTTATACAGTAACATC	TTTC	204
Exón 52 humano	7	1	TTATTTCTAAAAGTGTTTTGGCTG	TTTT	205
Exón 52 humano	8	1	TATTTCTAAAAGTGTTTTGGCTGG	TTTT	206
Exón 52 humano	9	1	ATTTCTAAAAGTGTTTTGGCTGGT	TTTT	207
Exón 52 humano	10	1	TTTCTAAAAGTGTTTTGGCTGGTC	TTTA	208
Exón 52 humano	11	1	TAAAAGTGTTTTGGCTGGTCTCAC	TTTC	209
Exón 52 humano	12	-1	CATAATACAAAGTAAAGTACAATT	TTTA	210
Exón 52 humano	13	-1	ACATAATACAAAGTAAAGTACAAT	TTTT	211
Exón 52 humano	14	1	GGCTGGTCTCACAATTGTACTTTA	TTTT	212
Exón 52 humano	15	1	GCTGGTCTCACAATTGTACTTTAC	TTTG	213

Exón 52 humano	16	1	CTTTGTATTATGTAAAAGGAATAC	TTTA	214
Exón 52 humano	17	1	TATTATGTAAAAGGAATACACAAC	TTTG	215
Exón 52 humano	18	1	TTCTTACAGGCAACAATGCAGGAT	TTTG	216
Exón 52 humano	19	1	GAACAGAGGCGTCCCCAGTTGGAA	TTTG	217
Exón 52 humano	20	-1	GGCAGCGGTAATGAGTTCTTCCAA	TTTG	218
Exón 52 humano	21	-1	TCAAATTTTGGGCAGCGGTAATGA	TTTT	219
Exón 52 humano	22	1	AAAAACAAGACCAGCAATCAAGAG	TTTG	220
Exón 52 humano	23	-1	TGTGTCCCATGCTTGTTAAAAAAC	TTTG	221
Exón 52 humano	24	1	TTAACAAGCATGGGACACACAAAG	TTTT	222
Exón 52 humano	25	1	TAACAAGCATGGGACACACAAAGC	TTTT	223
Exón 52 humano	26	1	AACAAGCATGGGACACACAAAGCA	TTTT	224
Exón 52 humano	27	1	ACAAGCATGGGACACACAAAGCAA	TTTA	225
Exón 52 humano	28	-1	TTGAAACTTGTCATGCATCTTGCT	TTTA	226
Exón 52 humano	29	-1	ATTGAAACTTGTCATGCATCTTGC	TTTT	227
Exón 52 humano	30	-1	TATTGAAACTTGTCATGCATCTTG	TTTT	228
Exón 52 humano	31	1	AATAAAAACTTAAGTTCATATATC	TTTC	229
Exón 50 humano	1	-1	GTGAATATATTATTGGATTTCTAT	TTTG	230
Exón 50 humano	2	-1	AAGATAATTCATGAACATCTTAAT	TTTG	231
Exón 50 humano	3	-1	ACAGAAAAGCATACACATTACTTA	TTTA	232
Exón 50 humano	4	1	CTGTTAAAGAGGAAGTTAGAAGAT	TTTT	233
Exón 50 humano	5	1	TGTTAAAGAGGAAGTTAGAAGATC	TTTC	234
Exón 50 humano	6	-1	CCGCCTTCCACTCAGAGCTCAGAT	TTTA	235
Exón 50 humano	7	-1	CCCTCAGCTCTTGAAGTAAACGGT	TTTG	236
Exón 50 humano	8	1	CTTCAAGAGCTGAGGGCAAAGCAG	TTTA	237
Exón 50 humano	9	-1	AACAAATAGCTAGAGCCAAAGAGA	TTTG	238
Exón 50 humano	10	-1	GAACAAATAGCTAGAGCCAAAGAG	TTTT	239
Exón 50 humano	11	1	GCTCTAGCTATTTGTTCAAAAGTG	TTTG	240
Exón 50 humano	12	1	TTCAAAAGTGCAACTATGAAGTGA	TTTG	241
Exón 50 humano	13	-1	TCTCTCACCCAGTCATCACTTCAT	TTTC	242
Exón 50 humano	14	-1	CTCTCTCACCCAGTCATCACTTCA	TTTT	243
Exón 43 humano	1	1	tatatatatatatatTTTTCTCTT	TTTG	244
Exón 43 humano	2	1	TCTCTTTCTATAGACAGCTAATTC	tTTT	245
Exón 43 humano	3	1	CTCTTTCTATAGACAGCTAATTCA	TTTT	246
Exón 43 humano	4	-1	AAACAGTAAAAAAATGAATTAGCT	TTTA	247
Exón 43 humano	5	1	TCTTTCTATAGACAGCTAATTCAT	TTTC	248
Exón 43 humano	6	-1	AAAACAGTAAAAAAATGAATTAGC	TTTT	249
Exón 43 humano	7	1	TATAGACAGCTAATTCATTTTTTT	TTTC	250
Exón 43 humano	8	-1	TATTCTGTAATATAAAAATTTTAA	TTTA	251
Exón 43 humano	9	-1	ATATTCTGTAATATAAAAATTTTA	TTTT	252

Exón 43 humano	10	1	TTTACTGTTTTAAAATTTTTATAT	TTTT	253
Exón 43 humano	11	1	TTACTGTTTTAAAATTTTTATATT	TTTT	254
Exón 43 humano	12	1	TACTGTTTTAAAATTTTTATATTA	TTTT	255
Exón 43 humano	13	1	ACTGTTTTAAAATTTTTATATTAC	TTTT	256
Exón 43 humano	14	1	CTGTTTTAAAATTTTTATATTACA	TTTA	257
Exón 43 humano	15	1	AAAATTTTTATATTACAGAATATA	TTTT	258
Exón 43 humano	16	1	AAATTTTTATATTACAGAATATAA	TTTA	259
Exón 43 humano	17	-1	TTGTAGACTATCTTTTATATTCTG	TTTG	260
Exón 43 humano	18	1	TATATTACAGAATATAAAAGATAG	TTTT	261
Exón 43 humano	19	1	ATATTACAGAATATAAAAGATAGT	TTTT	262
Exón 43 humano	20	1	TATTACAGAATATAAAAGATAGTC	TTTA	263
Exón 43 humano	21	-1	CAATGCTGCTGTCTTCTTGCTATG	TTTG	264
Exón 43 humano	22	1	CAATGGGAAAAAGTTAACAAAATG	TTTC	265
Exón 43 humano	23	-1	TGCAAGTATCAAGAAAAATATATG	TTTC	266
Exón 43 humano	24	1	TCTTGATACTTGCAGAAATGATTT	TTTT	267
Exón 43 humano	25	1	CTTGATACTTGCAGAAATGATTTG	TTTT	268
Exón 43 humano	26	1	TTGATACTTGCAGAAATGATTTGT	TTTC	269
Exón 43 humano	27	1	TTTTCAGGGAACTGTAGAATTTAT	TTTG	270
Exón 43 humano	28	-1	CATGGAGGGTACTGAAATAAATTC	TTTC	271
Exón 43 humano	29	-1	CCATGGAGGGTACTGAAATAAATT	TTTT	272
Exón 43 humano	30	1	CAGGGAACTGTAGAATTTATTTCA	TTTT	273
Exón 43 humano	31	-1	TCCATGGAGGGTACTGAAATAAAT	TTTT	274
Exón 43 humano	32	1	AGGGAACTGTAGAATTTATTTCAG	TTTC	275
Exón 43 humano	33	-1	TTCCATGGAGGGTACTGAAATAAA	TTTT	276
Exón 43 humano	34	-1	CCTGTCTTTTTTCCATGGAGGGTA	TTTC	277
Exón 43 humano	35	-1	CCCTGTCTTTTTTCCATGGAGGGT	TTTT	278
Exón 43 humano	36	-1	TCCCTGTCTTTTTTCCATGGAGGG	TTTT	279
Exón 43 humano	37	1	TTTCAGTACCCTCCATGGAAAAAA	TTTA	280
Exón 43 humano	38	1	AGTACCCTCCATGGAAAAAAGACA	TTTC	281
Exón 6 humano	1	1	AGTTTGCATGGTTCTTGCTCAAGG	TTTA	282
Exón 6 humano	2	-1	ATAAGAAAATGCATTCCTTGAGCA	TTTC	283
Exón 6 humano	3	-1	CATAAGAAAATGCATTCCTTGAGC	TTTT	284
Exón 6 humano	4	1	CATGGTTCTTGCTCAAGGAATGCA	TTTG	285
Exón 6 humano	5	-1	ACCTACATGTGGAAATAAATTTTC	TTTG	286
Exón 6 humano	6	-1	GACCTACATGTGGAAATAAATTTT	TTTT	287
Exón 6 humano	7	-1	TGACCTACATGTGGAAATAAATTT	TTTT	288
Exón 6 humano	8	1	CTTATGAAAATTTATTTCCACATG	TTTT	289
Exón 6 humano	9	1	TTATGAAAATTTATTTCCACATGT	TTTC	290
Exón 6 humano	10	-1	ATTACATTTTTGACCTACATGTGG	TTTC	291

Exón 6 humano	11	-1	CATTACATTTTTGACCTACATGTG	TTTT	292
Exón 6 humano	12	-1	TCATTACATTTTTGACCTACATGT	TTTT	293
Exón 6 humano	13	1	TTTCCACATGTAGGTCAAAAATGT	TTTA	294
Exón 6 humano	14	1	CACATGTAGGTCAAAAATGTAATG	TTTC	295
Exón 6 humano	15	-1	TTGCAATCCAGCCATGATATTTTT	TTTG	296
Exón 6 humano	16	-1	ACTGTTGGTTTGTTGCAATCCAGC	TTTC	297
Exón 6 humano	17	-1	CACTGTTGGTTTGTTGCAATCCAG	TTTT	298
Exón 6 humano	18	1	AATGCTCTCATCCATAGTCATAGG	TTTG	299
Exón 6 humano	19	-1	ATGTCTCAGTAATCTTCTTACCTA	TTTA	300
Exón 6 humano	20	-1	CAAGTTATTTAATGTCTCAGTAAT	TTTA	301
Exón 6 humano	21	-1	ACAAGTTATTTAATGTCTCAGTAA	TTTT	302
Exón 6 humano	22	1	GACTCTGATGACATATTTTTCCCC	TTTA	303
Exón 6 humano	23	1	TCCCCAGTATGGTTCCAGATCATG	TTTT	304
Exón 6 humano	24	1	CCCCAGTATGGTTCCAGATCATGT	TTTT	305
Exón 6 humano	25	1	CCCAGTATGGTTCCAGATCATGTC	TTTC	306
Exón 7 humano	1	1	TATTTGTCTTtgtgtatgtgtgta	TTTA	307
Exón 7 humano	2	1	TCTTtgtgtatgtgtgtatgtgta	TTTG	308
Exón 7 humano	3	1	tgtatgtgtgtatgtgtatgtgtt	TTtg	309
Exón 7 humano	4	1	AGGCCAGACCTATTTGACTGGAAT	ttTT	310
Exón 7 humano	5	1	GGCCAGACCTATTTGACTGGAATA	tTTA	311
Exón 7 humano	6	1	ACTGGAATAGTGTGGTTTGCCAGC	TTTG	312
Exón 7 humano	7	1	CCAGCAGTCAGCCACACAACGACT	TTTG	313
Exón 7 humano	8	-1	TCTATGCCTAATTGATATCTGGCG	TTTC	314
Exón 7 humano	9	-1	CCAACCTTCAGGATCGAGTAGTTT	TTTA	315
Exón 7 humano	10	1	TGGACTACCACTGCTTTTAGTATG	TTTC	316
Exón 7 humano	11	1	AGTATGGTAGAGTTTAATGTTTTC	TTTT	317
Exón 7 humano	12	1	GTATGGTAGAGTTTAATGTTTTCA	TTTA	318
Exón 8 humano	1	-1	AGACTCTAAAAGGATAATGAACAA	TTTG	319
Exón 8 humano	2	1	ACTTTGATTTGTTCATTATCCTTT	TTTA	320
Exón 8 humano	3	-1	TATATTTGAGACTCTAAAAGGATA	TTTC	321
Exón 8 humano	4	1	ATTTGTTCATTATCCTTTTAGAGT	TTTG	322
Exón 8 humano	5	-1	GTTTCTATATTTGAGACTCTAAAA	TTTG	323
Exón 8 humano	6	-1	GGTTTCTATATTTGAGACTCTAAA	TTTT	324
Exón 8 humano	7	-1	TGGTTTCTATATTTGAGACTCTAA	TTTT	325
Exón 8 humano	8	1	TTCATTATCCTTTTAGAGTCTCAA	TTTG	326
Exón 8 humano	9	1	AGAGTCTCAAATATAGAAACCAAA	TTTT	327
Exón 8 humano	10	1	GAGTCTCAAATATAGAAACCAAAA	TTTA	328
Exón 8 humano	11	-1	CACTTCCTGGATGGCTTCAATGCT	TTTC	329
Exón 8 humano	12	1	GCCTCAACAAGTGAGCATTGAAGC	TTTT	330

Exón 8 humano	13	1	CCTCAACAAGTGAGCATTGAAGCC	TTTG	331
Exón 8 humano	14	-1	GGTGGCCTTGGCAACATTTCCACT	TTTA	332
Exón 8 humano	15	-1	GTCACTTTAGGTGGCCTTGGCAAC	TTTA	333
Exón 8 humano	16	-1	ATGATGTAACTGAAAATGTTCTTC	TTTG	334
Exón 8 humano	17	-1	CCTGTTGAGAATAGTGCATTTGAT	TTTA	335
Exón 8 humano	18	1	CAGTTACATCATCAAATGCACTAT	TTTT	336
Exón 8 humano	19	1	AGTTACATCATCAAATGCACTATT	TTTC	337
Exón 8 humano	20	-1	CACACTTTACCTGTTGAGAATAGT	TTTA	338
Exón 8 humano	21	1	CTGTTTTATATGCATTTTTAGGTA	TTTT	339
Exón 8 humano	22	1	TGTTTTATATGCATTTTTAGGTAT	TTTC	340
Exón 8 humano	23	1	ATATGCATTTTTAGGTATTACGTG	TTTT	341
Exón 8 humano	24	1	TATGCATTTTTAGGTATTACGTGC	TTTA	342
Exón 8 humano	25	1	TAGGTATTACGTGCACatatatat	TTTT	343
Exón 8 humano	26	1	AGGTATTACGTGCACatatatata	TTTT	344
Exón 8 humano	27	1	GGTATTACGTGCACatatatatat	TTTA	345
Exón 55 humano	1	-1	AGCAACAACTATAATATTGTGCAG	TTTA	346
Exón 55 humano	2	1	GTTCCTCCATCTTTCTCTTTTTAT	TTTA	347
Exón 55 humano	3	1	TCTTTTTATGGAGTTCACTAGGTG	TTTC	348
Exón 55 humano	4	1	TATGGAGTTCACTAGGTGCACCAT	TTTT	349
Exón 55 humano	5	1	ATGGAGTTCACTAGGTGCACCATT	TTTT	350
Exón 55 humano	6	1	TGGAGTTCACTAGGTGCACCATTC	TTTA	351
Exón 55 humano	7	1	ATAATTGCATCTGAACATTTGGTC	TTTA	352
Exón 55 humano	8	1	GTCCTTTGCAGGGTGAGTGAGCGA	TTTG	353
Exón 55 humano	9	-1	TTCCAAAGCAGCCTCTCGCTCACT	TTTC	354
Exón 55 humano	10	1	CAGGGTGAGTGAGCGAGAGGCTGC	TTTG	355
Exón 55 humano	11	1	GAAGAAACTCATAGATTACTGCAA	TTTG	356
Exón 55 humano	12	-1	CAGGTCCAGGGGGAACTGTTGCAG	TTTC	357
Exón 55 humano	13	-1	CCAGGTCCAGGGGGAACTGTTGCA	TTTT	358
Exón 55 humano	14	-1	AGCTTCTGTAAGCCAGGCAAGAAA	TTTC	359
Exón 55 humano	15	1	TTGCCTGGCTTACAGAAGCTGAAA	TTTC	360
Exón 55 humano	16	-1	CTTACGGGTAGCATCCTGTAGGAC	TTTC	361
Exón 55 humano	17	-1	CTCCCTTGGAGTCTTCTAGGAGCC	TTTA	362
Exón 55 humano	18	-1	ACTCCCTTGGAGTCTTCTAGGAGC	TTTT	363
Exón 55 humano	19	-1	ATCAGCTCTTTTACTCCCTTGGAG	TTTC	364
Exón 55 humano	20	1	CGCTTTAGCACTCTTGTGGATCCA	TTTC	365
Exón 55 humano	21	1	GCACTCTTGTGGATCCAATTGAAC	TTTA	366
Exón 55 humano	22	-1	TCCCTGGCTTGTCAGTTACAAGTA	TTTG	367
Exón 55 humano	23	-1	GTCCCTGGCTTGTCAGTTACAAGT	TTTT	368
Exón 55 humano	24	-1	TTTTGTCCCTGGCTTGTCAGTTAC	TTTG	369

Exón 55 humano	25	-1	GTTTTGTCCCTGGCTTGTCAGTTA	TTTT	370
Exón 55 humano	26	1	TACTTGTAACTGACAAGCCAGGGA	TTTG	371
Exón 51 G1 humano		1	gCTCCTACTCAGACTGTTACTCTG	TTTA	372
Exón 52 G1 humano		1	taccatgtattgctaaacaaagta	TTTC	373
Exón 51 G3 humano		-1	attgaagagtaacaatttgagcca	TTTA	374
Exón 23 G1 de ratón		1	aggctctgcaaagttctTTGAAAG	TTTG	375
Exón 23 G2 de ratón		1	AAAGAGCAACAAAATGGCttcaac	TTTG	376
Exón 23 G3 de ratón		1	AAAGAGCAATAAAATGGCttcaac	TTTG	377
Exón 23 G4 de ratón		-1	AAAGAACTTTGCAGAGCctcaaaa	TTTC	378
Exón 23 G5 de ratón		-1	ctgaatatctatgcattaataact	TTTA	379
Exón 23 G6 de ratón		-1	tattatattacagggcatattata	TTTC	380
Exón 23 G7 de ratón		1	Aggtaagccgaggtttggccttta	TTTC	381
Exón 23 G8 de ratón		1	cccagagtccttcaaagatattga	TTTA	382

***** En esta tabla, las letras mayúsculas representan los nucleótidos que se alinean con la secuencia de exones del gen. Las letras minúsculas representan nucleótidos que se alinean con la secuencia de intrones del gen.

TABLA 7 - Secuencias de ARNg

Exón de ARNg dirigido	Guía n.º	Cadena	Secuencia de ARNg*	PAM	SEQ ID NO.
Exón 51 humano	4	1	aaaaaggaaaaaagaagaaaaaga	tttt	383
Exón 51 humano	5	1	Caaaaaggaaaaaagaagaaaaag	tttt	384
Exón 51 humano	6	1	GCaaaaaggaaaaaagaagaaaaa	tttc	385
Exón 51 humano	7	1	UUUUGCaaaaaggaaaaaagaaga	tttt	386
Exón 51 humano	8	1	UUUUUGCaaaaaggaaaaaagaag	tttt	387
Exón 51 humano	9	1	GUUUUUGCaaaaaggaaaaaagaa	tttc	388
Exón 51 humano	10	1	AUUUUGGGUUUUUGCaaaaaggaa	tttt	389
Exón 51 humano	11	1	UAUUUUGGGUUUUUGCaaaaagga	tttt	390
Exón 51 humano	12	1	AUAUUUUGGGUUUUUGCaaaaagg	tttt	391
Exón 51 humano	13	1	AAUAUUUUGGGUUUUUGCaaaaag	tttc	392
Exón 51 humano	14	1	GCUAAAAUAUUUUGGGUUUUUGCa	tttt	393
Exón 51 humano	15	1	AGCUAAAAUAUUUUGGGUUUUUGC	tttt	394
Exón 51 humano	16	1	GAGCUAAAAUAUUUUGGGUUUUUG	tttG	395
Exón 51 humano	17	1	AGAGUAACAGUCUGAGUAGGAGCU	TTTT	396

Exón 51 humano	18	1	CAGAGUAACAGUCUGAGUAGGAGC	TTTA	397
Exón 51 humano	19	-1	GUGACACAACCUGUGGUUACUAAG	TTTC	398
Exón 51 humano	20	-1	GGUUACUAAGGAAACUGCCAUCU	TTTG	399
Exón 51 humano	21	-1	AAGGAAACUGCCAUCUCCAAACUA	TTTC	400
Exón 51 humano	22	-1	AUCAUCAAGCAGAAGGUAUGAGAA	TTTT	401
Exón 51 humano	23	-1	AGCAGAAGGUAUGAGAAAAAAUGA	TTTA	402
Exón 51 humano	24	-1	GCAGAAGGUAUGAGAAAAAAUGAU	TTTT	403
Exón 51 humano	25	-1	UAAAAGUUGGCAGAAGUUUUUCUU	TTTA	404
Exón 51 humano	26	-1	AAAAGUUGGCAGAAGUUUUUCUUU	TTTT	405
Exón 51 humano	27	1	GGUGGAAAAUCUUCAUUUUAAAGA	TTTT	406
Exón 51 humano	28	1	UGGUGGAAAAUCUUCAUUUUAAAG	TTTT	407
Exón 51 humano	29	1	UUGGUGGAAAAUCUUCAUUUUAAA	TTTC	408
Exón 51 humano	30	1	GUGAUUGGUGGAAAAUCUUCAUUU	TTTA	409
Exón 51 humano	31	1	CUAGGAGAGUAAAGUGAUUGGUGG	TTTT	410
Exón 51 humano	32	1	UCUAGGAGAGUAAAGUGAUUGGUG	TTTC	411
Exón 51 humano	33	1	CUGGUGGGAAAUGGUCUAGGAGA	TTTA	412
Exón 45 humano	1	-1	guagcacacuguuuaaucuuuucu	tttg	413
Exón 45 humano	2	-1	cacacuguuuaaucuuuucucaaa	TTTa	414
Exón 45 humano	3	-1	acacuguuuaaucuuuucucaaau	TTTT	415
Exón 45 humano	4	-1	cacuguuuaaucuuuucucaaauA	TTTT	416
Exón 45 humano	5	1	AUGUCUUUUUauuugagaaaagau	ttta	417
Exón 45 humano	6	1	AAGCCCCAUGUCUUUUUauuugag	tttt	418
Exón 45 humano	7	1	GAAGCCCCAUGUCUUUUUauuuga	tttc	419
Exón 45 humano	8	1	GUAAGAUACCAAAAAGGCAAAACA	TTTT	420
Exón 45 humano	9	1	UGUAAGAUACCAAAAAGGCAAAAC	TTTT	421
Exón 45 humano	10	1	CUGUAAGAUACCAAAAAGGCAAAA	TTTG	422
Exón 45 humano	11	1	GUUCCUGUAAGAUACCAAAAAGGC	TTTT	423
Exón 45 humano	12	1	AGUUCCUGUAAGAUACCAAAAAGG	TTTG	424
Exón 45 humano	13	1	UCCUGGAGUUCCUGUAAGAUACCA	TTTT	425
Exón 45 humano	14	1	AUCCUGGAGUUCCUGUAAGAUACC	TTTT	426
Exón 45 humano	15	-1	GGGAAGAAAUAAUUCAGCAAUCCU	TTTG	427
Exón 45 humano	16	-1	GGAAGAAAUAAUUCAGCAAUCCUC	TTTT	428
Exón 45 humano	17	-1	GAAGAAAUAAUUCAGCAAUCCUCA	TTTT	429
Exón 45 humano	18	-1	AAAACAGAUGCCAGUAUUCUACAG	TTTC	430
Exón 45 humano	19	-1	AAACAGAUGCCAGUAUUCUACAGG	TTTT	431
Exón 45 humano	20	-1	AACAGAUGCCAGUAUUCUACAGGA	TTTT	432
Exón 45 humano	21	-1	GAAUCUGCGGUGGCAGGAGGUCUG	TTTG	433
Exón 45 humano	22	-1	AGGUCUGCAAACAGCUGUCAGACA	TTTC	434
Exón 45 humano	23	-1	GGUCUGCAAACAGCUGUCAGACAG	TTTT	435

Exón 45 humano	24	-1	GUCUGCAAACAGCUGUCAGACAGA	TTTT	436
Exón 45 humano	25	-1	UCUGCAAACAGCUGUCAGACAGAA	TTTT	437
Exón 45 humano	26	-1	UAGGGCGACAGAUCUAAUAGGAAU	TTTC	438
Exón 45 humano	27	-1	AGGGCGACAGAUCUAAUAGGAAUG	TTTT	439
Exón 45 humano	28	1	UAAAGAAAGCUUAAAAAGUCUGCU	TTTT	440
Exón 45 humano	29	1	CUAAAGAAAGCUUAAAAAGUCUGC	TTTA	441
Exón 45 humano	30	1	AAAUAUUCUUCUAAAGAAAGCUUA	TTTT	442
Exón 45 humano	31	1	GAAAUAUUCUUCUAAAGAAAGCUU	TTTT	443
Exón 45 humano	32	1	UGAAAUAUUCUUCUAAAGAAAGCU	TTTA	444
Exón 45 humano	33	1	UCUCUCAUGAAAUAUUCUUCUAAA	TTTC	445
Exón 45 humano	34	1	AUAAUCUCUCAUGAAAUAUUCUUC	TTTA	446
Exón 44 humano	1	1	GCGUAUAUUUUUUGGUUAUACUGA	TTTG	447
Exón 44 humano	2	1	ucaagaaaaauagauggauuaugu	tttt	448
Exón 44 humano	3	1	aucaagaaaaauagauggauuaug	ttta	449
Exón 44 humano	4	1	CAGGUaaaagcauauggaucaaga	tttt	450
Exón 44 humano	5	1	GCAGGUaaaagcauauggaucaag	tttt	451
Exón 44 humano	6	1	UGCAGGUaaaagcauauggaucaa	tttc	452
Exón 44 humano	7	-1	CAGGCGAUUUGACAGAUCUGUUGA	TTTC	453
Exón 44 humano	8	1	AGAUCUGUCAAAUCGCCUGCAGGU	tttt	454
Exón 44 humano	9	1	CAGAUCUGUCAAAUCGCCUGCAGG	tttA	455
Exón 44 humano	10	1	GCCGCCAUUUCUCAACAGAUCUGU	TTTG	456
Exón 44 humano	11	-1	AAUGGCGGCGUUUUCAUUAUGAUA	TTTA	457
Exón 44 humano	12	1	AUUAAAUAUCUUUAUAUCAUAAUG	TTTT	458
Exón 44 humano	13	-1	UGAGAAUUGGGAACAUGCUAAAUA	TTTG	459
Exón 44 humano	14	-1	GGUAAGUCUUUGAUUUGUUUUUUC	TTTC	460
Exón 44 humano	15	1	AAAUACAAUUUCGAAAAAACAAAU	TTTG	461
Exón 44 humano	16	1	AAGAUAAAUACAAUUUCGAAAAAA	TTTG	462
Exón 44 humano	17	1	GCUGAAGAUAAAUACAAUUUCGAA	TTTT	463
Exón 44 humano	18	1	UGCUGAAGAUAAAUACAAUUUCGA	TTTT	464
Exón 44 humano	19	1	GUGCUGAAGAUAAAUACAAUUUCG	TTTT	465
Exón 44 humano	20	1	UGUGCUGAAGAUAAAUACAAUUUC	TTTC	466
Exón 44 humano	21	-1	GCACAUCUGGACUCUUUAACUUCU	TTTA	467
Exón 44 humano	22	1	UAAAGAGUCCAGAUGUGCUGAAGA	TTTA	468
Exón 44 humano	23	-1	AAGAUCAGGUUCUGAAGGGUGAUG	TTTC	469
Exón 44 humano	24	1	UUCAGAACCUGAUCUUUAAGAAGU	TTTA	470
Exón 44 humano	25	1	AAUAUAAUGAUGACAACAACAGUC	TTTT	471
Exón 44 humano	26	1	UAAUAUAAUGAUGACAACAACAGU	TTTG	472
Exón 53 humano	1	-1	UUUAUUUUUCCUUUUAUUCUAGUU	TTTC	473
Exón 53 humano	2	1	AAAGGAAAAAUAAAUAUAUAGUAG	TTTA	474

Exón 53 humano	3	1	UUUCAACUAGAAUAAAAGGAAAAA	TTTA	475
Exón 53 humano	4	1	AUUCUUUCAACUAGAAUAAAAGGA	TTTT	476
Exón 53 humano	5	1	AAUUCUUUCAACUAGAAUAAAAGG	TTTT	477
Exón 53 humano	6	1	GAAUUCUUUCAACUAGAAUAAAAG	TTTC	478
Exón 53 humano	7	1	AUUCUGAAUUCUUUCAACUAGAAU	TTTT	479
Exón 53 humano	8	1	GAUUCUGAAUUCUUUCAACUAGAA	TTTA	480
Exón 53 humano	9	-1	CAGAACCGGAGGCAACAGUUGAAU	TTTC	481
Exón 53 humano	10	-1	GGAGGCAACAGUUGAAUGAAAUGU	TTTA	482
Exón 53 humano	11	-1	UAUACAGUAGAUGCAAUCCAAAAG	TTTT	483
Exón 53 humano	12	-1	GAUGCAAUCCAAAAGAAAAUCACA	TTTC	484
Exón 53 humano	13	-1	AAUCACAGAAACCAAGGUUAGUAU	TTTG	485
Exón 53 humano	14	-1	AGGUUAGUAUCAAAGAUACCUUU	TTTA	486
Exón 53 humano	15	-1	GGUUAGUAUCAAAGAUACCUUUUU	TTTT	487
Exón 53 humano	16	-1	AGUAUCAAAGAUACCUUUUUAAAA	TTTA	488
Exón 53 humano	17	-1	GUAUCAAAGAUACCUUUUUAAAAU	TTTT	489
Exón 46 humano	1	-1	UGUUUGUGUCCCAGUUUGCAUUAA	TTTG	490
Exón 46 humano	2	1	CUGGGACACAAACAUGGCAAUUUA	TTTT	491
Exón 46 humano	3	1	ACUGGGACACAAACAUGGCAAUUU	TTTT	492
Exón 46 humano	4	1	AACUGGGACACAAACAUGGCAAUU	TTTA	493
Exón 46 humano	5	1	UAUUUGUUAAUGCAAACUGGGACA	TTTG	494
Exón 46 humano	6	-1	ACAAAUAGUUUGAGAACUAUGUUG	tttC	495
Exón 46 humano	7	-1	CAAAUAGUUUGAGAACUAUGUUGG	tttt	496
Exón 46 humano	8	-1	AAAUAGUUUGAGAACUAUGUUGGa	tttt	497
Exón 46 humano	9	-1	AUAGUUUGAGAACUAUGUUGGaaa	tttt	498
Exón 46 humano	10	-1	UAGUUUGAGAACUAUGUUGGaaaa	tttt	499
Exón 46 humano	11	-1	AGUUUGAGAACUAUGUUGGaaaaa	tttt	500
Exón 46 humano	12	1	UAGUUCUCAAACUAUUUGUUAAUG	TTTG	501
Exón 46 humano	13	1	UAuuuuuuuuuCCAACAUAGUUCU	TTTG	502
Exón 46 humano	14	-1	CUUCUUUCUCCAGGCUAGAAGAAC	TTTT	503
Exón 46 humano	15	1	CUUCUAGCCUGGAGAAAGAAGAAU	TTTT	504
Exón 46 humano	16	1	UCUUCUAGCCUGGAGAAAGAAGAA	TTTA	505
Exón 46 humano	17	1	AUUCUUUUGUUCUUCUAGCCUGGA	TTTC	506
Exón 46 humano	18	-1	CAAAAGAAUAUCUUGUCAGAAUUU	TTTG	507
Exón 46 humano	19	-1	CUGGAAAAGAGCAGCAACUAAAAG	TTTT	508
Exón 46 humano	20	-1	CAAGUCAAGGUAAUUUUAUUUUCU	TTTG	509
Exón 46 humano	21	-1	CAAAUCCCCCAGGGCCUGCUUGCA	TTTA	510
Exón 46 humano	22	1	AGGCCCUGGGGGAUUUGAGAAAAU	TTTT	511
Exón 46 humano	23	1	CAGGCCCUGGGGGAUUUGAGAAAA	TTTA	512
Exón 46 humano	24	1	CAAGCAGGCCCUGGGGGAUUUGAG	TTTT	513

Exón 46 humano	25	1	GCAAGCAGGCCCUGGGGGAUUUGA	TTTC	514
Exón 46 humano	26	1	GCAGAAAACCAAUGAUUGAAUUAA	TTTT	515
Exón 46 humano	27	1	GGCAGAAAACCAAUGAUUGAAUUA	TTTT	516
Exón 46 humano	28	1	GGGCAGAAAACCAAUGAUUGAAUU	TTTT	517
Exón 46 humano	29	1	UGGGCAGAAAACCAAUGAUUGAAU	TTTA	518
Exón 46 humano	30	-1	AUUAGGUUAUUCAUAGUUCCUUGC	TTTA	519
Exón 46 humano	31	1	AACUAUGAAUAACCUAAUGGGCAG	TTTT	520
Exón 46 humano	32	1	GAACUAUGAAUAACCUAAUGGGCA	TTTC	521
Exón 52 humano	1	-1	UAUUUCCUGUUAAAUUGUUUUCUA	TTTA	522
Exón 52 humano	2	1	GGUUUAUAGAAAACAAUUUAACAG	TTTC	523
Exón 52 humano	3	-1	AUACAGUAACAUCUUUUUUAUUUC	TTTA	524
Exón 52 humano	4	-1	UACAGUAACAUCUUUUUUAUUUCU	TTTT	525
Exón 52 humano	5	1	AUGUUACUGUAUAAGGGUUUAUAG	TTTT	526
Exón 52 humano	6	1	GAUGUUACUGUAUAAGGGUUUAUA	TTTC	527
Exón 52 humano	7	1	CAGCCAAAACACUUUUAGAAAUAA	TTTT	528
Exón 52 humano	8	1	CCAGCCAAAACACUUUUAGAAAUA	TTTT	529
Exón 52 humano	9	1	ACCAGCCAAAACACUUUUAGAAAU	TTTT	530
Exón 52 humano	10	1	GACCAGCCAAAACACUUUUAGAAA	TTTA	531
Exón 52 humano	11	1	GUGAGACCAGCCAAAACACUUUUA	TTTC	532
Exón 52 humano	12	-1	AAUUGUACUUUACUUUGUAUUAUG	TTTA	533
Exón 52 humano	13	-1	AUUGUACUUUACUUUGUAUUAUGU	TTTT	534
Exón 52 humano	14	1	UAAAGUACAAUUGUGAGACCAGCC	TTTT	535
Exón 52 humano	15	1	GUAAAGUACAAUUGUGAGACCAGC	TTTG	536
Exón 52 humano	16	1	GUAUUCCUUUUACAUAAUACAAAG	TTTA	537
Exón 52 humano	17	1	GUUGUGUAUUCCUUUUACAUAAUA	TTTG	538
Exón 52 humano	18	1	AUCCUGCAUUGUUGCCUGUAAGAA	TTTG	539
Exón 52 humano	19	1	UUCCAACUGGGGACGCCUCUGUUC	TTTG	540
Exón 52 humano	20	-1	UUGGAAGAACUCAUUACCGCUGCC	TTTG	541
Exón 52 humano	21	-1	UCAUUACCGCUGCCCAAAAUUUGA	TTTT	542
Exón 52 humano	22	1	CUCUUGAUUGCUGGUCUUGUUUUU	TTTG	543
Exón 52 humano	23	-1	GUUUUUUAACAAGCAUGGGACACA	TTTG	544
Exón 52 humano	24	1	CUUUGUGUGUCCCAUGCUUGUUAA	TTTT	545
Exón 52 humano	25	1	GCUUUGUGUGUCCCAUGCUUGUUA	TTTT	546
Exón 52 humano	26	1	UGCUUUGUGUGUCCCAUGCUUGUU	TTTT	547
Exón 52 humano	27	1	UUGCUUUGUGUGUCCCAUGCUUGU	TTTA	548
Exón 52 humano	28	-1	AGCAAGAUGCAUGACAAGUUUCAA	TTTA	549
Exón 52 humano	29	-1	GCAAGAUGCAUGACAAGUUUCAAU	TTTT	550
Exón 52 humano	30	-1	CAAGAUGCAUGACAAGUUUCAAUA	TTTT	551
Exón 52 humano	31	1	GAUAUAUGAACUUAAGUUUUUAUU	TTTC	552

Exón 50 humano	1	-1	AUAGAAAUCCAAUAAUAUAUUCAC	TTTG	553
Exón 50 humano	2	-1	AUUAAGAUGUUCAUGAAUUAUCUU	TTTG	554
Exón 50 humano	3	-1	UAAGUAAUGUGUAUGCUUUUCUGU	TTTA	555
Exón 50 humano	4	1	AUCUUCUAACUUCCUCUUUAACAG	TTTT	556
Exón 50 humano	5	1	GAUCUUCUAACUUCCUCUUUAACA	TTTC	557
Exón 50 humano	6	-1	AUCUGAGCUCUGAGUGGAAGGCGG	TTTA	558
Exón 50 humano	7	-1	ACCGUUUACUUCAAGAGCUGAGGG	TTTG	559
Exón 50 humano	8	1	CUGCUUUGCCCUCAGCUCUUGAAG	TTTA	560
Exón 50 humano	9	-1	UCUCUUUGGCUCUAGCUAUUUGUU	TTTG	561
Exón 50 humano	10	-1	CUCUUUGGCUCUAGCUAUUUGUUC	TTTT	562
Exón 50 humano	11	1	CACUUUUGAACAAAUAGCUAGAGC	TTTG	563
Exón 50 humano	12	1	UCACUUCAUAGUUGCACUUUUGAA	TTTG	564
Exón 50 humano	13	-1	AUGAAGUGAUGACUGGGUGAGAGA	TTTC	565
Exón 50 humano	14	-1	UGAAGUGAUGACUGGGUGAGAGAG	TTTT	566
Exón 43 humano	1	1	AAGAGAAAAauauauauauauaua	TTTG	567
Exón 43 humano	2	1	GAAUUAGCUGUCUAUAGAAAGAGA	tTTT	568
Exón 43 humano	3	1	UGAAUUAGCUGUCUAUAGAAAGAG	TTTT	569
Exón 43 humano	4	-1	AGCUAAUUCAUUUUUUUACUGUUU	TTTA	570
Exón 43 humano	5	1	AUGAAUUAGCUGUCUAUAGAAAGA	TTTC	571
Exón 43 humano	6	-1	GCUAAUUCAUUUUUUUACUGUUUU	TTTT	572
Exón 43 humano	7	1	AAAAAAAUGAAUUAGCUGUCUAUA	TTTC	573
Exón 43 humano	8	-1	UUAAAAUUUUUAUAUUACAGAAUA	TTTA	574
Exón 43 humano	9	-1	UAAAAUUUUUAUAUUACAGAAUAU	TTTT	575
Exón 43 humano	10	1	AUAUAAAAAUUUUAAAACAGUAAA	TTTT	576
Exón 43 humano	11	1	AAUAUAAAAAUUUUAAAACAGUAA	TTTT	577
Exón 43 humano	12	1	UAAUAUAAAAAUUUUAAAACAGUA	TTTT	578
Exón 43 humano	13	1	GUAAUAUAAAAAUUUUAAAACAGU	TTTT	579
Exón 43 humano	14	1	UGUAAUAUAAAAAUUUUAAAACAG	TTTA	580
Exón 43 humano	15	1	UAUAUUCUGUAAUAUAAAAAUUUU	TTTT	581
Exón 43 humano	16	1	UUAUAUUCUGUAAUAUAAAAAUUU	TTTA	582
Exón 43 humano	17	-1	CAGAAUAUAAAAGAUAGUCUACAA	TTTG	583
Exón 43 humano	18	1	CUAUCUUUUAUAUUCUGUAAUAUA	TTTT	584
Exón 43 humano	19	1	ACUAUCUUUUAUAUUCUGUAAUAU	TTTT	585
Exón 43 humano	20	1	GACUAUCUUUUAUAUUCUGUAAUA	TTTA	586
Exón 43 humano	21	-1	CAUAGCAAGAAGACAGCAGCAUUG	TTTG	587
Exón 43 humano	22	1	CAUUUUGUUAACUUUUUCCCAUUG	TTTC	588
Exón 43 humano	23	-1	CAUAUAUUUUUCUUGAUACUUGCA	TTTC	589
Exón 43 humano	24	1	AAAUCAUUUCUGCAAGUAUCAAGA	TTTT	590
Exón 43 humano	25	1	CAAAUCAUUUCUGCAAGUAUCAAG	TTTT	591

Exón 43 humano	26	1	ACAAAUCAUUUCUGCAAGUAUCAA	TTTC	592
Exón 43 humano	27	1	AUAAAUUCUACAGUUCCCUGAAAA	TTTG	593
Exón 43 humano	28	-1	GAAUUUAUUUCAGUACCCUCCAUG	TTTC	594
Exón 43 humano	29	-1	AAUUUAUUUCAGUACCCUCCAUGG	TTTT	595
Exón 43 humano	30	1	UGAAAUAAAUUCUACAGUUCCCUG	TTTT	596
Exón 43 humano	31	-1	AUUUAUUUCAGUACCCUCCAUGGA	TTTT	597
Exón 43 humano	32	1	CUGAAAUAAAUUCUACAGUUCCCU	TTTC	598
Exón 43 humano	33	-1	UUUAUUUCAGUACCCUCCAUGGAA	TTTT	599
Exón 43 humano	34	-1	UACCCUCCAUGGAAAAAAGACAGG	TTTC	600
Exón 43 humano	35	-1	ACCCUCCAUGGAAAAAAGACAGGG	TTTT	601
Exón 43 humano	36	-1	CCCUCCAUGGAAAAAAGACAGGGA	TTTT	602
Exón 43 humano	37	1	UUUUUUCCAUGGAGGGUACUGAAA	TTTA	603
Exón 43 humano	38	1	UGUCUUUUUUCCAUGGAGGGUACU	TTTC	604
Exón 6 humano	1	1	CCUUGAGCAAGAACCAUGCAAACU	TTTA	605
Exón 6 humano	2	-1	UGCUCAAGGAAUGCAUUUUCUUAU	TTTC	606
Exón 6 humano	3	-1	GCUCAAGGAAUGCAUUUUCUUAUG	TTTT	607
Exón 6 humano	4	1	UGCAUUCCUUGAGCAAGAACCAUG	TTTG	608
Exón 6 humano	5	-1	GAAAAUUUAUUUCCACAUGUAGGU	TTTG	609
Exón 6 humano	6	-1	AAAAUUUAUUUCCACAUGUAGGUC	TTTT	610
Exón 6 humano	7	-1	AAAUUUAUUUCCACAUGUAGGUCA	TTTT	611
Exón 6 humano	8	1	CAUGUGGAAAUAAAUUUUCAUAAG	TTTT	612
Exón 6 humano	9	1	ACAUGUGGAAAUAAAUUUUCAUAA	TTTC	613
Exón 6 humano	10	-1	CCACAUGUAGGUCAAAAAUGUAAU	TTTC	614
Exón 6 humano	11	-1	CACAUGUAGGUCAAAAAUGUAAUG	TTTT	615
Exón 6 humano	12	-1	ACAUGUAGGUCAAAAAUGUAAUGA	TTTT	616
Exón 6 humano	13	1	ACAUUUUUGACCUACAUGUGGAAA	TTTA	617
Exón 6 humano	14	1	CAUUACAUUUUUGACCUACAUGUG	TTTC	618
Exón 6 humano	15	-1	AAAAAUAUCAUGGCUGGAUUGCAA	TTTG	619
Exón 6 humano	16	-1	GCUGGAUUGCAACAAACCAACAGU	TTTC	620
Exón 6 humano	17	-1	CUGGAUUGCAACAAACCAACAGUG	TTTT	621
Exón 6 humano	18	1	CCUAUGACUAUGGAUGAGAGCAUU	TTTG	622
Exón 6 humano	19	-1	UAGGUAAGAAGAUUACUGAGACAU	TTTA	623
Exón 6 humano	20	-1	AUUACUGAGACAUUAAAUAACUUG	TTTA	624
Exón 6 humano	21	-1	UUACUGAGACAUUAAAUAACUUGU	TTTT	625
Exón 6 humano	22	1	GGGGAAAAAUAUGUCAUCAGAGUC	TTTA	626
Exón 6 humano	23	1	CAUGAUCUGGAACCAUACUGGGGA	TTTT	627
Exón 6 humano	24	1	ACAUGAUCUGGAACCAUACUGGGG	TTTT	628
Exón 6 humano	25	1	GACAUGAUCUGGAACCAUACUGGG	TTTC	629
Exón 7 humano	1	1	uacacacauacacaAAGACAAAUA	TTTA	630

Exón 7 humano	2	1	uacacauacacacauacacaAAGA	TTTG	631
Exón 7 humano	3	1	aacacauacacauacacacauaca	TTtg	632
Exón 7 humano	4	1	AUUCCAGUCAAAUAGGUCUGGCCU	ttTT	633
Exón 7 humano	5	1	UAUUCCAGUCAAAUAGGUCUGGCC	tTTA	634
Exón 7 humano	6	1	GCUGGCAAACCACACUAUUCCAGU	TTTG	635
Exón 7 humano	7	1	AGUCGUUGUGUGGCUGACUGCUGG	TTTG	636
Exón 7 humano	8	-1	CGCCAGAUAUCAAUUAGGCAUAGA	TTTC	637
Exón 7 humano	9	-1	AAACUACUCGAUCCUGAAGGUUGG	TTTA	638
Exón 7 humano	10	1	CAUACUAAAAGCAGUGGUAGUCCA	TTTC	639
Exón 7 humano	11	1	GAAAACAUUAAACUCUACCAUACU	TTTT	640
Exón 7 humano	12	1	UGAAAACAUUAAACUCUACCAUAC	TTTA	641
Exón 8 humano	1	-1	UUGUUCAUUAUCCUUUUAGAGUCU	TTTG	642
Exón 8 humano	2	1	AAAGGAUAAUGAACAAAUCAAAGU	TTTA	643
Exón 8 humano	3	-1	UAUCCUUUUAGAGUCUCAAAUAUA	TTTC	644
Exón 8 humano	4	1	ACUCUAAAAGGAUAAUGAACAAAU	TTTG	645
Exón 8 humano	5	-1	UUUUAGAGUCUCAAAUAUAGAAAC	TTTG	646
Exón 8 humano	6	-1	UUUAGAGUCUCAAAUAUAGAAACC	TTTT	647
Exón 8 humano	7	-1	UUAGAGUCUCAAAUAUAGAAACCA	TTTT	648
Exón 8 humano	8	1	UUGAGACUCUAAAAGGAUAAUGAA	TTTG	649
Exón 8 humano	9	1	UUUGGUUUCUAUAUUUGAGACUCU	TTTT	650
Exón 8 humano	10	1	UUUUGGUUUCUAUAUUUGAGACUC	TTTA	651
Exón 8 humano	11	-1	AGCAUUGAAGCCAUCCAGGAAGUG	TTTC	652
Exón 8 humano	12	1	GCUUCAAUGCUCACUUGUUGAGGC	TTTT	653
Exón 8 humano	13	1	GGCUUCAAUGCUCACUUGUUGAGG	TTTG	654
Exón 8 humano	14	-1	AGUGGAAAUGUUGCCAAGGCCACC	TTTA	655
Exón 8 humano	15	-1	GUUGCCAAGGCCACCUAAAGUGAC	TTTA	656
Exón 8 humano	16	-1	GAAGAACAUUUUCAGUUACAUCAU	TTTG	657
Exón 8 humano	17	-1	AUCAAAUGCACUAUUCUCAACAGG	TTTA	658
Exón 8 humano	18	1	AUAGUGCAUUUGAUGAUGUAACUG	TTTT	659
Exón 8 humano	19	1	AAUAGUGCAUUUGAUGAUGUAACU	TTTC	660
Exón 8 humano	20	-1	ACUAUUCUCAACAGGUAAAGUGUG	TTTA	661
Exón 8 humano	21	1	UACCUAAAAAUGCAUAUAAAACAG	TTTT	662
Exón 8 humano	22	1	AUACCUAAAAAUGCAUAUAAAACA	TTTC	663
Exón 8 humano	23	1	CACGUAAUACCUAAAAAUGCAUAU	TTTT	664
Exón 8 humano	24	1	GCACGUAAUACCUAAAAAUGCAUA	TTTA	665
Exón 8 humano	25	1	auauauauGUGCACGUAAUACCUA	TTTT	666
Exón 8 humano	26	1	uauauauauGUGCACGUAAUACCU	TTTT	667
Exón 8 humano	27	1	auauauauauGUGCACGUAAUACC	TTTA	668
Exón 55 humano	1	-1	CUGCACAAUAUUAUAGUUGUUGCU	TTTA	669

Exón 55 humano	2	1	AUAAAAAGAGAAAGAUGGAGGAAC	TTTA	670
Exón 55 humano	3	1	CACCUAGUGAACUCCAUAAAAAGA	TTTC	671
Exón 55 humano	4	1	AUGGUGCACCUAGUGAACUCCAUA	TTTT	672
Exón 55 humano	5	1	AAUGGUGCACCUAGUGAACUCCAU	TTTT	673
Exón 55 humano	6	1	GAAUGGUGCACCUAGUGAACUCCA	TTTA	674
Exón 55 humano	7	1	GACCAAAUGUUCAGAUGCAAUUAU	TTTA	675
Exón 55 humano	8	1	UCGCUCACUCACCCUGCAAAGGAC	TTTG	676
Exón 55 humano	9	-1	AGUGAGCGAGAGGCUGCUUUGGAA	TTTC	677
Exón 55 humano	10	1	GCAGCCUCUCGCUCACUCACCCUG	TTTG	678
Exón 55 humano	11	1	UUGCAGUAAUCUAUGAGUUUCUUC	TTTG	679
Exón 55 humano	12	-1	CUGCAACAGUUCCCCCUGGACCUG	TTTC	680
Exón 55 humano	13	-1	UGCAACAGUUCCCCCUGGACCUGG	TTTT	681
Exón 55 humano	14	-1	UUUCUUGCCUGGCUUACAGAAGCU	TTTC	682
Exón 55 humano	15	1	UUUCAGCUUCUGUAAGCCAGGCAA	TTTC	683
Exón 55 humano	16	-1	GUCCUACAGGAUGCUACCCGUAAG	TTTC	684
Exón 55 humano	17	-1	GGCUCCUAGAAGACUCCAAGGGAG	TTTA	685
Exón 55 humano	18	-1	GCUCCUAGAAGACUCCAAGGGAGU	TTTT	686
Exón 55 humano	19	-1	CUCCAAGGGAGUAAAAGAGCUGAU	TTTC	687
Exón 55 humano	20	1	UGGAUCCACAAGAGUGCUAAAGCG	TTTC	688
Exón 55 humano	21	1	GUUCAAUUGGAUCCACAAGAGUGC	TTTA	689
Exón 55 humano	22	-1	UACUUGUAACUGACAAGCCAGGGA	TTTG	690
Exón 55 humano	23	-1	ACUUGUAACUGACAAGCCAGGGAC	TTTT	691
Exón 55 humano	24	-1	GUAACUGACAAGCCAGGGACAAAA	TTTG	692
Exón 55 humano	25	-1	UAACUGACAAGCCAGGGACAAAAC	TTTT	693
Exón 55 humano	26	1	UCCCUGGCUUGUCAGUUACAAGUA	TTTG	694
Exón 51 G1 humano		1	CAGAGUAACAGUCUGAGUAGGAGc	TTTA	695
Exón 52 G1 humano		1	uacuuuguuuagcaauacauggua	TTTC	696
Exón 51 G3 humano		-1	uggcucaaauuguuacucuucaau	TTTA	697
Exón 23 G1 de ratón		1	CUUUCAAagaacuuugcagagccu	TTTG	698
Exón 23 G2 de ratón		1	guugaaGCCAUUUUGUUGCUCUUU	TTTG	699
Exón 23 G3 de ratón		1	guugaaGCCAUUUUAUUGCUCUUU	TTTG	700
Exón 23 G4 de ratón		-1	uuuugagGCUCUGCAAAGUUCUUU	TTTC	701
Exón 23 G5 de ratón		-1	aguuauuaaugcauagauauucag	TTTA	702
Exón 23 G6 de ratón		-1	uauaauaugcccuguaauauaaua	TTTC	703
Exón 23 G7 de ratón		1	uaaaggccaaaccucggcuuaccU	TTTC	704
Exón 23 G8 de ratón		1	ucaauaucuuugaaggacucuggg	TTTA	705

***** En esta tabla, las letras mayúsculas representan los nucleótidos de ARNgs que se alinean con la secuencia de exones del gen. Las letras minúsculas representan nucleótidos de ARNgs que se

alinean con la secuencia de intrones del gen.

VI. Tablas de secuencias

Tabla 8: Sitios genómicos diana para ARNgs en el exón 51 de *Dmd* de ratón

ID de ARNgs	Cadena	Sitio diana	La SEQ ID NO:	PAM
Ex51-SA1	3’	AGAGTAACAGTCTGACTGG	706	CAG
Ex51-SD	5’	GAAATGATCATCAAACAGA	707	AGG
Ex51-SA-2	3’	CACTAGAGTAACAGTCTGAC	708	TGG

Tabla 9: secuencias de ARNg dirigidas al exón 51 de *Dmd* de ratón

ID de ARNgs	Cadena	Sitio diana	La SEQ ID NO:	PAM
Ex51-SA1	3’	CCAGUCAGACUGUUACUCU	709	CAG
Ex51-SD	5’	UCUGUUUGAUGAUCAUUUC	710	AGG
Ex51-SA-2	3’	GUCAGACUGUUACUCUAGUG	711	TGG

Tabla 10: Secuencias genómicas diana para ARNgs dirigidos al exón 51 de *Dmd* humano

ID de ARNgs	Cadena	Sitio diana	La SEQ ID NO:	PAM
Ex51-SA	3’	AGAGTAACAGTCTGAGTAG	712	GAG
Ex51-SD	5’	GAGATGATCATCAAGCAGA	713	AGG
Ex51-SA-2	3’	CACCAGAGTAACAGTCTGAG	714	TAG

Tabla 11: secuencias de ARNgs dirigidas al exón 51 de *Dmd* humano

ID de ARNgs	Cadena	Sitio diana	La SEQ ID NO:	PAM
Ex51-SA	3’	CUACUCAGACUGUUACUCU	715	GAG
Ex51-SD	5’	UCUGCUUGAUGAUCAUCUC	716	AGG
Ex51-SA-2	3’	CUCAGACUGUUACUCUGGUG	717	TAG

Tabla 12: Secuencias genómicas sitios de direccionamiento dea ARNgs en varios exones de *Dmd* humano

ID de ARNgs	Cadena	Sitio diana	La SEQ ID NO:	PAM
Exón 51-#1	3’	CAGAGTAACAGTCTGAGTAG	947	GAG
Exón 51-#2	3’	CACCAGAGTAACAGTCTGAG	718	TAG
Exón 51-#3	3’	TATTTTGGGTTTTTGCAAAA	719	AGG
Exón 51-#4	3’	AGTAGGAGCTAAAATATTTT	720	GGG
Exón 51-#5	3’	GAGTAGGAGCTAAAATATTT	721	TGG
Exón 51-#6	3’	ACCAGAGTAACAGTCTGAGT	722	AGG
Exón 51-#7	5’	TCCTACTCAGACTGTTACTC	723	TGG
Exón 51-#8	5’	TACTCTGGTGACACAACCTG	724	TGG
Exón 51-#9	3’	GCAGTTTCCTTAGTAACCAC	725	AGG
Exón 51-#10	5’	GACACAACCTGTGGTTACTA	726	AGG
Exón 51-#11	3’	TGTCACCAGAGTAACAGTCT	727	GAG
Exón 51-#12	3’	AGGTTGTGTCACCAGAGTAA	728	CAG
Exón 51-#13	3’	AACCACAGGTTGTGTCACCA	729	GAG
Exón 51-#14	3’	GTAACCACAGGTTGTGTCAC	730	CAG
Exón 53-#1	5’	ATTTATTTTTCCTTTTATTC	731	TAG
Exón 53-#2	5’	TTTCCTTTTATTCTAGTTGA	732	AAG
Exón 53-#3	3’	TGATTCTGAATTCTTTCAAC	733	TAG

Exón 53-#4	3’	AATTCTTTCAACTAGAATAA	734	AAG
Exón 53-#6	5’	TTATTCTAGTTGAAAGAATT	735	CAG
Exón 53-#7	5’	TAGTTGAAAGAATTCAGAAT	736	CAG
Exón 53-#8	5’	AATTCAGAATCAGTGGGATG	737	AAG
Exón 53-#9	3’	ATTCTTTCAACTAGAATAAA	738	AGG
Exón 53-#10	5’	TTGAAAGAATTCAGAATCAG	739	TGG
Exón 53-#11	5’	TGAAAGAATTCAGAATCAGT	740	GGG
Exón 53-#12	3’	ACTGTTGCCTCCGGTTCTGA	741	AGG
Exón 44-#1	3’	CAGATCTGTCAAATCGCCTG	742	CAG
Exón 44-#2	3’	AAAACGCCGCCATTTCTCAA	743	CAG
Exón 44-#3	3’	AGATCTGTCAAATCGCCTGC	744	AGG
Exón 44-#4	3’	TATGGATCAAGAAAAATAGA	745	TGG
Exón 44-#5	3’	CGCCTGCAGGTAAAAGCATA	746	TGG
Exón 44-#6	5’	ATCCATATGCTTTTACCTGC	747	AGG
Exón 44-#8	5’	TTGACAGATCTGTTGAGAAA	748	TGG
Exón 44-#9	5’	ACAGATCTGTTGAGAAATGG	749	CGG
Exón 44-#11	5’	GGCGATTTGACAGATCTGTT	750	GAG
Exón 44-#13	5’	GGCGTTTTCATTATGATATA	751	AAG
Exón 44-#14	5’	ATGATATAAAGATATTTAAT	752	CAG
Exón 44-#15	5’	GATATTTAATCAGTGGCTAA	753	CAG
Exón 44-#16	5’	ATTTAATCAGTGGCTAACAG	754	AAG
Exón 44-#17	3’	AGAAACTGTTCAGCTTCTGT	755	TAG
Exón 43-#1	5’	GTTTTAAAATTTTTATATTA	756	CAG
Exón 43-#2	5’	TTTTATATTACAGAATATAA	757	AAG
Exón 43-#3	5’	ATATTACAGAATATAAAAGA	758	TAG
Exón 45-#1	3’	GTTCCTGTAAGATACCAAAA	759	AGG
Exón 45-#2	5’	TTGCCTTTTTGGTATCTTAC	760	AGG
Exón 45-#3	5’	TGGTATCTTACAGGAACTCC	761	AGG

Exón 45-#4	5’	ATCTTACAGGAACTCCAGGA	762	TGG
Exón 45-#5	3’	GCCGCTGCCCAATGCCATCC	763	TGG
Exón 45-#6	5’	CAGGAACTCCAGGATGGCAT	764	TGG
Exón 45-#7	5’	AGGAACTCCAGGATGGCATT	765	GGG
Exón 45-#8	5’	TCCAGGATGGCATTGGGCAG	766	CGG
Exón 45-#9	5’	GTCAGAACATTGAATGCAAC	767	TGG
Exón 45-#10	3’	AGTTCCTGTAAGATACCAAA	768	AAG
Exón 45-#11	3’	TGCCATCCTGGAGTTCCTGT	769	AAG
Exón 45-#12	5’	TTGGTATCTTACAGGAACTC	770	CAG
Exón 45-#13	3’	CGCTGCCCAATGCCATCCTG	771	GAG
Exón 45-#14	5’	AACTCCAGGATGGCATTGGG	772	CAG
Exón 45-#15	5’	GGGCAGCGGCAAACTGTTGT	773	CAG
Exón 52-#1	3’	AGATCTGTCAAATCGCCTGC	774	AGG
Exón 52-#2	3’	AATCCTGCATTGTTGCCTGT	775	AAG
Exón 52-#3	5’	CGCTGAAGAACCCTGATACT	776	AAG
Exón 52-#4	3’	GAACAAATATCCCTTAGTAT	777	CAG
Exón 52-#5	3’	CTGTAAGAACAAATATCCCT	778	TAG
Exón 52-#6	5’	CTAAGGGATATTTGTTCTTA	779	CAG
Exón 52-#8	5’	TGTTCTTACAGGCAACAATG	780	CAG
Exón 52-#9	5’	CAACAATGCAGGATTTGGAA	781	CAG
Exón 52-#10	5’	ACAATGCAGGATTTGGAACA	782	GAG
Exón 52-#11	5’	ATTTGGAACAGAGGCGTCCC	783	CAG
Exón 52-#12	5’	ACAGAGGCGTCCCCAGTTGG	784	AAG
Exón 2-#1	5’	TATTTTTTTATTTTGCATTT	785	TAG
Exón 2-#2	5’	TTATTTTGCATTTTAGATGA	786	AAG
Exón 2-#3	5’	ATTTTGCATTTTAGATGAAA	787	GAG
Exón 2-#4	5’	TTGCATTTTAGATGAAAGAG	788	AAG
Exón 2-#5	5’	ATGAAAGAGAAGATGTTCAA	789	AAG

Tabla 13: secuencias de ARNg para sitios de diana en varios exones de *Dmd* humanos

ID de ARNgs	Cadena	Sitio diana	SEQ ID NO:	PAM
Exón 51-#1	3’	CUACUCAGACUGUUACUCUG	790	GAG
Exón 51-#2	3’	CUCAGACUGUUACUCUGGUG	791	TAG
Exón 51-#3	3’	UUUUGCAAAAACCCAAAAUA	792	AGG
Exón 51-#4	3’	AAAAUAUUUUAGCUCCUACU	793	GGG
Exón 51-#5	3’	AAAUAUUUUAGCUCCUACUC	794	TGG
Exón 51-#6	3’	ACUCAGACUGUUACUCUGGU	795	AGG
Exón 51-#7	5’	GAGUAACAGUCUGAGUAGGA	796	TGG
Exón 51-#8	5’	CAGGUUGUGUCACCAGAGUA	797	TGG
Exón 51-#9	3’	GUGGUUACUAAGGAAACUGC	798	AGG
Exón 51-#10	5’	UAGUAACCACAGGUUGUGUC	799	AGG
Exón 51-#11	3’	AGACUGUUACUCUGGUGACA	800	GAG
Exón 51-#12	3’	UUACUCUGGUGACACAACCU	801	CAG
Exón 51-#13	3’	UGGUGACACAACCUGUGGUU	802	GAG
Exón 51-#14	3’	GUGACACAACCUGUGGUUAC	803	CAG
Exón 53-#1	5’	GAAUAAAAGGAAAAAUAAAU	804	TAG
Exón 53-#2	5’	UCAACUAGAAUAAAAGGAAA	805	AAG
Exón 53-#3	3’	GUUGAAAGAAUUCAGAAUCA	806	TAG
Exón 53-#4	3’	UUAUUCUAGUUGAAAGAAUU	807	AAG
Exón 53-#6	5’	AAUUCUUUCAACUAGAAUAA	808	CAG
Exón 53-#7	5’	AUUCUGAAUUCUUUCAACUA	809	CAG
Exón 53-#8	5’	CAUCCCACUGAUUCUGAAUU	810	AAG
Exón 53-#9	3’	UUUAUUCUAGUUGAAAGAAU	811	AGG
Exón 53-#10	5’	CUGAUUCUGAAUUCUUUCAA	812	TGG
Exón 53-#11	5’	ACUGAUUCUGAAUUCUUUCA	813	GGG
Exón 53-#12	3’	UCAGAACCGGAGGCAACAGU	814	AGG

Exón 44-#1	3’	CAGGCGAUUUGACAGAUCUG	815	CAG
Exón 44-#2	3’	UUGAGAAAUGGCGGCGUUUU	816	CAG
Exón 44-#3	3’	GCAGGCGAUUUGACAGAUCU	817	AGG
Exón 44-#4	3’	UCUAUUUUUCUUGAUCCAUA	818	TGG
Exón 44-#5	3’	UAUGCUUUUACCUGCAGGCG	819	TGG
Exón 44-#6	5’	GCAGGUAAAAGCAUAUGGAU	820	AGG
Exón 44-#8	5’	UUUCUCAACAGAUCUGUCAA	821	TGG
Exón 44-#9	5’	CCAUUUCUCAACAGAUCUGU	822	CGG
Exón 44-#11	5’	AACAGAUCUGUCAAAUCGCC	823	GAG
Exón 44-#13	5’	UAUAUCAUAAUGAAAACGCC	824	AAG
Exón 44-#14	5’	AUUAAAUAUCUUUAUAUCAU	825	CAG
Exón 44-#15	5’	UUAGCCACUGAUUAAAUAUC	826	CAG
Exón 44-#16	5’	CUGUUAGCCACUGAUUAAAU	827	AAG
Exón 44-#17	3’	ACAGAAGCUGAACAGUUUCU	828	TAG
Exón 43-#1	5’	UAAUAUAAAAAUUUUAAAAC	829	CAG
Exón 43-#2	5’	UUAUAUUCUGUAAUAUAAAA	830	AAG
Exón 43-#3	5’	UCUUUUAUAUUCUGUAAUAU	831	TAG
Exón 45-#1	3’	UUUUGGUAUCUUACAGGAAC	832	AGG
Exón 45-#2	5’	GUAAGAUACCAAAAAGGCAA	833	AGG
Exón 45-#3	5’	GGAGUUCCUGUAAGAUACCA	834	AGG
Exón 45-#4	5’	UCCUGGAGUUCCUGUAAGAU	835	TGG
Exón 45-#5	3’	GGAUGGCAUUGGGCAGCGGC	836	TGG
Exón 45-#6	5’	AUGCCAUCCUGGAGUUCCUG	837	TGG
Exón 45-#7	5’	AAUGCCAUCCUGGAGUUCCU	838	GGG
Exón 45-#8	5’	CUGCCCAAUGCCAUCCUGGA	839	CGG
Exón 45-#9	5’	GUUGCAUUCAAUGUUCUGAC	840	TGG
Exón 45-#10	3’	UUUGGUAUCUUACAGGAACU	841	AAG
Exón 45-#11	3’	ACAGGAACUCCAGGAUGGCA	842	AAG
Exón 45-#12	5’	GAGUUCCUGUAAGAUACCAA	843	CAG

Exón 45-#13	3’	CAGGAUGGCAUUGGGCAGCG	844	GAG
Exón 45-#14	5’	CCCAAUGCCAUCCUGGAGUU	845	CAG
Exón 45-#15	5’	ACAACAGUUUGCCGCUGCCC	846	CAG
Exón 52-#1	3’	GCAGGCGAUUUGACAGAUCU	847	AGG
Exón 52-#2	3’	ACAGGCAACAAUGCAGGAUU	848	AAG
Exón 52-#3	5’	AGUAUCAGGGUUCUUCAGCG	849	AAG
Exón 52-#4	3’	AUACUAAGGGAUAUUUGUUC	850	CAG
Exón 52-#5	3’	AGGGAUAUUUGUUCUUACAG	851	TAG
Exón 52-#6	5’	UAAGAACAAAUAUCCCUUAG	852	CAG
Exón 52-#8	5’	CAUUGUUGCCUGUAAGAACA	853	CAG
Exón 52-#9	5’	UUCCAAAUCCUGCAUUGUUG	854	CAG
Exón 52-#10	5’	UGUUCCAAAUCCUGCAUUGU	855	GAG
Exón 52-#11	5’	GGGACGCCUCUGUUCCAAAU	856	CAG
Exón 52-#12	5’	CCAACUGGGGACGCCUCUGU	857	AAG
Exón 2-#1	5’	ACAGAGGCGUCCCCAGUUGG	858	TAG
Exón 2-#2	5’	UCAUCUAAAAUGCAAAAUAA	859	AAG
Exón 2-#3	5’	UUUCAUCUAAAAUGCAAAAU	860	GAG
Exón 2-#4	5’	CUCUUUCAUCUAAAAUGCAA	861	AAG
Exón 2-#5	5’	UUGAACAUCUUCUCUUUCAU	862	AAG

Tabla 14: Secuencia genómica diana para ARNgs dirigidos al exón 51 de *Dmd* de perro

ID de ARNgs	Cadena	Sitio diana	SEQ ID NO:	PAM
Ex51-SA-2	3’	CACCAGAGTAACAGTCTGAC	863	TGG

Tabla 15: secuencia de ARNg dirigidas al exón 51 de *Dmd* de perro

ID de ARNgs	Cadena	Sitio diana	SEQ ID NO:	PAM

Ex51-SA-2	3’	GUCAGACUGUUACUCUGGUG	864	TGG

VII. Ejemplos

Los siguientes ejemplos se incluyen para demostrar las modalidades preferidas de la descripción. Los expertos en la técnica apreciarán que las técnicas descritas en los ejemplos a continuación representan las técnicas descubiertas por el inventor para que la práctica de la descripción pueda funcionar correctamente y, por lo tanto, puede considerarse que constituyen los modos preferidos para su práctica. No obstante, los expertos en la técnica, en función de la presente descripción, deben observar que se pueden realizar muchos cambios en las modalidades específicas descritas y seguir obteniendo un resultado igual o similar sin alejarse del espíritu y alcance de la descripción.

EJEMPLO 1 - Materiales y métodos

Aprobación del estudio. Todos los procedimientos experimentales que involucran animales en este estudio fueron revisados y aprobados por el Comité Institucional de Cuidado y Uso de Animales del Texas Southwestern Medical Center.

Eliminación del exón 50 mediada por CRISPR/Cas9 en ratones. Se clonaron dos regiones intrónicas específicas de ARN guía simple (ARNgs) que rodean la secuencia del exón 50 del locus de *Dmd* de ratón en el vector px330 mediante el uso de los siguientes cebadores: *Dmd* exón 50_F1: 5’-CACCGAAATGATGAGTGAAGTTATAT-3’ (SEQ ID NO: 926); *Dmd* exón 50_R1: 5’-AAACATATAACTTCACTCATCATTTC-3’ (SEQ ID NO: 927); *Dmd* exón 50_F2: 5’ CACCGGTTTGTTCAAAAGCGTGGCT-3’ (SEQ ID NO: 928); *Dmd* exón 50_R2: 5’-AAACAGCCACGCTTTTGAACAAAC-3’ (SEQ ID NO: 929).

Para la transcripción in vitro de ARNgs, se agregó la secuencia del promotor T7 a la plantilla de ARNgs mediante PCR mediante el uso de los siguientes cebadores: *Dmd* exán 50_T7-F1: GAATTGTAATACGACTCACTATAGGAATGATGAGTGAAGTTATAT (SEQ ID NO: 930); *Dmd* exón 50_T7-F2: GAATTGTAATACGACTCACTATAGGGTTTGTTCAAAAGCGTGGCT (SEQ ID NO: 931); *Dmd* exón 50_T7-Rv: AAAAGCACCGACTCGGTGCCAC (SEQ ID NO: 932).

Los productos de PCR purificados en gel se utilizaron como plantilla para la transcripción in vitro mediante el uso del kit MEGAshortscript T7 (Life Technologies). Los ARNgs se purificaron con el kit MEGAclear (Life Technologies) y se eluyeron con agua sin nucleasas (Ambion). La concentración de ARN guía se midió con un instrumento NanoDrop (Thermo Scientific).

Genotipado de ratones ΔEx50. Los ratones ΔEx50 fueron genotipados mediante el uso de cebadores que abarcan la región diana: Geno50-F: 5’-GGATTGACTGAAATGATGGCCAAGG-3’

(SEQ ID NO: 937); Geno50-R: 5'-CTGCCACGATTACTCTGCTTCCAG-3' (SEQ ID NO: 938). Las biopsias de cola se digirieron en 100 µL de NaOH 25 mM, EDTA 0,2 mM (pH 12) durante 20 min a 95 °C. Las colas se centrifugaron brevemente y luego se agregaron 100 µL de Tris 40 mM·HCl (pH 5) y se mezclaron para homogeneizar. Se usaron dos microlitros de esta reacción para reacciones de PCR posteriores con los cebadores a continuación, seguido de electroforesis en gel.

Plásmidos. El plásmido pSpCas9 (BB) -2A-GFP (PX458) que contiene el gen SpCas9 optimizado con codón humano con 2A-EGFP y la estructura principal de ARNgs se adquirió de Addgene (plásmido nº 48138). Los plásmidos AAV TRIPSR se obtuvieron del Dr. Dirk Grimm (Hospital Universitario de Heidelberg). La clonación de ARNgs se realizó mediante el uso de un sitio BbsI. El plásmido pGL3-CK8e se obtuvo del Dr. Stephen Hauschka (Departamento de Bioquímica, Universidad de Washington, Seattle, EE. UU.). El plásmido AAV-miniCMV-Cas9-PoliA corto se obtuvo del Dr. Dirk Grimm (Hospital Universitario de Heidelberg). Para generar el vector final AAV9-CK8-CRISPR/Cas9 utilizado en este manuscrito, se digirió AAV-miniCMV-Cas9-PoliA-corto con las enzimas PacI y NheI para eliminar el promotor miniCMV. El promotor CK8 se amplificó a partir del plásmido pGL3-CK8e mediante el uso de cebadores que contienen la secuencia de sitios PacI y NheI y se clonó en un vector digerido para generar el plásmido AAV-CK8-Cas9-PoliA corto.

Identificación y clonación de ARNgs para omitir el exón 51. Los ARN guía de *Dmd* exón 51 se definieron mediante el uso de crispr.mit.edu. Las secuencias guía se clonaron en el plásmido Addgene # 42230 (6), un regalo de Feng Zhang, mediante el uso de los siguientes cebadores: *Dmd* exón 51_F1: 5′- CACCGAGAGTAACAGTCTGACTGG -3' (SEQ ID NO: 942); *Dmd* exón 51_R1: 5′-AAACGTCAGACTGTTACTCTAGTGC-3′ (SEQ ID NO: 943); *Dmd* exón 51_F2: 5′-CACCGCACTAGAGTAACAGTCTGAC -3′ (SEQ ID NO: 944); *Dmd* exón 51_R2: 5′-AAACCCAGTCAGACTGTTACTCTC -3′ (SEQ ID NO: 945). Las secuencias guía se probaron en cultivo utilizando células 10T1/2 antes de la clonación en la estructura principal de AAV.

Montaje triplicado de ARNgs en la estructura principal de AAV mediante el uso del sistema Golden Gate. El montaje del sistema de clonación de la estructura principal de TRISPR de AAV se basa en dos etapas consecutivas de Golden Gate Assembly. Primera etapa del montaje del ARNg en plásmido donante. Se realiza la hibridación de oligonucleótidos calentando una reacción que contiene 2,5 µl de cada oligo (0,5 µM), 5 µl de amortiguador NE 2 (NEB) y 40 µL de ddH_2O a 95 °C durante 5 minutos mediante el uso de un bloque de calentamiento. Para la reacción de montaje en la mezcla de plásmidos donante, se mezclan 40 fmol (~100 ng) de la estructura principal de destino, 1 µL de oligos hibridados y diluidos, 0,75 µL de Esp3I, 1 µL de amortiguador tango (ambos de Thermo Scientific), 1 µL de ADN ligasa T4 (400 U/µL) (NEB), así como ATP y DTT a una concentración final de 1 mM en un volumen total de 10 µL. Con un termociclador, se realizan de 25 a 50 ciclos de 37 °C/3 min

seguidos de 20 °C/5 minutos. Desnaturalizar la enzima de restricción y la ligasa calentando a 80 °C durante 20 minutos. Usar 3 µL de esta reacción para la transformación de bacterias quimiocompetentes, que se recupera en SOC (37 °C, 800 rpm, 40 min) y extienda sobre placas de LB-Agar que contienen cloranfenicol (25 µg/mL). Los oligonucleótidos hibridados que codifican para el ARNgs se clonan en plásmidos donantes que llevan el marcador de selección negativo *ccdB* (para reducir el fondo durante la clonación), así como el gen de resistencia al cloranfenicol. Para probar el montaje correcto, los plásmidos se secuencian mediante el uso del cebador Dono-R-5'-GTATGTTGTGTGGAATTGTGAG-3 '(SEC ID NO: 948). La segunda etapa es que tres de estos plásmidos donantes que conducen la expresión de un ARNgs bajo control transcripcional del promotor U6, H1 o 7SK se agrupan en un segundo montaje Golden Gate junto con un plásmido receptor que transporta ITR de AAV. La reacción de montaje contendrá los cuatro plásmidos: plásmido donante - # 1-U6-ARNgs, plásmido donante- # 2-H1-ARNgs, plásmido donante # 3-7SK-ARNgs y plásmido receptor que contiene la ITR. La digestión con BbsI generará excedentes únicos para cada fragmento (U6, H1, 7SK, estructura principal del destinatario). Durante el procedimiento de ligadura, estos excedentes sobresalen, solo se obtiene un plásmido circularizado, cuando los tres casetes coinciden entre sí.

Medición de la creatina quinasa (CK) sérica. La CK sérica de ratón se midió mediante el núcleo de fenotipado metabólico en UT Southwestern Medical Center. La sangre se extrajo de la vena submandibular y el nivel de CK en suero se midió mediante VITROS Chemistry 7 Products CK Slides para medir cuantitativamente la actividad de CK utilizando el sistema de química VITROS 250.

Estudios caninos *in vivo*. Las inyecciones intramusculares (IM) se realizaron en 1 mes de edad ΔE50 perros MD bajo anestesia general ventilada. Se realizó una inyección única en 4 sitios diferentes del músculo tibial craneal izquierdo. Todos los perros recibieron la premedicación de un opiáceo (buprenorfina), antibiosis perioperatoria y 4 días de analgesia postoperatoria (carprofeno). Dos perros afectados recibieron rAAV mezclados con componentes mioeditantes, AAV-Cas9 y AAV-ARNgs-ex51, que se prepararon en solución de Ringer lactato a una concentración final de 1E13vg por músculo inyectado.

EJEMPLO 2 - Resultados

Un modelo humanizado de DMD. La región de mutación de punto de interés más común en pacientes con DMD es la región entre el exón 45 y el 51, y la omisión del exón 51 podría usarse para tratar al grupo más grande (13-14%) de los pacientes. Para investigar la omisión del exón 51 mediado por CRISPR/Cas9 *in vivo*, los inventores generaron un modelo de ratón que imita la región del «punto de interés» humano eliminando el exón 50 mediante el uso del sistema de CRISPR/Cas9 dirigido por

2 ARNgs (la Figura 1A). La eliminación del exón 50 se confirmó mediante la secuenciación del ADN (Figura 1B). La eliminación del exón 50 colocó el gen de la distrofina fuera del marco, lo que lleva a la ausencia de proteína distrofina en el músculo esquelético y el corazón (Figura 1C-E). Los ratones que carecen del exón 50 mostraron cambios musculares distróficos pronunciados a los 2 meses de edad (Figura 1E). El análisis del suero de los ratones delta-exón 50 mostró un aumento significativo en los niveles de creatina quinasa (CK), lo que indica daño muscular (Figura 1F). En conjunto, la expresión de la proteína distrofina, la histología muscular y los niveles de CK en suero validaron el fenotipo distrófico del modelo de ratón ΔEx50.

Restauración de la expresión de distrofina mediante una estrategia de corte único para omitir el exón 51. Cas9 de *S. pyogenes* requiere NAG/NGG como una secuencia PAM para generar una ruptura de ADN de cadena doble. Curiosamente, los sitios aceptores y donantes universales de empalmes de exones contienen NAG o NGG (Figura 3B). Por lo tanto, para corregir el marco de lectura y la expresión distrofina en el modelo de ratón ΔEx50, los inventores generaron ARNgs que se dirigió a los sitios de donador y aceptor de corte y empalme del exón 51 para eliminarlo, recreando así la proteína distrofina en el marco. Para evaluar si los ARNgs guía fueron capaces de cortar de manera eficiente, los inventores primero evaluaron su efectividad en líneas celulares humanas y de ratón (Figura 5). Para determinar la manera más eficiente de corregir el marco de lectura de DMD, los inventores compararon 2 estrategias diferentes: (1) estrategia de guía doble en la que una copia de un primer sitio de receptor de corte y empalme dirigido al ARNgs (ARNgs-SA) y una copia de un segundo sitio de receptor de donante dirigido al ARNgs (ARNgs-SD) se clonaron en el vector rAAV9-ARNgs; (2) estrategia por triplicado en la que los inventores clonaron 3 copias del mismo ARNgs (ARNgs-SA) en el vector rAAV9-ARNgs (Figura 3C). La expresión de cada copia de ARNgs-SA fue dirigida por un promotor de ARN diferente (U6, H1 y 7SK). Los inventores generaron AAV-Cas9 utilizando un vector AAV-Cas9 (CK8-Cas9-PoliA corto), que emplea un Promotor CK8 para dirigir la expresión de las SpCas9 humanizadas específicamente en los músculos esqueléticos y tejidos del corazón. Tras la inyección intramuscular (IM) de ratones P12 con AAV, se analizaron los tejidos musculares. RT-PCR de ARN de los ratones ΔEx50 inyectados con AAV-Tri-SA y AAV-SA + SD mostraron que la eliminación del exón 51 **(**ΔEx50-51) permitió el corte y empalme del exón 49 al 52 (Figura 2A, banda inferior). La secuenciación de productos RT-PCR de la banda de ΔEx50-51 confirmó que el exón 49 empalmó al exón 52 (Figura 2B). Inesperadamente, el análisis de RT-PCR mostró que una única estrategia de corte que utiliza una versión por triplicado de ARNgs-SA (AAV-Tri-SA) es tan eficiente como usar dos ARNgs - ARNgs-SA y ARNgs-SD (AAV-SA + SD).

Para evaluar más a fondo la eficacia de la estrategia de edición de AAV-Tri-SA, los inventores realizaron un análisis histológico del músculo inyectado para evaluar el número de fibras que

expresan distrofina en secciones musculares completas. Curiosamente, la distrofina inmunodeficiencia de criosecciones musculares de Los ratones ΔEx50 inyectados con AAV-Tri-SA revelaron un número significativamente mayor de fibras positivas para distrofina (promedio de 43 ± 0,9 %) en comparación con el músculo de ratones ΔEx50 inyectados con AAV-SA + SD (promedio de 31 ± 0,1 %) (Figuras 3D-E, Figura 6). El análisis de transferencia Western confirmó la restauración de la expresión de distrofina en el músculo esquelético. (Figuras 3F-G). La tinción del músculo con hematoxilina y eosina (H&E) mostró que las características histopatológicas de la distrofia muscular, como las miofibras necróticas, disminuyeron en el músculo TA a las 3 semanas de la administración de AAV (Figura 4A). El análisis cuantitativo de la distribución de las áreas de miofibras mostró un claro aumento en el tamaño de la fibra para los músculos tratados con AAV-Tri-SA y AAV-SA-SD en comparación con los músculos ΔEx50 (Figura 4B). Sin embargo, los músculos tratados con AAV-Tri-SA revelaron una mayor disminución en la frecuencia de las fibras pequeñas (<500 μm) en comparación con los músculos tratados con AAV-SA + SD. En conjunto, estos resultados demuestran que apuntar al sitio del receptor de corte y empalme del exón 51 con un solo corte usando AAV-Tri-SA es altamente eficiente para restaurar la expresión de distrofina en DMD. Este enfoque es útil para muchos trastornos que pueden corregirse con la omisión de exón.

Adaptación de la estrategia de edición genómica de corte de ADN único. Cas9 de *S. pyogenes* guiado por ARNgs se une al locus genómico diana junto a un PAM y genera una ruptura de ADN de cadena doble (DSB) de 3 nucleótidos que preceden a la secuencia de PAM. Para evaluar más a fondo la eficacia del método que se dirige al sitio del aceptor de corte y empalme, los inventores diseñaron una segunda construcción de guía triple de ARNgs (ARNgs-ex51-SA2), que se dirige a una región adyacente al sitio del aceptor de corte y empalme del exón 51. Este ARNg usa una secuencia PAM de 3 nucleótidos más en el exón para generar el DSB cerca del sitio del aceptor de corte y empalme para el exón 51 (la Figura 7A-Figura 7B). El corte cerca de la región del aceptor de corte y empalme y dentro de la secuencia del exón dio lugar a eventos de reestructuración y omisión de exón. Además, el diseño del ARNgs en la secuencia del exón que muestra una mayor conservación que la secuencia del intrón a través de las especies facilita la traducción del ARNgs a otras especies.

La actividad de corte de ADN de Cas9 junto con ARNgs-ex51-SA2 se evaluó en fibroblastos de ratón 10T1/2 utilizando el ensayo de endonucleasa I T7 (T7E1) no coincidente específico (Figura 8A). Para investigar el tipo de mutaciones generadas por Cas9 junto con ARNgs-51-SA2, se realizó un análisis genómico de secuenciación profunda. El análisis de secuenciación reveló que el 9,3 % de las mutaciones contenía una única inserción de adenosina (A) que localizaba 3 nucleótidos 3' de la secuencia de PAM. Además, 7,3 % de las mutaciones contenía eliminaciones que cubrían el sitio del aceptor de corte y empalme y un sitio potenciador decorte y empalme exónico altamente previsto

para el exón 51 (Figura 8B). El ARNgs-ex51-SA2 corresponde a una región altamente conservada del gen *Dmd* (Figuras 8C-D), y los inventores probaron la capacidad de Cas9 y ARNgs-51 humano para cortar el locus de *Dmd* humano en células 293T. El ensayo T7E1 reveló una escisión clara en el sitio predicho (Figura 8E). De manera similar, el análisis de secuencia reveló que Cas9 junto con ARNgs-ex51-SA2 humano generó la misma inserción de adenosina (A) y un rango diferente de eliminaciones alrededor del sitio de escisión (Figura 8F).

Para la administración *in vivo* de Cas9 y ARNgs-ex51-SA2 al músculo esquelético y al tejido cardíaco, se utilizó el virus adenoasociado 9 (AAV9), que muestra un tropismo preferencial para estos tejidos. Para mejorar aún más la expresión específica de los músculos, se empleó un vector AAV9-Cas9 (CK8e-Cas9-PoliA corto), que contiene un casete regulador de CK específico de los músculos, conocido como Promotor CK8e, que es altamente específico para la expresión en los músculos y el corazón (Figura 9A). En conjunto, este casete específico de músculo de 436 pb y el ADNc Cas9 de 4101 pb se encuentran dentro del límite de empaquetamiento de AAV9. La expresión de cada ARNgs fue dirigida por uno de los tres promotores de la ARN polimerasa III (U6, H1 y 7SK) (Figura 9B).

Corrección del marco de lectura de distrofina en ratones ΔEx50 mediante un solo corte de ADN. El ARNgs-ex51-SA2 se administró a ratones en copia triple (AAV-Tri-SA2), junto con un Cas9 (AAV-Cas9), mediante inyección intramuscular (IM). Tras la inyección, se analizaron los tejidos musculares. La eficacia de direccionamiento *in vivo* se estimó mediante RT-PCR con cebadores para secuencias en los exones 48 y 53 y el ensayo T7E1 para las regiones genómicas dirigidas. Para investigar si se logró una escisión eficaz de la diana, los inventores amplificaron una región de 771 pb que abarca el sitio diana y la analizaron utilizando el ensayo T7EI (Figura 10A). La actividad de SpCas9 con el ARNgs correspondiente se analizó en el sitio diana. Los ensayos T7EI revelaron mutagénesis del locus de *Dmd* después de la administración de AAV-Cas9 y AAV9-ARNgs-51-SA2 (Figura 10A). Para investigar el tipo de mutaciones generadas en los ratones ΔEx50 inyectados con Cas9 y AAV9s que expresan ARNgs, los productos de amplificación de PCR genómica que abarcan el sitio diana se analizaron mediante un análisis de secuenciación profunda de amplicón. La secuenciación profunda de la región diana indicó que el 27,9 % del total de las lecturas contenía cambios en el sitio genómico diana (Figura 10B). En promedio, el 15 % de las mutaciones identificadas contenían la misma inserción A observada en células 10T1/2 de ratón y células 293 humanas in vitro. Las eliminaciones identificadas utilizando este método abarcaron un sitio potenciador de corte y empalme exónico altamente previsto para el exón 51 (Figura 10B).

Los productos de RT-PCR de ARN del músculo de ratones ΔEx50 inyectados con AAV9-Cas9 y AAV9-ARNgs-51 mostraron que la eliminación del exón 51 (ΔEx50-51) permitió el corte y empalme del exón 49 al 52 (Figura 11A, banda inferior). Mediante la secuenciación de productos RT-PCR de la

banda de ΔEx50-51, se confirmó que el exón 49 se empalmó al exón 52. Para definir mejor las mutaciones introducidas por la estrategia de edición de genes, los productos de amplificación de RT-PCR de 4 muestras se sometieron directamente a clonación de timidina a adenosina (TOPO-TA) basada en topoisomerasa sin purificación en gel, y luego se secuenciaron. Sorprendentemente, el análisis de secuencia de 40 clones de cada muestra mostró que además de los productos de ADNc omitidos por el exón 51 (ΔEx50-51) identificado en el 15 % de los clones secuenciados, ratones ΔEx50 inyectados con AAV9-Cas9 y AAV9-ARNgs-51 mostraron una alta frecuencia de eventos de reestructuración. De los clones secuenciados, el 63 % contenía una inserción de un solo nucleótido en la secuencia del exón 51 (Figuras 11 B-C). La mutación de inserción más dominante vista fue una inserción A.

En los geles, el tamaño de la inserción A no se distinguía de los productos de ADNc no editados, por lo que se realizó un análisis de secuenciación profunda para determinar la abundancia de esta inserción en comparación con otras inserciones pequeñas. La secuenciación profunda de la banda superior que contiene el producto de ADNc no editado y los productos de ADNc con reestructuración indicó que el 69,22 % de las lecturas totales contenían productos de ADNc con reestructuración con una inserción A, el 17.71 % contenía el producto de ADNc no editado, y el resto contenía pequeñas eliminaciones e inserciones (Figura 11D). El análisis de secuenciación profunda de los ratones ΔEx50 no inyectados confirmó que la inserción A es el resultado de la edición generada por Cas9. Estos resultados de la secuenciación profunda del amplicón confirmaron los resultados de la clonación y secuenciación de TOPO-TA. Tomados en conjunto, el análisis por RT-PCR reveló que los ratones ΔEx50 inyectados con AAV9-Cas9 y AAV9-ARNgs-51-SA2 mostraron una alta frecuencia de eventos de reestructuración con productos de ADNc que contienen una inserción A en la secuencia del exón 51 además de los eventos de omisión del exón 51 que resultan de la eliminación en una región potenciadora de corte y empalme exónica altamente conservada.

Restauración de la expresión de distrofina después de la administración intramuscular de AAV9 de Cas9 y ARNgs-51-SA2. Sorprendentemente, la inmunotinción con distrofina de las criosecciones musculares de los ratones ΔEx50 inyectados con AAV-Tri-SA2 revelaron un número significativamente mayor de fibras positivas para distrofina con un promedio de restauración del 99 % de las fibras normales (Figura 12A, Figura 13). El análisis de transferencia Western confirmó la restauración de la expresión de distrofina en el músculo esquelético. (Figura 12C, Figura 12D). La tinción del músculo con hematoxilina y eosina (H&E) mostró que las características histopatológicas de la distrofia muscular, como las miofibras necróticas, se corrigieron en el músculo TA a las 3 semanas de la administración de AAV (Figura 12B y la Figura 14). Este método, que utiliza un diseño distinto de ARNgs, representa un gran avance en la eficiencia de la corrección de DMD con

aplicabilidad directa a los pacientes con las mutaciones de distrofina más comunes.

Rescate de la expresión de la distrofina después de las inyecciones intramusculares de AAV9-Cas9 combinadas con diferentes AAV9 que expresan una copia simple o una copia triple de ARNgs. Para evaluar el beneficio de la expresión del promotor triple de ARNgs-ex51-SA2 in vivo, se investigaron diferentes construcciones, donde la expresión de ARNgs fue dirigida por un solo promotor de ARN polimerasa III (U6 o H1 o 7SK) y, por separado, por tres ARN polimerasa III promotores (U6, H1 y 7SK) (Figura 15A). Los inventores administraron el ARNgs-ex51-SA2 en una sola copia dirigida por el promotor U6 (AAV9-U6-ARNgs-51-SA2), el promotor H1 (AAV9-H1-ARNgs-51-SA2), el promotor 7SK (AAV9 -7SK-ARNgs-51-SA2) y copia triple (AAV9-Triple-ARNgs-51-SA2). Tras la inyección intramuscular (IM) de ratones P12 con AAV9, se analizaron los tejidos musculares. Inesperadamente, la inmunotinción de distrofina de las criosecciones musculares de los ratones ΔEx50 inyectados con AAV9-Triple-ARNgs-51-SA2 revelaron un número significativamente mayor de fibras positivas para distrofina con un promedio de restauración de 95 % de las fibras normales en comparación con ratones ΔEx50 inyectados con AAV9-U6-ARNgs-51-SA2, AAV-H1-ARNgs-51-SA2 y AAV-7SK-ARNgs-51-SA2 con un promedio de 70 %; 40 % y 50 % de restauración de las fibras normales respectivamente (Figuras 15B).

Rescate de la estructura y función muscular después de la administración sistémica de AAV9-Cas9 y AAV9-ARNgs-51-SA2. La administración sistémica de AAV9-Cas9 y AAV9-ARNgs-51-SA2 a ratones P4 ΔEx50 produjon una expresión generalizada de distrofina en el corazón, tríceps, músculo tibial anterior (TA) y diafragma en ratones ΔEx50 con edición génica a las 4 y 8 semanas después de la inyección (Figura 16A y FIGURA 17A). El análisis de transferencia Western confirmó la restauración de la expresión de distrofina en el músculo esquelético y el corazón (Figura 16B y la Figura 17B). La prueba de fuerza de agarre también mostró un aumento significativo en la fuerza muscular de ratones ΔEx50 a las 4 semanas después de la inyección de AAV9 intraperitoneal en comparación con ratones de control ΔEx50 (control de tipo salvaje 92,6 ± 1,63; control ΔEx50 50,5 ± 1,85; ΔEx50-AAV9-ARNgs-51 79,7 ± 2,63) (Figura 18A). Consistentemente, los ratones ΔEx50 con edición génica con AAV9-ARNgs-51-SA2 también mostraron reducciones significativas en las concentraciones de CK en suero en comparación con ratones ΔEx50 de control (Figura 18B).

Corrección de la expresión de distrofina en un modelo canino de distrofia muscular de Duchenne. Para evaluar más a fondo la eficacia y el potencial terapéutico de este nuevo enfoque, los inventores investigaron la corrección de la mutación causante de la enfermedad en un modelo de perro con DMD, el perro ΔE50-MD, que alberga una mutación con cambio de sentido en el sitio de corte y empalme del donante en 5’ del exón 50 que resulta en la eliminación del exón 50 ((Walmsley *et al*., 2010). El perro ΔE50-MD es un modelo canino ideal para la investigación de la edición de

genes como un método para corregir permanentemente las mutaciones de DMD más comunes en los seres humanos.

Los inventores utilizaron ARNgs (ARNgs-ex51-SA2) dirigido al mismo locus genómico de la región aceptora de corte y empalme. La secuencia ARNgs-ex51-SA2 está altamente conservada. Las secuencias diana de ARNgs-ex51-SA2 de ratón y ARNgs-ex51-SA2 de perro (ARNgs-D-ex51-SA2) difieren solo en un solo nucleótido (Tabla 4). Los inventores administraron el ARNgs-D-ex51-SA2 en copia triple (AAV-D-Tri-SA2). Tras la inyección intramuscular (IM) de perros de 1 mes con AAV, se analizaron los tejidos musculares. Sorprendentemente, la inmunotinción con distrofina de las criosecciones musculares de los ratones ΔEx50 inyectados con AAV-Tri-SA2 revelaron un número significativamente mayor de fibras positivas para distrofina (Figura 19). El análisis de transferencia Western confirmó la restauración de la expresión de distrofina en el músculo esquelético (Figura 20). La tinción del músculo con hematoxilina y eosina (H&E) mostró que las características histopatológicas de la distrofia muscular, como las miofibras necróticas, disminuyeron en el músculo tibial cranial a las 6 semanas de la administración de AAV (Figura 21). Este método, que utiliza un diseño distinto de ARNgs, representa un gran avance en la eficiencia de la corrección de DMD con aplicabilidad directa a los pacientes con las mutaciones de distrofina más comunes.

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Todas las composiciones y/o métodos descritos y reivindicados en la presente se pueden elaborar y utilizar sin experimentación innecesaria, tal como lo indica la descripción que antecede. Si bien las composiciones y los métodos de la presente descripción se describieron en términos de modalidades preferidas, será evidente para los expertos en la técnica que se pueden aplicar variaciones en las composiciones y/o los métodos y las etapas o la secuencia de etapas de los métodos descritos en la presente sin apartarse del concepto, espíritu y alcance de la descripción. Más específicamente, resultará evidente que es posible sustituir los agentes descritos en la presente con determinados agentes tanto química como fisiológicamente relacionados y obtener los mismos resultados o resultados similares. Se considera que todas dichas modificaciones y sustitutos similares evidentes para los expertos en la técnica quedan comprendidos por el espíritu, alcance y concepto de la descripción, tal como se define en las reivindicaciones adjuntas.

VII. Referencias

Las referencias que figuran a continuación se incorporan específicamente a la presente mediante esta referencia en la medida en que proporcionan ejemplos de procedimientos u otros detalles complementarios a los establecidos en la presente.

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SE REIVINDICA LO SIGUIENTE:

1. Un ácido nucleico que comprende:

una secuencia que codifica un primer ARN guía de DMD que se dirige a una primera secuencia diana genómica,

una secuencia que codifica un segundo ARN guía de DMD que se dirige a una segunda secuencia diana genómica,

una secuencia que codifica un primer promotor, en donde el primer promotor dirige la expresión de la secuencia que codifica el primer ARN guía de DMD, y

una secuencia que codifica un segundo promotor, en donde el segundo promotor dirige la expresión de la secuencia que codifica el segundo ARN guía de DMD,

en donde cada una de la primera secuencia diana genómica y la segunda secuencia diana genómica comprende un sitio aceptor de corte y empalme de distrofina.

2. El ácido nucleico de la reivindicación 1, en donde la secuencia que codifica el primer promotor y la secuencia que codifica el segundo promotor son idénticas.

3. El ácido nucleico de la reivindicación 1, en donde la secuencia que codifica el primer promotor y la secuencia que codifica el segundo promotor no son idénticas.

4. El ácido nucleico de cualquiera de las reivindicaciones 1-3, en donde la primera secuencia diana genómica y la segunda secuencia diana genómica son idénticas.

5. El ácido nucleico de cualquiera de las reivindicaciones 1-3, en donde la primera secuencia diana genómica y la segunda secuencia diana genómica no son idénticas.

6. El ácido nucleico de cualquiera de las reivindicaciones 1-5, en donde el ácido nucleico comprende, además:

una secuencia que codifica un tercer ARN guía de DMD que se dirige a una tercera secuencia diana genómica, y

una secuencia que codifica un tercer promotor, en donde el tercer promotor dirige la expresión de la secuencia que codifica el tercer ARN guía de DMD,

en donde la tercera secuencia diana genómica comprende un sitio aceptor de corte y empalme de distrofina.

7. El ácido nucleico de la reivindicación 6, en donde al menos dos de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor y la secuencia que codifica el tercer promotor son idénticas.

8. El ácido nucleico de la reivindicación 6, en donde al menos dos de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor y la secuencia que codifica el tercer promotor no son idénticas.

9. El ácido nucleico de cualquiera de las reivindicaciones 6-8, en donde al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica y la tercera secuencia diana genómica son idénticas.

10. El ácido nucleico de cualquiera de las reivindicaciones 6-8, en donde al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica y la tercera secuencia diana genómica no son idénticas.

11. El ácido nucleico de cualquiera de las reivindicaciones 6-10, en donde el ácido nucleico comprende, además:

una secuencia que codifica un cuarto ARN guía de DMD que se dirige a una cuarta secuencia diana genómica, y

una secuencia que codifica un cuarto promotor, en donde el cuarto promotor dirige la expresión de la cuarta secuencia que codifica el ARN guía de DMD,

en donde la cuarta secuencia diana genómica comprende un sitio aceptor de corte y empalme de distrofina.

12. El ácido nucleico de la reivindicación 11, en donde al menos dos de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor y la secuencia que codifica el cuarto promotor son idénticas.

13. El ácido nucleico de la reivindicación 11, en donde al menos dos de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor y la secuencia que codifica el cuarto promotor no son idénticas.

14. El ácido nucleico de cualquiera de las reivindicaciones 11-13, en donde al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica, la tercera secuencia diana genómica y la cuarta secuencia diana genómica son idénticas.

15. El ácido nucleico de cualquiera de las reivindicaciones 11-13, en donde al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica, la tercera secuencia diana genómica y la cuarta secuencia diana genómica no son idénticas.

16. El ácido nucleico de cualquiera de las reivindicaciones 11-15, en donde el ácido nucleico comprende, además:

una secuencia que codifica un quinto ARN guía de DMD que se dirige a una quinta secuencia diana genómica, y

una secuencia que codifica un quinto promotor, en donde el quinto promotor dirige la expresión de la secuencia que codifica el quinto ARN guía de DMD,

en donde la quinta secuencia diana genómica comprende un sitio aceptor de corte y empalme de distrofina.

17. El ácido nucleico de la reivindicación 16, en donde al menos dos de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor y la secuencia que codifica el quinto promotor son idénticas.

18. El ácido nucleico de la reivindicación 16, en donde al menos dos de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor son idénticas y la secuencia que codifica el quinto promotor no son idénticas.

19. El ácido nucleico de cualquiera de las reivindicaciones 16-18, en donde al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica, la tercera secuencia diana genómica, la cuarta secuencia diana genómica y la quinta secuencia diana genómica son idénticas.

20. El ácido nucleico de cualquiera de las reivindicaciones 16-18, en donde al menos dos de la primera secuencia diana genómica, la segunda secuencia diana genómica, la tercera secuencia diana genómica, la cuarta secuencia diana genómica y la quinta secuencia diana genómica no son idénticas.

21. El ácido nucleico de cualquiera de las reivindicaciones 16-20, en donde el ácido nucleico comprende, además:

al menos una secuencia que codifica un ARN guía de DMD adicional que se dirige a una secuencia diana genómica, y

al menos un promotor adicional, en donde el promotor adicional dirige la expresión de la secuencia que codifica el ARN guía de DMD adicional,

en donde la secuencia diana genómica adicional comprende un sitio aceptor de corte y empalme de distrofina.

22. El ácido nucleico de cualquiera de las reivindicaciones 1-21, en donde el sitio aceptor de corte y empalme de distrofina es el sitio aceptor de corte y empalme 5’ del exón 51.

23. El ácido nucleico de cualquiera de las reivindicaciones 1-23, en donde la secuencia que codifica el primer promotor o la secuencia que codifica el segundo promotor comprende una secuencia que codifica un promotor constitutivo.

24. El ácido nucleico de cualquiera de las reivindicaciones 1-23, en donde el primer promotor o el segundo promotor comprenden un promotor constitutivo.

25. El ácido nucleico de la reivindicación 20, en donde al menos una de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor y la secuencia que codifica el quinto promotor comprende una secuencia que codifica un promotor constitutivo.

26. El ácido nucleico de la reivindicación 20, en donde al menos uno del primer promotor, el segundo promotor, el tercer promotor, el cuarto promotor y el quinto promotor comprenden un promotor constitutivo.

27. El ácido nucleico de cualquiera de las reivindicaciones 1-23, en donde la secuencia que codifica el primer promotor o la secuencia que codifica el segundo promotor comprende una secuencia que codifica un promotor inducible.

28. El ácido nucleico de la reivindicación 20, en donde al menos uno del primer promotor, el segundo promotor, el tercer promotor, el cuarto promotor y el quinto promotor comprende un promotor inducible.

29. El ácido nucleico de cualquiera de las reivindicaciones 1-23, en donde la secuencia que codifica el primer promotor o la secuencia que codifica el segundo promotor comprende una secuencia que codifica un promotor específico del tipo celular.

30. El ácido nucleico de la reivindicación 20, en donde al menos una de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor y la secuencia que codifica el quinto promotor comprende un promotor específico del tipo celular.

31. El ácido nucleico de la reivindicación 29 o 30, en donde la secuencia que codifica un promotor específico de tipo celular comprende una secuencia que codifica un promotor específico de los músculos.

32. El ácido nucleico de cualquiera de las reivindicaciones 1-22, en donde la secuencia que codifica el primer promotor o la secuencia que codifica el segundo promotor comprende una secuencia que codifica un promotor U6, un promotor H1 o un promotor 7SK.

33. El ácido nucleico de la reivindicación 20, en donde al menos una de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor y la secuencia que codifica el quinto promotor comprende una secuencia que codifica un promotor U6, una secuencia que codifica un promotor H1 o una secuencia que codifica un promotor 7SK.

34. El ácido nucleico de la reivindicación 20, en donde al menos una de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor y la secuencia que codifica el quinto promotor comprende una secuencia que codifica un promotor U6.

35. El ácido nucleico de la reivindicación 20, en donde al menos una de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor y la secuencia que codifica el quinto promotor

comprende una secuencia que codifica un promotor H1.

36. El ácido nucleico de la reivindicación 20, en donde al menos una de la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor, la secuencia que codifica el tercer promotor, la secuencia que codifica el cuarto promotor y la secuencia que codifica el quinto promotor comprende una secuencia que codifica un promotor 7SK.

37. El ácido nucleico de la reivindicación 6,

en donde la secuencia que codifica el primer ARN guía de DMD, la secuencia que codifica el segundo ARN de guía DMD y la secuencia que codifica el tercer ARN guía de DMD son idénticas,

en donde la secuencia que codifica el primer promotor, la secuencia que codifica el segundo promotor y la secuencia que codifica el tercer promotor no son idénticas, y

en donde el sitio del aceptor de corte y empalme 5’ comprende un sitio del aceptor de corte y empalme 5’ del exón 51.

38. El ácido nucleico de la reivindicación 37, en donde la secuencia que codifica el primer promotor comprende una secuencia que codifica un promotor U6, la secuencia que codifica el segundo promotor comprende una secuencia que codifica un promotor H1, y la secuencia que codifica el tercer promotor comprende una secuencia que codifica un promotor 7SK.

39. El ácido nucleico de cualquiera de las reivindicaciones 1-38, en donde el ácido nucleico comprende, además, una secuencia de ADN.

40. El ácido nucleico de cualquiera de las reivindicaciones 1-38, en donde el ácido nucleico comprende, además, una secuencia de ARN.

41. El ácido nucleico de cualquiera de las reivindicaciones 1-40, en donde el ácido nucleico comprende, además, una o más secuencias que codifican una repetición terminal invertida (ITR).

42. El ácido nucleico de cualquiera de las reivindicaciones 1-40, en donde el ácido nucleico comprende, además, una secuencia que codifica una repetición terminal invertida (ITR) 5’ y una secuencia que codifica una ITR 3’.

43. El ácido nucleico de la reivindicación 42, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un virus adenoasociado (AAV).

44. El ácido nucleico de la reivindicación 43, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un virus adenoasociado (AAV) del serotipo 2 (AAV2).

45. El ácido nucleico de la reivindicación 43, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) y la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un AAV2.

46. El ácido nucleico de la reivindicación 43, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un virus adenoasociado (AAV) del serotipo 4 (AAV4).

47. El ácido nucleico de la reivindicación 46, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) y la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un AAV4.

48. El ácido nucleico de cualquiera de las reivindicaciones 43-47, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende o consiste en 145 nucleótidos.

49. El ácido nucleico de cualquiera de las reivindicaciones 43-47, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende o consiste en 115 nucleótidos.

50. El ácido nucleico de cualquiera de las reivindicaciones 43-47, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende o consiste en 141 nucleótidos.

51. El ácido nucleico de cualquiera de las reivindicaciones 1-50, en donde el ácido nucleico comprende además una secuencia de poliadenosina (poliA).

52. El ácido nucleico de la reivindicación 51, en donde la secuencia de poliA es una secuencia de poli A mini.

53. El ácido nucleico de cualquiera de las reivindicaciones 6-52, en donde la secuencia que codifica el primer ARN guía de DMD, la secuencia que codifica el segundo ARN de guía DMD, o la secuencia que codifica el tercer ARN guía de DMD comprende la secuencia de cualquiera de las SEQ ID NO. 60-382, 706-708 y 712-719.

54. El ácido nucleico de cualquiera de las reivindicaciones 6-52, en donde la secuencia que codifica el primer ARN guía de DMD, la secuencia que codifica el segundo ARN de guía DMD, o la secuencia que codifica el tercer ARN guía de DMD comprende la secuencia de la SEQ ID NO: 714.

55. El ácido nucleico de cualquiera de las reivindicaciones 6-52, en donde la secuencia que codifica el primer ARN guía de DMD, la secuencia que codifica el segundo ARN de guía DMD, y la secuencia que codifica el tercer ARN guía de DMD comprende la secuencia de la SEQ ID NO: 714.

56. Una célula que comprende el ácido nucleico de cualquiera de las reivindicaciones 1-55.

57. Una composición que comprende el ácido nucleico de cualquiera de las reivindicaciones 1-55.

58. Una célula que comprende la composición de la reivindicación 56.

59. Una composición que comprende la célula de la reivindicación 58.

60. Un vector que comprende el ácido nucleico de cualquiera de las reivindicaciones 1-55.

61. El vector de la reivindicación 60, en donde el vector comprende, además, una secuencia que codifica una repetición terminal invertida (ITR) de un elemento transponible.

62. El vector de la reivindicación 61, en donde el elemento trasnposable es un transposón.

63. El vector de la reivindicación 62, en donde el transposón es un transposón Tn7.

64. El vector de la reivindicación 63, en donde el vector comprende, además, una secuencia que codifica una ITR 5' de un transposón T7 y una secuencia que codifica una ITR 3' de un transposón T7.

65. El vector de cualquiera de las reivindicaciones 60-64, en donde el vector es un vector no viral.

66. El vector de la reivindicación 65, en donde el vector no viral es un plásmido.

67. El vector de cualquiera de las reivindicaciones 60-64, en donde el vector es un vector viral.

68. El vector de la reivindicación 67, en donde el vector viral es un vector del virus viral adenoasociado (AAV).

69. El vector de la reivindicación 69, en donde el vector AAV es defectuoso en la replicación o defectuoso en la replicación condicional.

70. El vector de la reivindicación 68 o 69, en donde el vector es un vector AAV recombinante.

71. El vector de cualquiera de las reivindicaciones 68-70, en donde el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 1 (AAV1), 2 (AAV2), 3 (AAV3), 4 (AAV4), 5 (AAV5), 6 (AAV6), 7 (AAV7), 8 (AAV8), 9 (AAV9), 10 (AAV10), 11 (AAV11) o cualquier combinación de estos.

72. El vector de cualquiera de las reivindicaciones 68-71, en donde el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 9 (AAV9).

73. El vector de cualquiera de las reivindicaciones 68-72, en donde el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 2 (AAV2).

74. El vector de cualquiera de las reivindicaciones 68-73, en donde el vector AAV comprende una secuencia aislada o derivada de un AAV2 y una secuencia aislada o derivada de un AAV9.

75. El vector de cualquiera de las reivindicaciones 68-72, en donde el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 4 (AAV4).

76. El vector de cualquiera de las reivindicaciones 68-72 o 75, en donde el vector AAV comprende una secuencia aislada o derivada de un AAV4 y una secuencia aislada o derivada de un AAV9.

77. El vector de cualquiera de las reivindicaciones 60-76, en donde el vector está optimizado para la expresión en células de mamíferos.

78. El vector de cualquiera de las reivindicaciones 60-77, en donde el vector está optimizado para la expresión en células humanas.

79. El vector de cualquiera de las reivindicaciones 60-78, en donde el vector comprende la

secuencia de ácidos nucleicos de la SEQ ID NO: 914, la SEQ ID NO. 915, la SEQ ID NO. 916 o la SEQ ID NO. 917.

80. Una composición que comprende el vector de cualquiera de las reivindicaciones 60-79.

81. La composición de la reivindicación 80, que comprende, además, un portador farmacéuticamente aceptable.

82. Una célula que comprende la composición de la reivindicación 80 o 81.

83. La célula de la reivindicación 82, en donde la célula es una célula humana.

84. La célula de la reivindicación 82 o 83, en donde la célula es una célula muscular o célula satélite.

85. La célula de la reivindicación 82 o 83, donde la célula es una célula madre pluripotente inducida (iPS).

86. Una composición que comprende la célula de cualquiera de las reivindicaciones 82-85.

87. Un ácido nucleico que comprende una secuencia que codifica un promotor y una secuencia que codifica una proteína Cas9 o un dominio de nucleasa de esta,

en donde la secuencia que codifica el promotor comprende una secuencia que codifica un promotor específico de los músculos.

88. El ácido nucleico de la reivindicación 87, en donde la secuencia que codifica el promotor específico de los músculos comprende una secuencia que codifica un promotor CK8.

89. El ácido nucleico de la reivindicación 87 o 88, en donde la secuencia que codifica el promotor específico de los músculos comprende una secuencia que codifica un promotor CK8e.

90. El ácido nucleico de cualquiera de las reivindicaciones 87-89, en donde la secuencia que codifica la proteína Cas9 o el dominio de nucleasa de esta se aísla o deriva de una secuencia que codifica una proteína Cas9 o el dominio de nucleasa de *S. pyogenes* de esta.

91. La proteína Cas9 o el dominio de nucleasa de esta se aísla o deriva de una secuencia que codifica una proteína Cas9 o el dominio de nucleasa de *S. aureus* de esta.

92. El ácido nucleico de cualquiera de las reivindicaciones 87-91, en donde la secuencia que codifica la proteína Cas9 o el dominio de nucleasa de esta está optimizada con codones para la expresión en un mamífero.

93. El ácido nucleico de cualquiera de las reivindicaciones 87-91, en donde la secuencia que codifica la proteína Cas9 o el dominio de nucleasa de esta está optimizada con codones para la expresión en un ser humano.

94. El ácido nucleico de cualquiera de las reivindicaciones 87-93, en donde el ácido nucleico comprende además una secuencia de poliA.

95. El ácido nucleico de la reivindicación 94, en donde la secuencia de poliA es una secuencia de

poli A mini.

96. El ácido nucleico de cualquiera de las reivindicaciones 1-94, en donde el ácido nucleico comprende, además, una o más secuencias que codifican una repetición terminal invertida (ITR).

97. El ácido nucleico de cualquiera de las reivindicaciones 1-94, en donde el ácido nucleico comprende, además, una secuencia que codifica una repetición terminal invertida (ITR) 5’ y una secuencia que codifica una ITR 3’.

98. El ácido nucleico de la reivindicación 97, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un virus adenoasociado (AAV).

99. El ácido nucleico de la reivindicación 98, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un virus adenoasociado (AAV) del serotipo 2 (AAV2).

100. El ácido nucleico de la reivindicación 99, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) y la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un AAV2.

101. El ácido nucleico de la reivindicación 98, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un virus adenoasociado (AAV) del serotipo 4 (AAV4).

102. El ácido nucleico de la reivindicación 46, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) y la secuencia que codifica una ITR 3’ comprende una secuencia aislada o derivada de un AAV4.

103. El ácido nucleico de cualquiera de las reivindicaciones 96-102, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende o consiste en 145 nucleótidos.

104. El ácido nucleico de cualquiera de las reivindicaciones 96-102, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende o consiste en 115 nucleótidos.

105. El ácido nucleico de cualquiera de las reivindicaciones 96-102, en donde la secuencia que codifica la repetición terminal invertida 5’ (ITR) o la secuencia que codifica una ITR 3’ comprende o consiste en 141 nucleótidos.

106. El ácido nucleico de cualquiera de las reivindicaciones 1-55 o 87-105, en donde el ácido nucleico comprende, además, una señal de localización nuclear.

107. El ácido nucleico de cualquiera de las reivindicaciones 87-106, en donde el ácido nucleico está optimizado para la expresión en células de mamíferos.

108. El ácido nucleico de cualquiera de las reivindicaciones 87-107, en donde el ácido nucleico está optimizado para la expresión en células humanas.

109. Una composición que comprende el ácido nucleico de cualquiera de las reivindicaciones 87-108.

110. Una célula que comprende el ácido nucleico de cualquiera de las reivindicaciones 87-108.

111. Una célula que comprende la composición de la reivindicación 109.

112. Una composición que comprende la célula de la reivindicación 110 o 111.

113. Un vector que comprende el ácido nucleico de cualquiera de las reivindicaciones 87-108.

114. El vector de la reivindicación 113, en donde el vector comprende, además, una secuencia que codifica una repetición terminal invertida (ITR) de un elemento transponible.

115. El vector de la reivindicación 114, en donde el elemento trasnposable es un transposón.

116. El vector de la reivindicación 115, en donde el transposón es un transposón Tn7.

117. El vector de la reivindicación 116, en donde el vector comprende, además, una secuencia que codifica una ITR 5’ de un transposón T7 y una secuencia que codifica una ITR 3’ de un transposón T7.

118. El vector de cualquiera de las reivindicaciones 113-117, en donde el vector es un vector no viral.

119. El vector de la reivindicación 118, en donde el vector no viral es un plásmido.

120. El vector de cualquiera de las reivindicaciones 113-117, en donde el vector es un vector viral.

121. El vector de la reivindicación 120, en donde el vector viral es un vector del virus viral adenoasociado (AAV).

122. El vector de la reivindicación 121, en donde el vector AAV es defectuoso en la replicación o defectuoso en la replicación condicional.

123. El vector de la reivindicación 121 o 122, en donde el vector es un vector AAV recombinante.

124. El vector de cualquiera de las reivindicaciones 121-123, en donde el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 1 (AAV1), 2 (AAV2), 3 (AAV3), 4 (AAV4), 5 (AAV5), 6 (AAV6), 7 (AAV7), 8 (AAV8), 9 (AAV9), 10 (AAV10), 11 (AAV11) o cualquier combinación de estos.

125. El vector de cualquiera de las reivindicaciones 121-124, en donde el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 9 (AAV9).

126. El vector de cualquiera de las reivindicaciones 121-125, en donde el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 2 (AAV2).

127. El vector de cualquiera de las reivindicaciones 121-126, en donde el vector AAV comprende una secuencia aislada o derivada de un AAV2 y una secuencia aislada o derivada de un AAV9.

128. El vector de cualquiera de las reivindicaciones 121-125, en donde el vector AAV comprende una secuencia aislada o derivada de un vector AAV del serotipo 4 (AAV4).

129. El vector de cualquiera de las reivindicaciones 121-125 o 128, en donde el vector AAV comprende una secuencia aislada o derivada de un AAV4 y una secuencia aislada o derivada de un AAV9.

130. El vector de cualquiera de las reivindicaciones 121-129, en donde el vector está optimizado para la expresión en células de mamíferos.

131. El vector de cualquiera de las reivindicaciones 121-130, en donde el vector está optimizado para la expresión en células humanas.

132. El vector de cualquiera de las reivindicaciones 113-132, en donde el vector comprende la secuencia de ácidos nucleicos de la SEQ ID NO: 899, la SEQ ID NO. 900, la SEQ ID NO. 901 o la SEQ ID NO. 902.

133. Una composición que comprende el vector de cualquiera de las reivindicaciones 113-132.

134. La composición de la reivindicación 133, que comprende, además, un portador farmacéuticamente aceptable.

135. Una célula que comprende la composición de la reivindicación 133 o 134.

136. Una célula que comprende el vector de cualquiera de las reivindicaciones 113-132.

137. La célula de la reivindicación 135 o 136, en donde la célula es una célula humana.

138. La célula de cualquiera de las reivindicaciones 135-137, en donde la célula es una célula muscular o célula satélite.

139. La célula de cualquiera de las reivindicaciones 135-137, donde la célula es una célula iPS o una célula iCM.

140. Una composición que comprende la célula de cualquiera de las reivindicaciones 135-139.

141. Una composición que comprende:

una primera secuencia de ácido nucleico que comprende una secuencia de ácido nucleico de cualquiera de las reivindicaciones 1-55 y

una segunda secuencia de ácido nucleico que comprende una secuencia de ácido nucleico de cualquiera de las reivindicaciones 87-108.

142. Una composición que comprende

un primer vector que comprende una secuencia de ácido nucleico de cualquiera de las reivindicaciones 1-55, y

un segundo vector que comprende una secuencia de ácido nucleico de cualquiera de las reivindicaciones 87-108.

143. Una composición que comprende

un vector de cualquiera de las reivindicaciones 60-79, y

un vector de cualquiera de las reivindicaciones 113-132.

144. La composición de cualquiera de las reivindicaciones 141-143, en donde la composición comprende, además, un portador farmacéuticamente aceptable.

145. Un método para corregir un defecto de distrofina, el método comprende poner en contacto una célula y una composición de cualquiera de las reivindicaciones 141-144 en condiciones adecuadas para la expresión del primer ARN guía de DMD, el segundo ARN guía de DMD y la proteína Cas9 o un dominio de nucleasa de esta, en donde al menos uno del primer ARN guía de DMD o el segundo ARN guía de DMD forma un complejo con la proteína Cas9 o el dominio de nucleasa de esta para formar al menos un complejo de Cas9-ARN guía de DMD, en donde el al menos un complejo de Cas9-ARN guía de DMD interrumpe un sitio de corte y empalme de distrofina e induce la omisión selectiva de un exón de DMD.

146. Un método para corregir un defecto de distrofina, el método comprende poner en contacto una célula y una composición de cualquiera de las reivindicaciones 141-144 en condiciones adecuadas para la expresión del primer ARN guía de DMD, el segundo ARN guía de DMD y la proteína Cas9 o un dominio de nucleasa de esta, en donde al menos uno del primer ARN guía de DMD o el segundo ARN guía de DMD forma un complejo con la proteína Cas9 o el dominio de nucleasa de esta para formar al menos un complejo de Cas9-ARN guía de DMD, en donde el al menos un complejo de Cas9-ARN guía de DMD induce la reestructuración de un marco de lectura de distrofina.

147. El método de la reivindicación 146, en donde la reestructuración de un marco de lectura de distrofina induce una inserción.

148. El método de la reivindicación 147, en donde la inserción comprende o consiste en un único nucleótido de adenosina.

149. Un método para inducir la omisión selectiva de un exón de DMD, el método comprende poner en contacto una célula y una composición de cualquiera de las reivindicaciones 141-144 en condiciones adecuadas para la expresión del primer ARN guía de DMD, el segundo ARN guía de DMD y la proteína Cas9 o un dominio de nucleasa de esta, en donde al menos uno del primer ARN guía de DMD o el segundo ARN guía de DMD forma un complejo con la proteína Cas9 o el dominio de nucleasa de esta para formar al menos un complejo de Cas9-ARN guía de DMD, en donde el al menos un complejo de Cas9-ARN guía de DMD interrumpe un sitio de corte y empalme de distrofina e induce la omisión selectiva de un exón de DMD.

150. Un método para inducir un evento de reestructuración de un marco de lectura de distrofina, el método comprende poner en contacto una célula y una composición de cualquiera de las reivindicaciones 141-144 en condiciones adecuadas para la expresión del primer ARN guía de DMD,

el segundo ARN guía de DMD y la proteína Cas9 o un dominio de nucleasa de esta, en donde al menos uno del primer ARN guía de DMD o el segundo ARN guía de DMD forma un complejo con la proteína Cas9 o el dominio de nucleasa de esta para formar al menos un complejo de Cas9-ARN guía de DMD, en donde el al menos un complejo de Cas9-ARN guía de DMD interrumpe un sitio de corte y empalme de distrofina e induce la reestructuración del marco de lectura de distrofina

151. El método de cualquiera de las reivindicaciones 145-150, en donde el al menos un complejo Cas9-ARN guía de DMD interrumpe un sitio de corte y empalme de distrofina e induce la omisión selectiva del exón 51 de un gen de DMD humana.

152. Una célula producida mediante el método de cualquiera de las reivindicaciones 145-151.

153. Un método para el tratamiento de la distrofia muscular en un sujeto que lo necesite, donde el método comprende administrarle al sujeto una cantidad terapéuticamente eficaz de una composición de cualquiera de las reivindicaciones 141-144.

154. El método de la reivindicación 153, en donde la composición se administra de forma local.

155. El método de las reivindicaciones 153 o 154, en donde la composición se administra directamente en un tejido muscular.

156. El método de cualquiera de las reivindicaciones 153-155, en donde la composición se mediante una inyección o infusión intramuscular.

157. El método de la reivindicación 155 o 156, en donde el tejido muscular comprende un tejido tibial anterior, un tejido de cuádriceps, un tejido del sóleo, un tejido del diafragma o un tejido del corazón.

158. El método de cualquiera de las reivindicaciones 153-157, en donde la composición se administra mediante una inyección intracardíaca.

159. El método de la reivindicación 153, en donde la composición se administra de forma sistémica.

160. El método de la reivindicación 159, en donde la composición se mediante una inyección o infusión intravenosa.

161. El método de cualquiera de las reivindicaciones 153-160, en donde, después de la administración de la composición, el sujeto muestra miofibras positivas a distrofina normales y miofibras positivas a distrofina de mosaico que contienen núcleos centralizados, o una combinación de estas.

162. El método de cualquiera de las reivindicaciones 153-161, en donde, después de la administración de la composición, el sujeto muestra una aparición o un aumento en el nivel de abundancia de miofibras positivas a distrofina normales en comparación con una ausencia o un nivel de abundancia de miofibras positivas a distrofina normales antes de la administración de la composición.

163. El método de cualquiera de las reivindicaciones 153-162, en donde, después de la administración de la composición, el sujeto muestra una aparición o un aumento en el nivel de abundancia de miofibras positivas a distrofina de mosaico que contienen núcleos centralizados en comparación con una ausencia o un nivel de abundancia de miofibras positivas a distrofina de mosaico que contienen centralizada núcleos centralizados antes de la administración de la composición.

164. El método de cualquiera de las reivindicaciones 153-163, en donde, después de la administración de la composición, el sujeto muestra un nivel menor de CK en suero en comparación con un nivel de CK en suero antes de la administración de la composición.

165. EL método de cualquiera de las reivindicaciones 153-164, en donde, después de la administración de la composición, el sujeto presenta una mejor resistencia de agarre en comparación con una resistencia de agarre antes de la administración de la composición.

166. El método de cualquiera de las reivindicaciones 153-165, en donde el sujeto es un neonato, bebé, niño, adulto joven o adulto.

167. El método de cualquiera de las reivindicaciones 153-166, en donde el sujeto tiene distrofia muscular.

168. El método de cualquiera de las reivindicaciones 153-167, en donde el sujeto es un portador genético de distrofia muscular.

169. El método de cualquiera de las reivindicaciones 153-168, en el que el sujeto es masculino.

170. El método de cualquiera de las reivindicaciones 153-168, en el que el sujeto es femenino.

171. El método de cualquiera de las reivindicaciones 153-170, en donde el sujeto parece ser asintomático y en donde un diagnóstico genético revela una mutación en una o ambas copias de un gen de *DMD* que altera la función del producto génico de *DMD*.

172. El método de cualquiera de las reivindicaciones 153-171, en donde el sujeto presenta un signo o síntoma temprano de distrofia muscular.

173. El método de la reivindicación 172, en donde el signo o síntoma temprano de la distrofia muscular comprende la pérdida de masa muscular o debilidad muscular proximal.

174. El método de la reivindicación 173, en donde la pérdida de masa muscular o debilidad muscular proximal se produce en una o ambas piernas y/o la pelvis, seguido por uno o más músculos de la parte superior del cuerpo.

175. El método de la reivindicación 174, en donde el signo o síntoma temprano de distrofia muscular comprende, además, pseudohipertrofia, baja resistencia, dificultad para pararse, dificultad para caminar, dificultad para subir una escalera o una combinación de estas.

176. El método de cualquiera de las reivindicaciones 153-175, en donde el sujeto presenta un signo

o síntoma progresivo de distrofia muscular.

177. El método de la reivindicación 176, en donde el signo o síntoma progresivo de distrofia muscular comprende desgaste del tejido muscular, reemplazo del tejido muscular con grasa o reemplazo del tejido muscular con tejido fibrótico.

178. El método de cualquiera de las reivindicaciones 153-177, en donde el sujeto presenta un signo o síntoma tardío de distrofia muscular.

179. El método de la reivindicación 178, en donde el signo o síntoma tardío de distrofia muscular comprende desarrollo óseo anormal, curvatura de la columna vertebral, pérdida de movimiento y parálisis.

180. El método de cualquiera de las reivindicaciones 153-179, en donde el sujeto presenta un signo o síntoma neurológico de distrofia muscular.

181. El método de la reivindicación 180, en donde el signo o síntoma neurológico de distrofia muscular comprende deficiencia intelectual y parálisis.

182. El método de cualquiera de las reivindicaciones 153-181, en donde la administración de la composición se produce antes de que el sujeto presente uno o más signos o síntomas progresivos, tardíos o neurológicos de distrofia muscular.

183. El método de cualquiera de las reivindicaciones 153-182, en donde el sujeto tiene menos de 10 años.

184. El método de la reivindicación 183, en donde el sujeto tiene menos de 5 años.

185. El método de la reivindicación 184, en donde el sujeto tiene menos de 2 años.

186. Uso de una cantidad terapéuticamente eficaz de una composición de cualquiera de las reivindicaciones 141-144 para el tratamiento de la distrofia muscular en un sujeto que lo necesite.

RESUMEN

La edición genómica mediada por CRISPR/Cas9 tiene un potencial clínico para el tratamiento de enfermedades genéticas, como la distrofia muscular de Duchenne (DMD), que es causada por mutaciones en el gen de la distrofina. En la presente, mediante el uso de tres promotores para dirigir la expresión del mismo ARN guía de DMD, se logró una forma más sólida y segura de edición genómica en un modelo de ratón humanizado para DMD con una eliminación en el exón 50 y en un modelo de perro ΔEx50-MD.