SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-111117- -00000-0000
Fecha: 2011-08-30 17:03:37 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 254

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

11-111117

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: VARIANTES DE UNION A ANTI-ALBÚMINA DE SUERO MEJORADAS.

SOLICITANTE: GLAXO GROUP LIMITED

DIRECCIÓN: Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN Reino Unido

APODERADO: CARLOS R. OLARTE

BOGOTÁ 30 de agosto de 2011

P2011/000156

19-09-2011

OLARTEMOURE

OLARTE MOURE & ASOCI/

Industria y Comercio
SUPERINTENDENCIA

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PETITORIO - FORMULARI(PATENTE PCT
ENTRADA EN FASE NACIONAL **P2011/000156**

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: GLAXO GROUP LIMITED
Dirección: Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN. Reino Unido.
Nacionalidad o Domicilio: Británica
Lugar de Constitución: Gran Bretaña
Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número _____

REPRESENTANTE O APODERADO

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Número 79782747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA.
Dirección: VER PAGINA ADJUNTA.
Nacionalidad o Domicilio: VER PAGINA ADJUNTA.

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2010/052007 Fecha Febrero 17, 2010

Publicación Internacional No. WO 2010/094722 Fecha Agosto 26, 2010

(6) **Título (54)** **VARIANTES DE UNION A ANTI-ALBÚMINA DE SUERO MEJORADAS.**

Clasificación Internacional (51) C07K 16/18.

Prioridad **SI** [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Febrero 19, 2009	61/153,746
US	Marzo 27, 2009	61/163,990

(9) **Comprobante de pago No.** 11- **Fecha** Agosto de 2011

ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. VER EXP Nº 09-149.371.
- [x] Documento de cesión del inventor al solicitante o a su causante. DECLARACION REGLA 4.17(iv)
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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PCT/EP2010/052007

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Nacionalidad: Alemana

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0084322

Bogotá D.C., Agosto 30 de 2011 - 13:40:09

RECIBIDO DE : OLAPTE MOURE & ASOCIADOS NI 830.122.370

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	408398561	30/08/2011	3.997.000.00

*** Conceptos Pagados ***

CANT.	PENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	571.000.00	571.000.00
				$571.000.00

==========

SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE***

Responsable: _____
- ******** -

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-111117- -00000-0000
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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 254

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

GLAXO GROUP LIMITED

PODER DE REPRESENTACION

Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario autorizado.

Certificado de Notario De Pinna en español firmado por James Kerr Milligan

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
   - Este documento Público
2. ha sido firmado por James Kerr Milligan
3. Quien ejerce funciones de Notario público
4. Lleva el sello del Notario público

CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad
8. No. G229474
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

Si el documento se usa en un país que no pertenece a la Convención de la Haya del 5 de octubre de 1961 debe pasar por la sección consular de la Misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 21 agosto-03.

Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Ofi.
Inglés - Español - Inglé
Resolución No. 2117 del 7 O

DE PINNA
NOTARIES

Yo, el infrascrito **JAMES KERR MILLIGAN**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

C E R T I F I C O:

QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada **"GLAXO GROUP LIMITED"**, Sociedad legalmente constituída y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número **305979**, con domicilio social en Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra;

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debiday suficientemente autorizado para firmar documentos de esta clase en nombre y representación de dicha Sociedad en virtud de un Poder otorgado por la referida Sociedad fechado 3 de julio de 2002.

Y QUE los objetos para los cuales se otorgó dicho Poder se encuentran dentro de los objetos o actividades de la citada Sociedad, de acuerdo con la Escritura Constitutiva y los Estatutos Sociales, los cuales he tenido a la vista.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy ece de agosto del año dos mil tres.

JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by / a été signé par: **James Kerr Milligan**

3. Acting in the capacity of / agissant en qualité de: **Notary Public**

4. Bears the seal/stamp of / est revêtu du sceau/timbre de: **The Said Notary Public**

   Certified/Attesté

5. at London/à Londres

6. the/le **14 August 2003**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs / par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No: **G229474**

9. Stamp: / timbre:

10. Signature: **J. Garbrah**

FOREIGN AND COMMONWEALTH OFFICE LONDON

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country.

OLARTERAISBECK
OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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Fax: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

Glaxo Group Limited

domiciled in

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents, Utility Models and Industrial Designs** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

Glaxo Group Limited

domiciliado en

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: _____

Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

City,Country/Ciudad,País: Brentford, Middlesex, England

Sheet No

Box No. VIII(ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT
The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII(I) to (v) (in general and the specific Notes to Box No. VIII(ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and *51bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to international application No. PCT/GB2010/052007

GLAXO GROUP LIMITED is entitled to apply for and be granted a patent by virtue of the following:

(i) transfer of entitlement from inventors ***Elena DE ANGELIS; Carolyn ENEVER; Haiqun LIU and Oliver SCHON*** to GlaxoSmithKline Services Unlimited by way of employment contract

(ii) an assignment from GlaxoSmithKline Services Unlimited to Glaxo Group Limited effective 19 February 2009

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII(ii)".

Box No. VIII(iii) DECLARATION: ENTITLEMENT TO CLAIM PRIORITY
The declaration must conform to the standardized wording provided for in Section 213; see Notes to Boxes Nos. VIII, VIII(i) to (v) (in general) and the specific Notes to Box No. VIII(iii) and 51*bis*.1(a)(iii)

Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51*bis*.1(a)(iii)):

in relation to international application No. PCT/EP2010/052007

GLAXO GROUP LIMITED is entitled to claim priority of earlier application Nos. *61/153,746 and 61/163,990* filed in the United States of America by virtue of the following:

(i) transfer of entitlement from ***Elena DE ANGELIS; Carolyn ENEVER; Haiqun LIU and Oliver SCHON*** to GlaxoSmithKline Services Unlimited by way of employment contract

(ii) an assignment from GlaxoSmithKline Services Unlimited to Glaxo Group Limited effective 19 February 2009

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII(iii)".

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

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International Bureau

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26 August 2010 (26.08.2010)

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(30) Priority Data:
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(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DE ANGELIS, Elena** [GB/GB]; Domantis Limited, 315 Cambridge Science Park, Cambridge, Cambridgeshire CB4 0WG (GB). **ENEVER, Carolyn** [GB/GB]; Domantis Limited, 315 Cambridge Science Park, Cambridge, Cambridgeshire CB4 0WG (GB). **LIU, Haiqun** [CN/GB]; Domantis Limited, 315 Cambridge Science Park, Cambridge, Cambridgeshire CB4 0WG (GB). **SCHON, Oliver** [DE/GB]; Domantis Limited, 315 Cambridge Science Park, Cambridge, Cambridgeshire CB4 0WG (GB).

(74) Agents: **CLUBE, Jasper Rupert** et al.; GlaxoSmithKline, Global Patents CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(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, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2010/094722 A2

(54) Title: IMPROVED ANTI-SERUM ALBUMIN BINDING VARIANTS

(57) Abstract: The invention relates to improved variants of the anti-serum albumin immunoglobulin single variable domain DOM7h-14, as well as ligands and drug conjugates comprising such variants, compositions, nucleic acids, vectors and hosts.

IMPROVED ANTI-SERUM ALBUMIN BINDING VARIANTS

The invention relates to improved variants of the anti-serum albumin immunoglobulin single variable domain DOM7h-14, as well as ligands and drug conjugates comprising such variants, compositions, nucleic acids, vectors and hosts.

BACKGROUND OF THE INVENTION

WO04003019 and WO2008/096158 disclose anti-serum albumin (SA) binding moieties, such as anti-SA immunoglobulin single variable domains (dAbs), which have therapeutically-useful half-lives. These documents disclose monomer anti-SA dAbs as well as multi-specific ligands comprising such dAbs, eg, ligands comprising an anti-SA dAb and a dAb that specifically binds a target antigen, such as TNFR1. Binding moieties are disclosed that specifically bind serum albumins from more than one species, eg human/mouse cross-reactive anti-SA dAbs.

WO05118642 and WO2006/059106 disclose the concept of conjugating or associating an anti-SA binding moiety, such as an anti-SA immunoglobulin single variable domain, to a drug, in order to increase the half-life of the drug. Protein, peptide and NCE (new chemical entity) drugs are disclosed and exemplified. WO2006/059106 discloses the use of this concept to increase the half-life of insulintropic agents, eg, incretin hormones such as glucagon-like peptide (GLP)-1.

Reference is also made to Holt *et al*, "Anti-Serum albumin domain antibodies for extending the half-lives of short lived drugs", Protein Engineering, Design & Selection, vol 21, no 5, pp283-288, 2008.

WO2008/096158 discloses DOM7h-14, which is a good anti-SA dAb. It would be desirable to provide improved dAbs that are variants of DOM7h-14 and that specifically bind serum albumin, preferably albumins from human and non-human species, which would provide utility in animal models of disease as well as for human therapy and/or diagnosis. It would also be desirable to provide for the choice between

relatively modest- and high-affinity anti-SA binding moieties (dAbs). Such moieties could be linked to drugs, the anti-SA binding moiety being chosen according to the contemplated end-application. This would allow the drug to be better tailored to treating and/or preventing chronic or acute indications, depending upon the choice of anti-SA binding moiety. It would also be desirable to provide anti-dAbs, that are monomeric or substantially so in solution. This would especially be advantageous when the anti-SA dAb is linked to a binding moiety, eg, a dAb, that specifically binds a cell-surface receptor, such as TNFR1, with the aim of antagonizing the receptor. The monomeric state of the anti-SA dAb is useful in reducing the chance of receptor cross-linking, since multimers are less likely to form which could bind and cross-link receptors (eg, TNFR1) on the cell surface, thus increasing the likelihood of receptor agonism and detrimental receptor signaling.

SUMMARY OF THE INVENTION

Aspects of the present invention solve these problems.

To this end, the present inventors surprisingly found that beneficial mutations can be targeted to the CDR3 region 92 to 96 (position numbering according to Kabat) compared of DOM7h-14.

In one aspect the invention, therefore, provides an anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises at least one mutation in CDR3 region 92 to 96 (position numbering according to Kabat) compared to DOM7h-14, and wherein the variant has from 1 to 8 changes compared to the amino acid sequence of DOM7h-14. There is also provided an anti-serum albumin (SA) binding moiety comprising CDR3 of a variant of this aspect of the invention.

Another aspect of the invention provides an anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises a Ser at position 22 and a Glu at position 42 (numbering according to Kabat)

compared to DOM7h-14, and wherein the variant has from 0 to 4 further changes compared to the amino acid sequence of DOM7h-14.

Embodiments of any aspect of the invention provide DOM7h-14 variants of good anti-serum albumin affinities. The choice of variant can allow for tailoring of half-life according to the desired therapeutic and/or prophylactic setting. For example, in one embodiment, the affinity of the variant for serum albumin is relatively high, such that the variant would be useful for inclusion in products that find utility in treating and/or preventing chronic or persistent diseases, conditions, toxicity or other chronic indications. In one embodiment, the affinity of the variant for serum albumin is relatively modest, such that the variant would be useful for inclusion in products that find utility in treating and/or preventing acute diseases, conditions, toxicity or other acute indications. In one embodiment, the affinity of the variant for serum albumin is intermediate, such that the variant would be useful for inclusion in products that find utility in treating and/or preventing acute or chronic diseases, conditions, toxicity or other acute or chronic indications.

It is conceivable that a molecule with an appropriately high affinity and specificity for serum albumin would stay in circulation long enough to have the desired therapeutic effect. (Tomlinson, *Nature Biotechnology* **22**, 521 - 522 (2004)). Here, a high affinity anti-SA variant would stay in serum circulation matching that of the species' serum albumin (WO2008096158). Once in circulation, any fused therapeutic agent to the AlbudAb™ variant (an AlbudAb is an anti-serum albumin dAb or immunoglobulin single variable domain), be it NCE, peptide or protein, consequently would be able to act longer on its target and exhibit a longer lasting therapeutic effect. This would allow for targeting chronic or persistent diseases without the need of frequent dosing.

A variant with moderate affinity (but specificity to SA) would only stay in serum circulation for a short time (eg, for a few hours or a few days) allowing for the specific targeting of therapeutic targets involved in acute diseases by the fused therapeutic agent.

This way it is possible to tailor the anti-SA-containing product to the therapeutic disease area by choosing an anti-SA variant with the appropriate albumin binding affinity and/or serum half-life.

An aspect of the invention provides a multispecific ligand comprising any anti-SA variant as described above and a binding moiety that specifically binds a target antigen other than SA.

An aspect of the invention provides a fusion product, eg, a fusion protein or fusion with a peptide or NCE (new chemical entity) drug, comprising a polypeptide, protein, peptide or NCE drug fused or conjugated (for an NCE) to any variant as described above, wherein the variant is DOM7h-14-10 (or a variant having an amino acid that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of DOM7h-14-10). DOM7h-14-10 gives only a modest drop in affinity when fused or conjugated to partner, making it useful in fusion products.

An aspect of the invention provides a composition comprising a variant, fusion protein or ligand of any preceding aspect and a pharmaceutically acceptable diluent, carrier, excipient or vehicle.

An aspect of the invention provides a method of treating or preventing a disease or disorder in a patient, comprising administering at least one dose of a variant according to any aspect or embodiment of the invention to said patient.

An aspect of the invention provides a polypeptide fusion or conjugate comprising an anti-serum albumin dAb as disclosed herein (eg, DOM7h-14-10) and an incretin or insulinotropic agent, eg, exendin-4, GLP-1(7-37), GLP-1(6-36) or any incretin or insulinotropic agent disclosed in WO06/059106, these agents being explicitly incorporated herein by reference as though written herein for inclusion in the present invention and claims below.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Amino-acid sequence alignment for DOM7h-14 variant dAbs. A "." at a particular position indicates the same amino as found in DOM7h-14 at that position. The CDRs are indicated by underlining and bold text (the first underlined sequence is CDR1, the second underlined sequence is CDR2 and the third underlined sequence is CDR3).

Figure 2: Kinetic parameters of DOM7h-14 variants. KD units = nM; Kd units = sec^{-1}; Ka units = M^{-1} sec^{-1}. The notation A e-B means A x 10^{-B} and C e D means C x 10^{D}. The overall kinetic ranges in various species, as supported by the examples below, are indicated. Optional ranges are also provided for use in particular therapeutic settings (acute or chronic indications, conditions or diseases and "intermediate" for use in both chronic and acute settings). High affinity dAbs and products comprising these are useful for chronic settings. Medium affinity dAbs and products comprising these are useful for intermediate settings. Low affinity dAbs and products comprising these are useful for acute settings. The affinity in this respect is the affinity for serum albumin. Various example anti-serum dAbs and fusion proteins are listed, and these support the ranges disclosed. Many of the examples have favourable kinetics in human and one or more non-human animals (eg, in human and *Cynomolgus* monkey and/or mouse). Choice of dAb or product comprising this can be tailored, according to the invention, depending on the setting (eg, chronic or acute) to be treated therapeutically.

DETAILED DESCRIPTION OF THE INVENTION

Within this specification the invention has been described, with reference to embodiments, in a way which enables a clear and concise specification to be written. It is intended and should be appreciated that embodiments may be variously combined or separated without parting from the invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art (e.g., in cell culture, molecular genetics, nucleic acid chemistry, hybridization techniques and

biochemistry). Standard techniques are used for molecular, genetic and biochemical methods (see generally, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2d ed. (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. and Ausubel *et al.*, Short Protocols in Molecular Biology (1999) 4th Ed, John Wiley & Sons, Inc. which are incorporated herein by reference) and chemical methods.

As used herein, the term "antagonist of Tumor Necrosis Factor Receptor 1 (TNFR1)" or "anti-TNFR1 antagonist" or the like refers to an agent (e.g., a molecule, a compound) which binds TNFR1 and can inhibit a (i.e., one or more) function of TNFR1. For example, an antagonist of TNFR1 can inhibit the binding of TNFα to TNFR1 and/or inhibit signal transduction mediated through TNFR1. Accordingly, TNFR1-mediated processes and cellular responses (e.g., TNFα-induced cell death in a standard L929 cytotoxicity assay) can be inhibited with an antagonist of TNFR1.

A "patient" is any animal, eg, a mammal, eg, a non-human primate (such as a baboon, rhesus monkey or Cynomolgus monkey), mouse, human, rabbit, rat, dog, cat or pig. In one embodiment, the patient is a human.

As used herein, "peptide" refers to about two to about 50 amino acids that are joined together via peptide bonds.

As used herein, "polypeptide" refers to at least about 50 amino acids that are joined together by peptide bonds. Polypeptides generally comprise tertiary structure and fold into functional domains.

As used herein an antibody refers to IgG, IgM, IgA, IgD or IgE or a fragment (such as a Fab , $F(ab')_2$, Fv, disulphide linked Fv, scFv, closed conformation multispecific antibody, disulphide-linked scFv, diabody) whether derived from any species naturally producing an antibody, or created by recombinant DNA technology; whether isolated from serum, B-cells, hybridomas, transfectomas, yeast or bacteria.

As used herein, "antibody format" refers to any suitable polypeptide structure in which one or more antibody variable domains can be incorporated so as to confer binding specificity for antigen on the structure. A variety of suitable antibody formats are known in the art, such as, chimeric antibodies, humanized antibodies, human antibodies, single chain antibodies, bispecific antibodies, antibody heavy chains,

antibody light chains, homodimers and heterodimers of antibody heavy chains and/or light chains, antigen-binding fragments of any of the foregoing (*e.g.*, a Fv fragment (*e.g.*, single chain Fv (scFv), a disulfide bonded Fv), a Fab fragment, a Fab' fragment, a $F(ab')_2$ fragment), a single antibody variable domain (*e.g.*, a dAb, V_H, V_{HH}, $V_{L)}$, and modified versions of any of the foregoing (*e.g.*, modified by the covalent attachment of polyethylene glycol or other suitable polymer or a humanized V_{HH}).

The phrase "immunoglobulin single variable domain" refers to an antibody variable domain (V_H, V_{HH}, V_L) that specifically binds an antigen or epitope independently of different V regions or domains. An immunoglobulin single variable domain can be present in a format (*e.g.*, homo- or hetero-multimer) with other variable regions or variable domains where the other regions or domains are not required for antigen binding by the single immunoglobulin variable domain (*i.e.*, where the immunoglobulin single variable domain binds antigen independently of the additional variable domains). A "domain antibody" or "dAb" is the same as an "immunoglobulin single variable domain" as the term is used herein. A "single immunoglobulin variable domain" is the same as an "immunoglobulin single variable domain" as the term is used herein. A "single antibody variable domain" or an "antibody single variable domain" is the same as an "immunoglobulin single variable domain" as the term is used herein. An immunoglobulin single variable domain is in one embodiment a human antibody variable domain, but also includes single antibody variable domains from other species such as rodent (for example, as disclosed in WO 00/29004, the contents of which are incorporated herein by reference in their entirety), nurse shark and *Camelid* V_{HH} dAbs. Camelid V_{HH} are immunoglobulin single variable domain polypeptides that are derived from species including camel, llama, alpaca, dromedary, and guanaco, which produce heavy chain antibodies naturally devoid of light chains. The V_{HH} may be humanized.

A "domain" is a folded protein structure which has tertiary structure independent of the rest of the protein. Generally, domains are responsible for discrete functional properties of proteins, and in many cases may be added, removed or transferred to other proteins without loss of function of the remainder of the protein and/or of the domain. A "single antibody variable domain" is a folded polypeptide

domain comprising sequences characteristic of antibody variable domains. It therefore includes complete antibody variable domains and modified variable domains, for example, in which one or more loops have been replaced by sequences which are not characteristic of antibody variable domains, or antibody variable domains which have been truncated or comprise N- or C-terminal extensions, as well as folded fragments of variable domains which retain at least the binding activity and specificity of the full-length domain.

In the instant application, the term "prevention" and "preventing" involves administration of the protective composition prior to the induction of the disease or condition. "Treatment" and "treating" involves administration of the protective composition after disease or condition symptoms become manifest. "Suppression" or "suppressing" refers to administration of the composition after an inductive event, but prior to the clinical appearance of the disease or condition.

As used herein, the term "dose" refers to the quantity of ligand administered to a subject all at one time (unit dose), or in two or more administrations over a defined time interval. For example, dose can refer to the quantity of ligand (*e.g.*, ligand comprising an immunoglobulin single variable domain that binds target antigen) administered to a subject over the course of one day (24 hours) (daily dose), two days, one week, two weeks, three weeks or one or more months (*e.g.*, by a single administration, or by two or more administrations). The interval between doses can be any desired amount of time. The term "pharmaceutically effective" when referring to a dose means sufficient amount of the ligand, domain or pharmaceutically active agent to provide the desired effect. The amount that is "effective" will vary from subject to subject, depending on the age and general condition of the individual, the particular drug or pharmaceutically active agent and the like. Thus, it is not always possible to specify an exact "effective" amount applicable for all patients. However, an appropriate "effective" dose in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

Methods for pharmacokinetic analysis and determination of ligand (eg, single variable domain, fusion protein or multi-specific ligand) half-life will be familiar to

those skilled in the art. Details may be found in *Kenneth, A et al:* Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists and in *Peters et al,* Pharmacokinetc analysis: A Practical Approach (1996). Reference is also made to "Pharmacokinetics", M Gibaldi & D Perron, published by Marcel Dekker, 2nd Rev. ex edition (1982), which describes pharmacokinetic parameters such as t alpha and t beta half lives and area under the curve (AUC). Optionally, all pharmacokinetic parameters and values quoted herein are to be read as being values in a human. Optionally, all pharmacokinetic parameters and values quoted herein are to be read as being values in a mouse or rat or *Cynomolgus* monkey.

Half lives (t½ alpha and t½ beta) and AUC can be determined from a curve of serum concentration of ligand against time. The WinNonlin analysis package, eg version 5.1 (available from Pharsight Corp., Mountain View, CA94040, USA) can be used, for example, to model the curve. When two-compartment modeling is used, in a first phase (the alpha phase) the ligand is undergoing mainly distribution in the patient, with some elimination. A second phase (beta phase) is the phase when the ligand has been distributed and the serum concentration is decreasing as the ligand is cleared from the patient. The t alpha half life is the half life of the first phase and the t beta half life is the half life of the second phase. Thus, in one embodiment, in the context of the present invention, the variable domain, fusion protein or ligand has a tα half–life in the range of (or of about) 15 minutes or more. In one embodiment, the lower end of the range is (or is about) 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 10 hours, 11 hours or 12 hours. In addition, or alternatively, the variable domain, fusion protein or ligand according to the invention will have a tα half life in the range of up to and including 12 hours (or about 12 hours). In one embodiment, the upper end of the range is (or is about) 11, 10, 9, 8, 7, 6 or 5 hours. An example of a suitable range is (or is about) 1 to 6 hours, 2 to 5 hours or 3 to 4 hours.

In one embodiment, the present invention provides the variable domain, fusion protein or ligand according to the invention has a tβ half–life in the range of (or of about) 2.5 hours or more. In one embodiment, the lower end of the range is (or is about) 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 10 hours , 11 hours, or 12 hours. In

addition, or alternatively, the tβ half–life is (or is about) up to and including 21 or 25 days. In one embodiment, the upper end of the range is (or is about)12 hours, 24 hours, 2 days, 3 days, 5 days, 10 days, 15 days, 19 days, 20 days, 21 days or 22 days. For example, the variable domain, fusion protein or ligand according to the invention will have a tβ half life in the range 12 to 60 hours (or about 12 to 60 hours). In a further embodiment, it will be in the range 12 to 48 hours (or about 12 to 48 hours). In a further embodiment still, it will be in the range 12 to 26 hours (or about 12 to 26 hours).

As an alternative to using two-compartment modeling, the skilled person will be familiar with the use of non-compartmental modeling, which can be used to determine terminal half-lives (in this respect, the term "terminal half-life" as used herein means a terminal half-life determined using non-compartmental modeling). The WinNonlin analysis package, eg version 5.1 (available from Pharsight Corp., Mountain View, CA94040, USA) can be used, for example, to model the curve in this way. In this instance, in one embodiment the single variable domain, fusion protein or ligand has a terminal half life of at least (or at least about) 8 hours, 10 hours, 12 hours, 15 hours, 28 hours, 20 hours, 1 day, 2 days, 3 days, 7 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days or 25 days. In one embodiment, the upper end of this range is (or is about) 24 hours, 48 hours, 60 hours or 72 hours or 120 hours. For example, the terminal half-life is (or is about) from 8 hours to 60 hours, or 8 hours to 48 hours or 12 to 120 hours, eg, in man.

In addition, or alternatively to the above criteria, the variable domain, fusion protein or ligand according to the invention has an AUC value (area under the curve) in the range of (or of about) 1 mg.min/ml or more. In one embodiment, the lower end of the range is (or is about) 5, 10, 15, 20, 30, 100, 200 or 300 mg.min/ml. In addition, or alternatively, the variable domain, fusion protein or ligand according to the invention has an AUC in the range of (or of about) up to 600 mg.min/ml. In one embodiment, the upper end of the range is (or is about) 500, 400, 300, 200, 150, 100, 75 or 50 mg.min/ml. Advantageously the variable domain, fusion protein or ligand will have an AUC in (or about in) the range selected from the group consisting of the following: 15 to 150 mg.min/ml, 15 to 100 mg.min/ml, 15 to 75 mg.min/ml, and 15 to 50mg.min/ml.

"Surface Plasmon Resonance": Competition assays can be used to determine if a specific antigen or epitope, such as human serum albumin, competes with another antigen or epitope, such as cynomolgus serum albumin, for binding to a serum albumin binding ligand described herein, such as a specific dAb. Similarly competition assays can be used to determine if a first ligand such as dAb, competes with a second ligand such as a dAb for binding to a target antigen or epitope. The term "competes" as used herein refers to substance, such as a molecule, compound, preferably a protein, which is able to interfere to any extent with the specific binding interaction between two or more molecules. The phrase "does not competitively inhibit" means that substance, such as a molecule, compound, preferably a protein, does not interfere to any measurable or significant extent with the specific binding interaction between two or more molecules. The specific binding interaction between two or more molecules preferably includes the specific binding interaction between a single variable domain and its cognate partner or target. The interfering or competing molecule can be another single variable domain or it can be a molecule that is structurally and/or functionally similar to a cognate partner or target.

The term "binding moiety" refers to a domain that specifically binds an antigen or epitope independently of a different epitope or antigen binding domain. A binding moiety may be a domain antibody (dAb) or may be a domain which is a derivative of a non-immunoglobulin protein scaffold, eg, a scaffold selected from the group consisting of CTLA-4, lipocalin, SpA, an affibody, an avimer, GroEl, transferrin, GroES and fibronectin, which binds to a ligand other than the natural ligand (in the case of the present invention, the moiety binds serum albumin). See WO2008/096158, which discloses examples of protein scaffolds and methods for selecting antigen or epitope-specific binding domains from repertoires (see Examples 17 to 25). These specific disclosures of WO2008/096158 are expressly incorporated herein by reference as though explicitly written herein and for use with the present invention, and it is contemplated that any part of such disclosure can be incorporated into one or more claims herein).

In a first aspect, the invention provides an anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises at least one mutation in CDR3 region 92 to 96 (position numbering according to Kabat) compared to DOM7h-14, and wherein the variant has from 1 to 8 changes compared to the amino acid sequence of DOM7h-14.

Optionally, the variant comprises a AQG(X1)(X2)(X3)P(X4)T motif, wherein A is at position 89 (according to Kabat), and at least one of (X1) to (X4) represents an amino acid change compared to the sequence of DOM7h-14.

In one embodiment, position 95 (according to Kabat) is Pro. Additionally or alternatively, in one embodiment position 89 (according to Kabat) is Ala. Additionally or alternatively, in one embodiment position 90 (according to Kabat) is Gln. Additionally or alternatively, in one embodiment position 91 (according to Kabat) is Gly. Additionally or alternatively, in one embodiment position 97 (according to Kabat) is Thr.

In an embodiment, the variant comprises a mutation at each of positions 92, 93 and 94 and optionally position 96 (numbering according to Kabat) compared to DOM7h-14.

Optionally, the variant comprises one or more amino acid residues selected from

Position 92 = L or F,
Position 93 = R, M or K,
Position 94 = H or K, and
Position 96 = K or M (numbering according to Kabat).

In one embodiment, the variant comprises a Lys or Met at position 96 (numbering according to Kabat) compared to DOM7h-14. In this embodiment, optionally the variant comprises one or more amino acid residues selected from

Position 92 = L or F,
Position 93 = R, M or K, and

Position 94 = H or K (numbering according to Kabat).

In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-14-10, DOM7h-14-18, DOM7h-14-28 and DOM7h-14-36 or has up to 4 changes compared to the selected amino acid sequence, wherein the variant comprises at least one mutation in CDR3 region 92 to 96 (position numbering according to Kabat) compared to DOM7h-14.

An aspect of the invention provides an anti-serum albumin (SA) binding moiety comprising CDR3 of a variant according to the first aspect of the invention. In one embodiment, the SA-binding moiety comprises CDR1 of the selected variant or an amino acid sequence that is at least 50% identical to CDR1 of the selected variant. Additionally or alternatively, in an embodiment the SA-binding moiety comprises CDR2 of the selected variant or an amino acid sequence that is at least 50% identical to CDR2 of the selected variant.

In a further aspect of the invention, there is provided an anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises a Ser at position 22 and a Glu at position 42 (numbering according to Kabat) compared to DOM7h-14, and wherein the variant has from 0 to 4 further changes compared to the amino acid sequence of DOM7h-14. In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of DOM7h-14-19 or has up to 4 changes compared to the amino acid sequence of DOM7h-14-19, wherein the variant comprises a Ser at position 22 and a Glu at position 42 (numbering according to Kabat) compared to DOM7h-14.

In one embodiment, the variant or binding moiety according to any aspect or embodiment of the invention comprises one or more of the following kinetic characteristics:-

(a) The variant or moiety comprises a binding site that specifically binds human SA with a dissociation constant (KD) from (or from about) 0.1 to (or to about)

10000 nM, optionally from (or from about) 1 to (or to about) 6000 nM, as determined by surface plasmon resonance;

(b) The variant or moiety comprises a binding site that specifically binds human SA with an off-rate constant (K_d) from (or from about) 1.5×10^{-4} to (or to about) 0.1 sec^{-1}, optionally from (or from about) 3×10^{-4} to (or to about) 0.1 sec^{-1} as determined by surface plasmon resonance;

(c) The variant or moiety comprises a binding site that specifically binds human SA with an on-rate constant (K_a) from (or from about) 2×10^6 to (or to about) 1×10^4 $M^{-1}sec^{-1}$, optionally from (or from about) 1×10^6 to (or to about) 2×10^4 $M^{-1}sec^{-1}$ as determined by surface plasmon resonance;

(d) The variant or moiety comprises a binding site that specifically binds *Cynomolgus* monkey SA with a dissociation constant (KD) from (or from about) 0.1 to (or to about) 10000 nM, optionally from (or from abou)t 1 to (or to about) 6000 nM, as determined by surface plasmon resonance;

(e) The variant or moiety of any preceding claim, wherein the variant comprises a binding site that specifically binds *Cynomolgus* monkey SA with an off-rate constant (K_d) from (or from about) 1.5×10^{-4} to (or to about) 0.1 sec^{-1}, optionally from (or from about) 3×10^{-4} to (or to about) 0.1 sec^{-1} as determined by surface plasmon resonance;

(f) The variant or moiety of any preceding claim, wherein the variant comprises a binding site that specifically binds *Cynomolgus* monkey SA with an on-rate constant (K_a) from (or from about) 2×10^6 to (or to about) 1×10^4 $M^{-1}sec^{-1}$, optionally from (or from about) 1×10^6 to (or to about) 5×10^3 $M^{-1}sec^{-1}$ as determined by surface plasmon resonance;

(g) The variant or moiety comprises a binding site that specifically binds rat SA with a dissociation constant (KD) from (or from about) 1 to (or to about) 10000

nM, optionally from (or from about) 20 to (or to about) 6000 nM, as determined by surface plasmon resonance;

(h) The variant or moiety comprises a binding site that specifically binds rat SA with an off-rate constant (K_d) from (or from about) 2 x 10^{-3} to (or to about) 0.15 sec^{-1} , optionally from (or from about) 9 x 10^{-3} to (or to about) 0.14 sec^{-1} as determined by surface plasmon resonance;

(i) The variant or moiety comprises a binding site that specifically binds rat SA with an on-rate constant (K_a) from (or from about) 2 x 10^6 to (or to about) 1 x 10^4 $M^{-1}sec^{-1}$, optionally from (or from about) 1 x 10^6 to (or to about) 3 x 10^4 $M^{-1}sec^{-1}$ as determined by surface plasmon resonance;

(j) The variant or moiety comprises a binding site that specifically binds mouse SA with a dissociation constant (KD) from (or from about) 1 to (or to about) 10000 nM as determined by surface plasmon resonance;

(k) The variant or moiety comprises a binding site that specifically binds mouse SA with an off-rate constant (K_d) from (or from about) 2 x 10^{-3} to (or to about) 0.15 sec^{-1} as determined by surface plasmon resonance; and/or

(l) The variant or moiety comprises a binding site that specifically binds mouse SA with an on-rate constant (K_a) from (or from about) 2 x 10^6 to (or to about) 1 x 10^4 $M^{-1}sec^{-1}$, optionally from (or from about) 2 x 10^6 to (or to about) 1.5 x 10^4 $M^{-1}sec^{-1}$ as determined by surface plasmon resonance.

Optionally, the variant or moiety has

I: a KD according to (a) and (d), a K_d according to (b) and (e), and a K_a according to (c) and (f); or

II: a KD according to (a) and (g), a K_d according to (b) and (h), and a K_a according to (c) and (i); or

III: a KD according to (a) and (j), a K_d according to (b) and (k), and a K_a according to (c) and (l); or

IV: kinetics according to I and II; or

V: kinetics according to I and III; or

VI: kinetics according to I, II and III.

The invention also provides a ligand comprising a variant or moiety of any preceding aspect or embodiment of the invention. For example, the ligand can be a dual-specific ligand (see WO04003019 for examples of dual-specific ligands). In one aspect, the invention provides a multispecific ligand comprising an anti-SA variant or moiety of any preceding aspect or embodiment of the invention and a further binding moiety that specifically binds a target antigen other than SA. The or each binding moiety can be any binding moiety that specifically binds a target, eg, the moiety is an antibody, antibody fragment, scFv, Fab, dAb or a binding moiety comprising a non-immunoglobulin protein scaffold. Such moieties are disclosed in detail in WO2008/096158 (see examples 17 to 25, which disclosure is incorporated herein by reference). Examples of non-immunoglobulin scaffolds are CTLA-4, lipocallin, staphylococcal protein A (spA), Affibody™, Avimers™, GroEL and fibronectin.

In one embodiment, a linker is provided between the anti-target binding moiety and the anti-SA single variant or moiety, the linker comprising the amino acid sequence AST, optionally ASTSGPS, eg, where anti-SA and anti-target dAbs are used. Alternative linkers are described in WO2007085814 (incorporated herein by reference) and WO2008/096158 (see the passage at page 135, line 12 to page 140, line 14, which disclosure and all sequences of linkers are expressly incorporated herein by reference as though explicitly written herein and for use with the present invention, and it is contemplated that any part of such disclosure can be incorporated into one or more claims herein).

In one embodiment of the multispecific ligand, the target antigen may be, or be part of, polypeptides, proteins or nucleic acids, which may be naturally occurring or

synthetic. In this respect, the ligand of the invention may bind the target antigen and act as an antagonist or agonist (e.g., EPO receptor agonist). One skilled in the art will appreciate that the choice is large and varied. They may be for instance, human or animal proteins, cytokines, cytokine receptors, where cytokine receptors include receptors for cytokines, enzymes, co-factors for enzymes or DNA binding proteins. Suitable cytokines and growth factors include, but are preferably not limited to: ApoE, Apo-SAA, BDNF, Cardiotrophin-1, EGF, EGF receptor, ENA-78, Eotaxin, Eotaxin-2, Exodus-2, EpoR, FGF-acidic, FGF-basic, fibroblast growth factor-10, FLT3 ligand, Fractalkine (CX3C), GDNF, G-CSF, GM-CSF, GF-β1, insulin, IFN-γ, IGF-I, IGF-II, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8 (72 a.a.), IL-8 (77 a.a.), IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-16, IL-17, IL-18 (IGIF), Inhibin α, Inhibin β, IP-10, keratinocyte growth factor-2 (KGF-2), KGF, Leptin, LIF, Lymphotactin, Mullerian inhibitory substance, monocyte colony inhibitory factor, monocyte attractant protein, M-CSF, MDC (67 a.a.), MDC (69 a.a.), MCP-1 (MCAF), MCP-2, MCP-3, MCP-4, MDC (67 a.a.), MDC (69 a.a.), MIG, MIP-1α, MIP-1β, MIP-3α, MIP-3β, MIP-4, myeloid progenitor inhibitor factor-1 (MPIF-1), NAP-2, Neurturin, Nerve growth factor, β-NGF, NT-3, NT-4, Oncostatin M, PDGF-AA, PDGF-AB, PDGF-BB, PF-4, RANTES, SDF1α, SDF1β, SCF, SCGF, stem cell factor (SCF), TARC, TGF-α, TGF-β, TGF-β2, TGF-β3, tumour necrosis factor (TNF), TNF-α, TNF-β, TNF receptor I, TNF receptor II, TNIL-1, TPO, VEGF, VEGF receptor 1, VEGF receptor 2, VEGF receptor 3, GCP-2, GRO/MGSA, GRO-β, GRO-γ, HCC1, 1-309, HER 1, HER 2, HER 3 and HER 4, CD4, human chemokine receptors CXCR4 or CCR5, non-structural protein type 3 (NS3) from the hepatitis C virus, , TNF-alpha, IgE, IFN-gamma, MMP-12, CEA, H. pylori, TB, influenza, Hepatitis E, MMP-12, internalizing receptors that are over-expressed on certain cells, such as the epidermal growth factor receptor (EGFR), ErBb2 receptor on tumor cells, an internalising cellular receptor, LDL receptor, FGF2 receptor, ErbB2 receptor, transferrin receptor, PDGF receptor, VEGF receptor, PsmAr, an extracellular matrix protein, elastin, fibronectin, laminin, α1-antitrypsin, tissue factor protease inhibitor, PDK1, GSK1, Bad, caspase-9, Forkhead, an

antigen of Helicobacter pylori, an antigen of Mycobacterium tuberculosis, and an antigen of influenza virus. It will be appreciated that this list is by no means exhaustive.

In one embodiment, the multispecific ligand comprises an anti-SA dAb variant or moiety of the invention and an anti-TNFR1 binding moiety, eg, an anti-TNFR1 dAb. Optionally, the ligand has only one anti-TNFR1 binding moiety (eg, dAb) to reduce the chance of receptor cross-linking. In one embodiment, the anti-SA dAb variant is DOM7h-14-10.

In one embodiment, the anti-TNFR1 binding moiety is DOM1h-131-206 disclosed in WO2008149148 (the amino acid sequence of which and the nucleotide sequence of which, as disclosed in that PCT application, are expressly incorporated herein by reference as though explicitly written herein and for use with the present invention, and it is contemplated that any part of such disclosure can be incorporated into one or more claims herein). In one embodiment, the multispecific ligand comprises or consists of the amino acid sequence of DOM1h-131-206 and the amino acid sequence of DOM7h-14-10.

In one embodiment, the anti-TNFR1 binding moiety or dAb is any such moiety or dAb disclosed in co-pending application USSN 61/153,746, the disclosure of which is incorporated herein by reference. In one embodiment, the anti-TNFR1 binding moiety comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of DOM1h-574-156, DOM1h-574-72, DOM1h-574-109, DOM1h-574-138, DOM1h-574-162 or DOM1h-574-130 or the amino acid sequence of any anti-TNFR1 dAb disclosed in Table 3. In one embodiment, the multispecific ligand comprises or consists of the amino acid sequence of DOM1h-574-156 and the amino acid sequence of DOM7h-14-10.

In one embodiment, the ligand of the invention is a fusion protein comprising a variant or moiety of the invention fused directly or indirectly to one or more polypeptides. For example, the fusion protein can be a "drug fusion" as disclosed in WO2005/113642 (the disclosure of which is incorporated herein by reference), comprising a variant or moiety of the invention and a polypeptide drug as defined in that PCT application.

As used herein, "drug" refers to any compound (e.g., small organic molecule, nucleic acid, polypeptide) that can be administered to an individual to produce a beneficial, therapeutic or diagnostic effect through binding to and/or altering the function of a biological target molecule in the individual. The target molecule can be an endogenous target molecule encoded by the individual's genome (e.g. an enzyme, receptor, growth factor, cytokine encoded by the individual's genome) or an exogenous target molecule encoded by the genome of a pathogen (e. g. an enzyme encoded by the genome of a virus, bacterium, fungus, nematode or other pathogen). Suitable drugs for use in fusion proteins and conjugates comprising an anti-SA dAb variant of the invention are disclosed in WO2005/118642 and WO2006/059106 (the entire disclosures of which are incorporated herein by reference, and including the entire list of specific drugs as though this list were expressly written herein, and it is contemplated that such incorporation provides disclosure of specific drugs for inclusion in claims herein). For example, the drug can be glucagon-like peptide 1 (GLP-1) or a variant, interferon alpha 2b or a variant or exendin-4 or a variant.

In one embodiment, the invention provides a drug conjugate as defined and disclosed in WO2005/118642 and WO2006/059106, wherein the conjugate comprises a variant or moiety of the invention. In one example, the drug is covalently linked to the variant or moiety (eg, the variant or moiety and the drug are expressed as part of a single polypeptide). Alternatively, in an example, the drug is non-covalently bonded or associated with the variant or moiety. The drug can be covalently or noncovalently bonded to the variant or moiety directly or indirectly (e.g., through a suitable linker and/or noncovalent binding of complementary binding partners (e.g., biotin and avidin)). When complementary binding partners are employed, one of the binding partners can be covalently bonded to the drug directly or through a suitable linker moiety, and the complementary binding partner can be covalently bonded to the variant or moiety directly or through a suitable linker moiety. When the drug is a polypeptide or peptide, the drug composition can be a fusion protein, wherein the polypeptide or peptide, drug and the polypeptide binding moiety are discrete parts (moieties) of a continuous polypeptide chain. As described herein, the polypeptide binding moieties

and polypeptide drug moieties can be directly bonded to each other through a peptide bond, or linked through a suitable amino acid, or peptide or polypeptide linker.

A ligand which contains one single variable domain (monomer) variant or moiety of the invention or more than one single variable domain or moiety (multimer, fusion protein, conjugate, and dual specific ligand as defined herein) which specifically binds to serum albumin, can further comprise one or more entities selected from, but preferably not limited to a label, a tag, an additional single variable domain, a dAb, an antibody, an antibody fragment, a marker and a drug. One or more of these entities can be located at either the COOH terminus or at the N terminus or at both the N terminus and the COOH terminus of the ligand comprising the single variable domain or moiety, (either immunoglobulin or non-immunoglobulin single variable domain). One or more of these entities can be located at either the COOH terminus, or the N terminus, or both the N terminus and the COOH terminus of the single variable domain or moiety which specifically binds serum albumin of the ligand which contains one single variable domain (monomer) or moiety or more than one single variable domains or moieties (multimer, fusion protein, conjugate, and dual specific ligand as defined herein). Non-limiting examples of tags which can be positioned at one or both of these termini include a HA, his or a myc tag. The entities, including one or more tags, labels and drugs, can be bound to the ligand which contains one single variable domain (monomer) or more than one single variable domain or moiety (multimer, fusion protein, conjugate, and dual specific ligand as defined herein), which binds serum albumin, either directly or through linkers as described above.

An aspect of the invention provides a fusion product, eg, a fusion protein or fusion with a peptide or conjugate with an NCE (new chemical entity) drug, comprising a polypeptide drug fused or conjugated (for an NCE) to any variant or moiety as described above, optionally wherein the variant or moiety is DOM7h-14-10 (or a variant having an amino acid that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of DOM7h-14-10). DOM7h-14-10 gives only a modest drop in affinity when fused or conjugated to partner, making them useful in fusion products.

The invention provides a composition comprising a variant, fusion protein, conjugate or ligand of any aspect of the invention and a pharmaceutically acceptable diluent, carrier, exipient or vehicle.

Also encompassed herein is an isolated nucleic acid encoding any of the variants, moieties, fusion proteins, conjugates or ligands described herein, e.g., a ligand which contains one single variable domain (monomer) variant of the invention or more than one single variable domain (e.g., multimer, fusion protein, conjugate, and dual specific ligand as defined herein) variant which specifically binds to serum albumin, or which specifically binds both human serum albumin and at least one non-human serum albumin, or functionally active fragments thereof. Also encompassed herein is a vector and/or an expression vector, a host cell comprising the vector, e.g., a plant or animal cell and/or cell line transformed with a vector, a method of expressing and/or producing one or more variants, moieties, fusion proteins or ligands which contains one single variable domain (monomer) variant or moiety or more than one single variable domain variants or moieties (e.g., multimer, fusion protein, conjugate, and dual specific ligand as defined herein) which specifically binds to serum albumin, or fragment(s) thereof encoded by said vectors, including in some instances culturing the host cell so that the one or more variants, moieties, fusion proteins or ligands or fragments thereof are expressed and optionally recovering the ligand which contains one single variable domain or moiety (monomer) or more than one single variable domain or moiety (e.g., multimer, fusion protein, conjugate, and dual specific ligand as defined herein) which specifically binds to serum albumin, from the host cell culture medium. Also encompassed are methods of contacting a ligand described herein with serum albumin, including serum albumin and/or non-human serum albumin(s), and/or one or more targets other than serum albumin, where the targets include biologically active molecules, and include animal proteins, cytokines as listed above, and include methods where the contacting is in vitro as well as administering any of the variants, moieties, fusion proteins or ligands described herein to an individual host animal or cell *in vivo* and/or *ex vivo*. Preferably, administering ligands described herein which comprises a single variable domain (immunoglobulin or non-immunoglobulin) directed to serum

albumin and/or non-human serum albumin(s), and one or more domains directed to one or more targets other than serum albumin, will increase the half life, including the T beta and/or terminal half life, of the anti-target ligand. Nucleic acid molecules encoding the variants, fusion proteins or single domain containing ligands or fragments thereof, including functional fragments thereof, are contemplated herein. Vectors encoding the nucleic acid molecules, including but preferably not limited to expression vectors, are contemplated herein, as are host cells from a cell line or organism containing one or more of these expression vectors. Also contemplated are methods of producing any variant, fusion protein or ligand, including, but preferably not limited to any of the aforementioned nucleic acids, vectors and host cells.

An aspect of the invention provides a nucleic acid comprising a nucleotide sequence encoding a variant according to the invention or a multispecific ligand of the invention or fusion protein of the invention.

An aspect of the invention provides a nucleic acid comprising the nucleotide sequence of a DOM7h-14 variant selected from DOM7h-14-10, DOM7h-14-18, DOM7h-14-28, DOM7h-14-36 and DOM7h-14-19 or a nucleotide sequence that is at least 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99% identical to said selected sequence.

An aspect of the invention provides a vector comprising the nucleic acid of the invention. An aspect of the invention provides an isolated host cell comprising the vector.

Reference is made to WO2008/096158 for details of library vector systems, combining single variable domains, characterization of dual specific ligands, structure of dual specific ligands, scaffolds for use in constructing dual specific ligands, uses of anti-serum albumin dAbs and multispecific ligands and half-life-enhanced ligands, and compositions and formulations of comprising anti-serum albumin dAbs. These disclosures are incorporated herein by reference to provide guidance for use with the present invention, including for variants, moieties, ligands, fusion proteins, conjugates, nucleic acids, vectors, hosts and compositions of the present invention.

DOM7h-11 variant sequences, which are not according to the invention, are disclosed in a co-pending US provisional patent application entitled IMPROVED ANTI-SERUM ALBUMIN BINDING VARIANTS, filed on the same day as the present application. These sequences of DOM7h-11 variants (SEQ ID NO:s 1-10 in the co-pending application) are incorporated herein by reference as though explicitly written herein.

SEQUENCES

Table 1: Amino Acid Sequences of DOM7h-14 Variant dAbs

DOM7h-14-10 (SEQ ID NO: 1)
DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKR

DOM7h-14-18 (SEQ ID NO:2)
DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLMKPMTFGQGTKVEIKR

DOM7h-14-19 (SEQ ID NO: 3)
DIQMTQSPSSLSASVGDRVTISCRASQWIGSQLSWYQQKPGEAPKLLIMWRSSLQSGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCAQGAALPRTFGQGTKVEIKR

DOM7h-14-28 (SEQ ID NO: 4)
DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCAQGAALPKTFGQGTKVEIKR

DOM7h-14-36 (SEQ ID NO: 5)
DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCAQGFKKPRTFGQGTKVEIKR

Table 2: Nucleotide Sequences of DOM7h-14 Variant dAbs

DOM7h-14-10 (SEQ ID NO: 6)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT CACC ATCACTTGCC GGGCAAGTCA GTGGATTGGG TCTCAGTTAT CTTGGTACCA GC AGAAACCA GGGAAAGCCC CTAAGCTCCT GATCATGTGG CGTTCCTCGT TGCAAAGT

GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCAT
CAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCTCAG GGTTTGAGGC
ATCCTAAGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-14-18 (SEQ ID NO: 7)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT
CACC ATCACTTGCC GGGCAAGTCA GTGGATTGGG TCTCAGTTAT CTTGGTACCA GC
AGAAACCA GGGAAAGCCC CTAAGCTCCT GATCATGTGG CGTTCCTCGT TGCAAAGT
GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCAT
CAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCTCAG GGTCTTATGA
AGCCTATGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-14-19 (SEQ ID NO: 8)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT
CACC ATCTCTTGCC GGGCAAGTCA GTGGATTGGG TCTCAGTTAT CTTGGTACCA GC
AGAAACCA GGGGAAGCCC CTAAGCTCCT GATCATGTGG CGTTCCTCGT TGCAAAGT
GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCAT
CAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCTCAG GGTGCGGCGT
TGCCTAGGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-14-28 (SEQ ID NO: 9)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT
CACC ATCACTTGCC GGGCAAGTCA GTGGATTGGG TCTCAGTTAT CTTGGTACCA GC
AGAAACCA GGGAAAGCCC CTAAGCTCCT GATCATGTGG CGTTCCTCGT TGCAAAGT
GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCAT
CAGCAG TCTGCAACCT GAAGATTTTG CTACATACTA CTGTGCTCAG GGTGCGGCGT
TGCCTAAGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-14-36 (SEQ ID NO: 10)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT
CACC ATCACTTGCC GGGCAAGTCA GTGGATTGGG TCTCAGTTAT CTTGGTACCA GC
AGAAACCA GGGAAAGCCC CTAAGCTCCT GATCATGTGG CGTTCCTCGT TGCAAAGT
GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCAT
CAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCTCAG GGTTTTAAGA
AGCCTCGGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

Table 3: Amino Acid Sequences of anti-TNFR1 dAbs

>DOM1h-509 (SEQ ID NO: 11)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSQYRMHWVRQAPGKSLEWVSSIDTRGSST
YYADPVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKAVTMFSPFFDYWGQGTLV
TVSS

>DOM1h-510 (SEQ ID NO: 12)
EVQLLESGGGLVQPGGSLRLSCAASGFTFADYGMRWVRQAPGKGLEWVSSITRTGRVT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWRNRHGEYLADFDYWGQG
TLVTVSS

>DOM1h-543 (SEQ ID NO: 13)
EVQLLESGGGLVQPGGSLRLSCAASGFTFMRYRMHWVRQAPGKGLEWVSSIDSNGSST
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRTERSPVFDYWGQGTLV
TVSS

>DOM1h-549 (SEQ ID NO: 14)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVDYEMHWVRQAPGKGLEWVSSISESGTTT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKRRFSASTFDYWGQGTLVT
VSS

>DOM1h-574 (SEQ ID NO: 15)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGHWEPFDYWGQGTLVT
VSS

>DOM1h-574-1 (SEQ ID NO: 16)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPYDYWGQGTLVT
VSS

>DOM1h-574-2 (SEQ ID NO: 17)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-7 (SEQ ID NO: 18)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-8 (SEQ ID NO: 19)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTGGHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-9 (SEQ ID NO: 20)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT
YYADSVKGRFTISRDNSKNTLYMQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-10 (SEQ ID NO: 21)
EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKDLEWVSQISNTGGHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-11 (SEQ ID NO: 22)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDHWGQGTLVT
VSS

>DOM1h-574-12 (SEQ ID NO: 23)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-13 (SEQ ID NO: 24)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-14 (SEQ ID NO: 25)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-15 (SEQ ID NO: 26)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-16 (SEQ ID NO: 27)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-17 (SEQ ID NO: 28)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTGDHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-18 (SEQ ID NO: 29)

EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKDLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-19 (SEQ ID NO: 30)
EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKDLEWVSQISNTGDHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-25 (SEQ ID NO: 31)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-26 (SEQ ID NO: 32)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFEYWGQGTLVT
VSS

>DOM1h-574-27 (SEQ ID NO: 33)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTLVT
VSS

>DOM1h-574-28 (SEQ ID NO: 34)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-29 (SEQ ID NO: 35)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

>DOM1h-574-30 (SEQ ID NO: 36)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAAYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-31 (SEQ ID NO: 37)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFNYWGQGTLVT
VSS

>DOM1h-574-32 (SEQ ID NO: 38)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-33 (SEQ ID NO: 39)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNSLYLQMNSLRAEDTAVYYCAIYTGRWVPFDNWGQGTLVT
VSS

>DOM1h-574-35 (SEQ ID NO: 40)
EVQLLESGGGLVQPGGSLRLSCAASGFTFITYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFQYWGQGTLVT
VSS

>DOM1h-574-36 (SEQ ID NO: 41)
EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-37 (SEQ ID NO: 42)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-38 (SEQ ID NO: 43)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-39 (SEQ ID NO: 44)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-40 (SEQ ID NO: 45)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFKYWGQGTLVT
VSS

>DOM1h-574-53 (SEQ ID NO: 46)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSKYSMGWVRQAPGKGLEWVSQISNTGERR
YYADSVKGRFTISRDNPKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFEYWGQGTLVT
VSS

>DOM1h-574-54 (SEQ ID NO: 47)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVNYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPYEYWGQGTLVT
VTS

>DOM1h-574-65 (SEQ ID NO: 48)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-66 (SEQ ID NO: 49)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTLVT
VSS

>DOM1h-574-67 (SEQ ID NO: 50)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-68 (SEQ ID NO: 51)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

>DOM1h-574-69 (SEQ ID NO: 52)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-70 (SEQ ID NO: 53)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAVYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-71 (SEQ ID NO: 54)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTLVT
VSS

>DOM1h-574-72 (SEQ ID NO: 55)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-73 (SEQ ID NO: 56)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

>DOM1h-574-74 (SEQ ID NO: 57)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-75 (SEQ ID NO: 58)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-76 (SEQ ID NO: 59)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTLVT
VSS

>DOM1h-574-77 (SEQ ID NO: 60)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-78 (SEQ ID NO: 61)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

>DOM1h-574-79 (SEQ ID NO: 62)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-84 (SEQ ID NO: 63)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-85 (SEQ ID NO: 64)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTLVT
VSS

>DOM1h-574-86 (SEQ ID NO: 65)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-87 (SEQ ID NO: 66)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

>DOM1h-574-88 (SEQ ID NO: 67)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-90 (SEQ ID NO: 68)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKFSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-91 (SEQ ID NO: 69)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-92 (SEQ ID NO: 70)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-93 (SEQ ID NO: 71)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-94 (SEQ ID NO: 72)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAAYYCAIYTGRWPDFDYWGQGTLVT
VSS

>DOM1h-574-95 (SEQ ID NO: 73)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAAYYCAIYTGRWPDFEYWGQGTLVT
VSS

>DOM1h-574-96 (SEQ ID NO: 74)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFDYWGQGTLVT
VSS

>DOM1h-574-97 (SEQ ID NO: 75)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFEYWGQGTLVT
VSS

>DOM1h-574-98 (SEQ ID NO: 76)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFDYWGQGTLVT
VSS

>DOM1h-574-99 (SEQ ID NO: 77)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFEYWGQGTLVT
VSS

>DOM1h-574-100 (SEQ ID NO: 78)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISAWGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-101 (SEQ ID NO: 79)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDGGQRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-102 (SEQ ID NO: 80)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDSGYRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-103 (SEQ ID NO: 81)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDGGTRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-104 (SEQ ID NO: 82)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDKGTRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-105 (SEQ ID NO: 83)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISETGRRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-106 (SEQ ID NO: 84)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQINNTGSTT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-107 (SEQ ID NO: 85)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-108 (SEQ ID NO: 86)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-109 (SEQ ID NO: 87)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-110 (SEQ ID NO: 88)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-111 (SEQ ID NO: 89)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

>DOM1h-574-112 (SEQ ID NO: 90)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-113 (SEQ ID NO: 91)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRR
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-114 (SEQ ID NO: 92)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQILNTADRT
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-115 (SEQ ID NO: 93)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-116 (SEQ ID NO: 94)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRR
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-117 (SEQ ID NO: 95)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRR
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-118 (SEQ ID NO: 96)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAVYTGRWVSFEYWGQGTLVT
VSS

>DOM1h-574-119 (SEQ ID NO: 97)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCALYTGRWVSFEYWGQGTLVT
VSS

>DOM1h-574-120 (SEQ ID NO: 98)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAVYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-121 (SEQ ID NO: 99)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCALYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-122 (SEQ ID NO: 100)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTADRR
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-123 (SEQ ID NO: 101)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-124 (SEQ ID NO: 102)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR
YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-125 (SEQ ID NO: 103)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTADRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-126 (SEQ ID NO: 104)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-127 (SEQ ID NO: 105)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRR
YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-128 (SEQ ID NO: 106)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTADRR
YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-129 (SEQ ID NO: 107)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIVNTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-130 (SEQ ID NO: 108)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-131 (SEQ ID NO: 109)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-132 (SEQ ID NO: 110)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

>DOM1h-574-133 (SEQ ID NO: 111)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-134 (SEQ ID NO: 112)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYSHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-135 (SEQ ID NO: 113)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-137 (SEQ ID NO: 114)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYTDAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-138 (SEQ ID NO: 115)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-139 (SEQ ID NO: 116)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-140 (SEQ ID NO: 117)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-141 (SEQ ID NO: 118)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-142 (SEQ ID NO: 119)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-143 (SEQ ID NO: 120)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-144 (SEQ ID NO: 121)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTADRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-145 (SEQ ID NO: 122)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTGDRR
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-146 (SEQ ID NO: 123)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTGDRR
YYDDAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-147 (SEQ ID NO: 124)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWGPFVYWGQGTLVT
VSS

>DOM1h-574-148 (SEQ ID NO: 125)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFAYWGQGTLVT
VSS

>DOM1h-574-149 (SEQ ID NO: 126)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWGPFQYWGQGTLVT
VSS

>DOM1h-574-150 (SEQ ID NO: 127)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFQYWGQGTLVT
VSS

>DOM1h-574-151 (SEQ ID NO: 128)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-152 (SEQ ID NO: 129)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFQYWGQGTLVT
VSS

>DOM1h-574-153 (SEQ ID NO: 130)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFQYWGQGTLVT
VSS

>DOM1h-574-154 (SEQ ID NO: 131)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-155 (SEQ ID NO: 132)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-156 (SEQ ID NO: 133)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-157 (SEQ ID NO: 134)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

>DOM1h-574-158 (SEQ ID NO: 135)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

>DOM1h-574-159 (SEQ ID NO: 136)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-160 (SEQ ID NO: 137)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-161 (SEQ ID NO: 138)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYSHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-162 (SEQ ID NO: 139)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT
YYSHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-163 (SEQ ID NO: 140)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT
YYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-164 (SEQ ID NO: 141)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-165 (SEQ ID NO: 142)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-166 (SEQ ID NO: 143)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-167 (SEQ ID NO: 144)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-169 (SEQ ID NO: 145)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-170 (SEQ ID NO: 146)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-171 (SEQ ID NO: 147)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRT
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-172 (SEQ ID NO: 148)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRT
YYDHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-173 (SEQ ID NO: 149)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRR
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-174 (SEQ ID NO: 150)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRR
YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-175 (SEQ ID NO: 151)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRR
YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-176 (SEQ ID NO: 152)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRR
YYDHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-177 (SEQ ID NO: 153)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRR
YYDHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-178 (SEQ ID NO: 154)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRR
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-179 (SEQ ID NO: 155)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRR
YYDDAVKGRFTITRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-180 (SEQ ID NO: 156)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-4 (SEQ ID NO: 157)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFEYWGQGTLVT
VSS

>DOM1h-574-168 (SEQ ID NO: 158)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

Table 4: Nucleotide sequences of anti-TNFR1 dAbs

>DOM1h-509 (SEQ ID NO: 157)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTAGTCAGTATAGGATGCATTGGGTCCGCCA
GGCTCCAGGGAAGAGTCTAGAGTGGGTCTCAAGTATTGATACTAGGGGTTCGTCTACA
TACTACGCAGACCCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAAGCTGTGACGATGTTTTCTCCTTTTTTTGACTACTGGGGTCAGGGAACCCTGGTC
ACCGTCTCGAGC

>DOM1h-510 (SEQ ID NO: 158)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTACGCGGACTGGTCGTGTTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAATGGCGGAATCGGCATGGTGAGTATCTTGCTGATTTTGACTACTGGGGTCAGGGA
ACCCTGGTCACCGTCTCGAGC

>DOM1h-543 (SEQ ID NO: 159)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCGATTGATTCTAATGGTTCTAGTACA

TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAAGATCGTACGGAGCGTTCGCCGGTTTTTGACTACTGGGGTCAGGGAACCCTGGTC
ACCGTCTCGAGC

>DOM1h-549 (SEQ ID NO: 160)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTCCCTGCGTC
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTAGTGAGAGTGGTACGACGACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAACGTCGTTTTTCTGCTTCTACGTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574 (SEQ ID NO: 161)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAATATACGGGTCATTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-1 (SEQ ID NO: 162)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAATATACGGGTCGTTGGGAGCCTTATGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-2 (SEQ ID NO: 163)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-4 (SEQ ID NO: 164)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA

GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAATATACGGGTCGTTGGGAGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-180 (SEQ ID NO: 165)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-7 (SEQ ID NO: 166)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-8 (SEQ ID NO: 167)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGATGGGTCCGCCA
GGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACA
GTCTCGAGC

>DOM1h-574-9 (SEQ ID NO: 168)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATATCCCGCGACAATTCCAAGAACA
CGCTGTATATGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-10 (SEQ ID NO: 169)

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TCTCCTGTGCAGCCTCCGGATTCACCTTTGGTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGATCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-11 (SEQ ID NO: 170)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAATATACGGGTCGTTGGGAGCCTTTTGACCACTGGGGTCAGGGGACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-12 (SEQ ID NO: 171)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-13 (SEQ ID NO: 172)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-14 (SEQ ID NO: 173)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-15 (SEQ ID NO: 174)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-16 (SEQ ID NO: 175)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGATGGGTCCGCCA
GGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACA
GTCTCGAGC

>DOM1h-574-17 (SEQ ID NO: 176)
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GGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACA
GTCTCGAGC

>DOM1h-574-18 (SEQ ID NO: 177)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGGTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGATCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-19 (SEQ ID NO: 178)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGGTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGATCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-25 (SEQ ID NO: 179)

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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-26 (SEQ ID NO: 180)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-27 (SEQ ID NO: 181)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCGGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGAAGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-28 (SEQ ID NO: 182)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-29 (SEQ ID NO: 183)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-30 (SEQ ID NO: 184)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGATCGTAGA
TACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGCATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-31 (SEQ ID NO: 185)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTAACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-32 (SEQ ID NO: 186)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-33 (SEQ ID NO: 187)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACT
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGTGCCTTTTGACAACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-35 (SEQ ID NO: 188)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTCAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-36 (SEQ ID NO: 189)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGGTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCGGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-37 (SEQ ID NO: 190)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTTTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAAGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-38 (SEQ ID NO: 191)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGTGATCGTAGA
TACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-39 (SEQ ID NO: 192)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTAGA
TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-40 (SEQ ID NO: 193)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-53 (SEQ ID NO: 194)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGAGCGTAGA
TACTACGCAGACTCAGTGAAGGGCCGGTTCACCATCTCCCGCGACAATCCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-54 (SEQ ID NO: 195)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCGGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCACGAGC

>DOM1h-574-65 (SEQ ID NO: 196)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGATCGTAGA
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GTCTCGAGC

>DOM1h-574-66 (SEQ ID NO: 197)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGATCGTAGA
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-67 (SEQ ID NO: 198)
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GTCTCGAGC

>DOM1h-574-68 (SEQ ID NO: 199)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGATCGTAGA
TACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-69 (SEQ ID NO: 200)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGATCGTAGA
TACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-70 (SEQ ID NO: 201)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GGTATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-71 (SEQ ID NO: 202)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-72 (SEQ ID NO: 203)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-73 (SEQ ID NO: 204)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-74 (SEQ ID NO: 205)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-75 (SEQ ID NO: 206)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGTGATCGTAGA
TACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-76 (SEQ ID NO: 207)
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GGCCCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGTGATCGTAGA
TACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGAAGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-77 (SEQ ID NO: 208)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGTGATCGTAGA
TACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-78 (SEQ ID NO: 209)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGTGATCGTAGA
TACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-79 (SEQ ID NO: 210)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGTGATCGTAGA
TACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-84 (SEQ ID NO: 211)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTAGA
TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-85 (SEQ ID NO: 212)
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TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-86 (SEQ ID NO: 213)
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GGCCCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTAGA
TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAAGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-87 (SEQ ID NO: 214)
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TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-88 (SEQ ID NO: 215)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTAGA
TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-90 (SEQ ID NO: 216)
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TACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-91 (SEQ ID NO: 217)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-92 (SEQ ID NO: 218)
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TACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-93 (SEQ ID NO: 219)
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TACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-94 (SEQ ID NO: 220)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGATCGTAGA
TACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGCATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-95 (SEQ ID NO: 221)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGATCGTAGA
TACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGCATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-96 (SEQ ID NO: 222)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-97 (SEQ ID NO: 223)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GATATATACGGGTCGGTGGCCCGACTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-98 (SEQ ID NO: 224)
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>DOM1h-574-99 (SEQ ID NO: 225)
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TACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-100 (SEQ ID NO: 226)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-101 (SEQ ID NO: 227)
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GGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGGACGGCGGTCAGAGGACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-102 (SEQ ID NO: 228)
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GGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGGACTCCGGTTACCGCACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-103 (SEQ ID NO: 229)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-104 (SEQ ID NO: 230)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-105 (SEQ ID NO: 231)
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GGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGGAGACCGGTCGCAGGACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-106 (SEQ ID NO: 232)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-107 (SEQ ID NO: 233)
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>DOM1h-574-108 (SEQ ID NO: 234)
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-109 (SEQ ID NO: 235)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-110 (SEQ ID NO: 236)
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GTCTCGAGC

>DOM1h-574-111 (SEQ ID NO: 237)
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TACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-112 (SEQ ID NO: 238)
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>DOM1h-574-113 (SEQ ID NO: 239)
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>DOM1h-574-114 (SEQ ID NO: 240)
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>DOM1h-574-115 (SEQ ID NO: 241)
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GTCTCGAGC

>DOM1h-574-116 (SEQ ID NO: 242)
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>DOM1h-574-117 (SEQ ID NO: 243)
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TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-118 (SEQ ID NO: 244)
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>DOM1h-574-119 (SEQ ID NO: 245)
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GTCTCGAGC

>DOM1h-574-120 (SEQ ID NO: 246)
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>DOM1h-574-121 (SEQ ID NO: 247)
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>DOM1h-574-122 (SEQ ID NO: 248)
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>DOM1h-574-123 (SEQ ID NO: 249)
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TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-124 (SEQ ID NO: 250)
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>DOM1h-574-125 (SEQ ID NO: 251)
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>DOM1h-574-127 (SEQ ID NO: 253)
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>DOM1h-574-128 (SEQ ID NO: 254)
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>DOM1h-574-129 (SEQ ID NO: 255)
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>DOM1h-574-130 (SEQ ID NO: 256)
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>DOM1h-574-131 (SEQ ID NO: 257)
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>DOM1h-574-132 (SEQ ID NO: 258)
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>DOM1h-574-133 (SEQ ID NO: 259)
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>DOM1h-574-134 (SEQ ID NO: 260)
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>DOM1h-574-135 (SEQ ID NO: 261)
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GTCTCGAGC

>DOM1h-574-137 (SEQ ID NO: 262)
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TACTACACAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-138 (SEQ ID NO: 263)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-139 (SEQ ID NO: 264)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-140 (SEQ ID NO: 265)
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>DOM1h-574-141 (SEQ ID NO: 266)
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>DOM1h-574-142 (SEQ ID NO: 267)
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>DOM1h-574-143 (SEQ ID NO: 268)
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>DOM1h-574-144 (SEQ ID NO: 269)
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>DOM1h-574-145 (SEQ ID NO: 270)
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>DOM1h-574-146 (SEQ ID NO: 271)
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>DOM1h-574-147 (SEQ ID NO: 272)
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>DOM1h-574-148 (SEQ ID NO: 273)
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>DOM1h-574-149 (SEQ ID NO: 274)
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GTCTCGAGC

>DOM1h-574-150 (SEQ ID NO: 275)
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>DOM1h-574-151 (SEQ ID NO: 276)
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GTCTCGAGC

>DOM1h-574-152 (SEQ ID NO: 277)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGCGCCTTTTCAGTACTGGGGTCAGGGAACTCTGGTCACC
GTCTCGAGC

>DOM1h-574-153 (SEQ ID NO: 278)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGTGCCTTTTCAGTACTGGGGTCAGGGCACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-154 (SEQ ID NO: 279)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACCGGTGATCGTAGA
TACTACGATCACTCTGTGAAGGGCCGGTTCACTATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-155 (SEQ ID NO: 280)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-156 (SEQ ID NO: 281)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-157 (SEQ ID NO: 282)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-158 (SEQ ID NO: 283)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-159 (SEQ ID NO: 284)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-160 (SEQ ID NO: 285)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-161 (SEQ ID NO: 286)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACTCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-162 (SEQ ID NO: 287)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACTCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-163 (SEQ ID NO: 288)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACACACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-164 (SEQ ID NO: 289)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACACACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-165 (SEQ ID NO: 290)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-166 (SEQ ID NO: 291)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-167 (SEQ ID NO: 292)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACCGGTGATCGTAGA
TACTACGATCACTCTGTGAAGGGCCGGTTCACTATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-168 (SEQ ID NO: 293)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACCGGTGATCGTAGA
TACTACGATCACTCTGTGAAGGGCCGGTTCACTATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-169 (SEQ ID NO: 294)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGCGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-170 (SEQ ID NO: 295)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-171 (SEQ ID NO: 296)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-172 (SEQ ID NO: 297)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTACA
TACTACGATCACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-173 (SEQ ID NO: 298)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTAGA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-174 (SEQ ID NO: 299)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTAGA
TACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-175 (SEQ ID NO: 300)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTAGA
TACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-176 (SEQ ID NO: 301)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTAGA
TACTACGATCACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-177 (SEQ ID NO: 302)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTAGA
TACTACGATCACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGGACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-178 (SEQ ID NO: 303)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTAGA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-179 (SEQ ID NO: 304)
GAGGTGCAGCTGCTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTAGA
TACTACGATGACGCGGTGAAGGGCCGGTTCACCATCACCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

Table 5: Anti-serum albumin dAb (DOM7h) fusions

(used in Rat studies):-

DOM7h-14/Exendin-4 fusion **DMS number 7138**

Amino acid sequence (SEQ ID NO: 305)

HGEGTFTSDLSEQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWES
SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGAALPRTFGQGTKVEIK
R

Nucleotide sequence (SEQ ID NO: 306)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGT
CTCAGTTATCTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCTCAGGGTGCGGCGTTGCCTAGGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

DOM7h-14-10/Exendin-4 fusion DMS number 7139

Amino acid sequence (SEQ ID NO: 307)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRS
SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIK
R

Nucleotide sequence (SEQ ID NO: 308)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGT
CTCAGTTATCTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

DOM7h-14-18/Exendin-4 fusion DMS number 7140

Amino acid sequence (SEQ ID NO: 309)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRS
SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLMKPMTFGQGTKVEIK
R

Nucleotide sequence (SEQ ID NO: 310)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGT
CTCAGTTATCTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCTCAGGGTCTTATGAAGCCTATGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

DOM7h-14-19/Exendin-4 fusion DMS number 7141

Amino acid sequence (SEQ ID NO: 311)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTISCRASQWIGSQLSWYQQKPGEAPKLLIMWPS
SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGAALPRTFGQGTKVEIK
R

Nucleotide sequence (SEQ ID NO: 312)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCTCTTGCCGGGCAAGTCAGTGGATTGGGTC
TCAGTTATCTTGGTACCAGCAGAAACCAGGGGAAGCCCCTAAGCTCCTGAT
CATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGT
GGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATT
TTGCTACGTACTACTGTGCTCAGGGTGCGGCGTTGCCTAGGACGTTCGGCCA
AGGGACCAAGGTGGAAATCAAACGG

DOM7h-11/Exendin-4 fusion DMS number 7142

Amino acid sequence (SEQ ID NO: 313)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPKLLIWFGSR
LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Nucleotide sequence (SEQ ID NO: 314)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGA
CGACGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCTGGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

DOM7h-11-12/Exendin-4 fusion DMS number 7147

Amino acid sequence (SEQ ID NO: 315)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILFGSR
LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Nucleotide sequence (SEQ ID NO: 316)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGA
CGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCTTGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

DOM7h-11-15/Exendin-4 fusion DMS number 7143

Amino acid sequence (SEQ ID NO: 317)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSR
LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Nucleotide sequence (SEQ ID NO: 318)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGA
CGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCCTTGCTTTTTCCCGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGT
GGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATT

TTGCTACGTACTACTGCGGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCA
AGGGACCAAGGTGGAAATCAAACGG

DOM7h14-10/ G4SC-NCE fusion

Amino acid sequence (SEQ ID NO: 319) encoding DOM7h14-10/G4SC

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSL
QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKRG
GGGSC

The C-terminal cysteine can be linked to a new chemical entity (pharmaceutical chemical compound, NCE), eg using maleimide linkage.

Nucleotide sequence (SEQ ID NO: 320) encoding DOM7h14-10/G4SC

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTC
CTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGAC
AGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTAC
TACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCCAAGGGACCAAG
GTGGAAATCAAACGGGGTGGCGGAGGGGGTTCCTGT

DOM7h14-10/TVAAPSC fusion

Amino acid sequence (SEQ ID NO: 321)

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSL
QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKRT
VAAPSC

The C-terminal cysteine can be linked to a new chemical entity (pharmaceutical chemical compound, NCE), eg using maleimide linkage.

Nucleotide sequence (SEQ ID NO: 322)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTC
CTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGAC
AGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTAC
TACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCCAAGGGACCAAG

GTGGAAATCAAACGGACCGTCGCTGCTCCATCTTGT

(used in mouse studies):-

DOM7h-11/DOM1m-21-23 fusion DMS number 5515

Amino acid sequence (SEQ ID NO: 323)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLS
WYQQKPGKAPKLLIWFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
AQAGTHPTTFGQGTKVEIKR

Amino acid plus nucleotide plus myc tag sequence (SEQ ID NO: 324)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLS
WYQQKPGKAPKLLIWFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
AQAGTHPTTFGQGTKVEIKRAAAEQKLISEEDLN

Nucleotide sequence (SEQ ID NO: 325)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC
CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA
GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC
CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGACGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCTGGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTT
CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA
ACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACG
ACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Nucleotide plus myc tag sequence (SEQ ID NO: 326)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC
CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA
GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC
CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGACGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCTGGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTT
CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA
ACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACG
ACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAACA
AAAACTCATCTCAGAAGAGGATCTGAATTAA

DOM7h-11-12/DOM1m-21-23 fusion **DMS number 5516**

Amino acid sequence (SEQ ID NO: 327)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS
WYQQKPGKAPKLLILFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA
QAGTHPTTFGQGTKVEIKR

Amino acid plus nucleotide plus myc tag sequence (SEQ ID NO: 328)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS
WYQQKPGKAPKLLILFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA
QAGTHPTTFGQGTKVEIKRAAAEQKLISEEDLN

Nucleotide sequence (SEQ ID NO: 329)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC
CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA

GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC
CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCTTGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTT
CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA
ACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACG
ACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Nucleotide plus myc tag sequence (SEQ ID NO: 330)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC
CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA
GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC
CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCTTGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTT
CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA
ACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACG
ACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAACA
AAAACTCATCTCAGAAGAGGATCTGAATTAA

DOM7h-11-15/DOM1m-21-23 fusion **DMS number 5517**

Amino acid sequence (SEQ ID NO: 331)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS
WYQQKPGKAPKLLILAFSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA
QAGTHPTTFGQGTKVEIKR

Amino acid plus nucleotide plus myc tag sequence(SEQ ID NO: 332)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS

WYQQKPGKAPKLLILAFSKLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA
QAGTHPTTFGQGTKVEIKRAAAEQKLISEEDLN

Nucleotide sequence (SEQ ID NO: 333)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC
CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA
GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC
CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCCTTGCTTTTTCCCGTTTGCAAAGTGGGGTCCCATCACGTTTC
AGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAA
CCTGAAGATTTTGCTACGTACTACTGCGGCGCAGGCTGGGACGCATCCTACGA
CGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Nucleotide plus myc tag sequence (SEQ ID NO: 334)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC
CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA
GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC
CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCCTTGCTTTTTCCCGTTTGCAAAGTGGGGTCCCATCACGTTTC
AGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAA
CCTGAAGATTTTGCTACGTACTACTGCGGCGCAGGCTGGGACGCATCCTACGA
CGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGGCGGCCGCAGAACAA
AAACTCATCTCAGAAGAGGATCTGAATTAA

where a myc-tagged molecule is indicated in this table, this was the version used in PK studies in the examples. Where no myc-tagged sequences are given, the PK studies in the examples were not done with myc-tagged material, ie, the studies were done with

the non-tagged constructs shown.

EXEMPLIFICATION

All numbering in the experimental section is according to Kabat (Kabat, E.A. National Institutes of Health (US) & Columbia University. Sequences of proteins of immunological interst, edn 5 (US Dept. Of Health and Human Services Public Health Service, National Institues of Health, Bethesda, MD, 1991)).

Derivation of DOM7h-11 and DOM7h-14 variants is described. DOM7h-11 variants are not according to the invention.

EXAMPLE 1: Vk Affinity Maturation

Selections:

HSA (Human Serum Albumin) and RSA (Rat Serum Albumin) antigens were obtained from Sigma (essentially fatty acid free, ~99% (agarose gel electrophoresis), lyophilized powder Cat. No. A3782 and A6414 respectively)

Biotinylated products of above two antigens were made by using EZ Link Sulfo-NHS-SS-Biotin (Pierce, Cat. No.21331). Free biotin reagent was removed by passing the samples twice through PD10 desalting column followed by overnight dialysis against 1000x excess volume of PBS at 4°C. Resulting product was tested by mass spec and 1-2 biotins per molecule were observed.

Affinity maturation libraries:

Both error-prone and CDR libraries were created using DOM7h-11 and DOM7h-14 parental dAbs (see WO2008/096158 for the sequences of DOM7h-11 and DOM7h-14). The CDR libraries were generated in the pDOM4 vector and the error prone libraries were generated in the pDOM33 vector (to allow for selection with or without protease

treatment). Vector pDOM4, is a derivative of the Fd phage vector in which the *gene III* signal peptide sequence is replaced with the yeast glycolipid anchored surface protein (GAS) signal peptide. It also contains a *c-myc* tag between the leader sequence and *gene III*, which puts the *gene III* back in frame. This leader sequence functions well both in phage display vectors but also in other prokaryotic expression vectors and can be universally used. pDOM33 is a modified version of the pDOM4 vector where the the c-myc tag has been removed which renders the dAb-phage fusion resistant to the protease trypsin. This allows the use of trypsin within the phage selection to select for dAbs that are more protease stable (see WO2008149143).

For error-prone maturation libraries, plasmid DNA encoding the dAb to be matured was amplified by PCR, using the GENEMORPH® II RANDOM MUTAGENESIS KIT (random, unique mutagenesis kit, Stratagene). The product was digested with *Sal* I and *Not* I and used in a ligation reaction with cut phage vector pDOM33.

For the CDR libraries, PCR reactions were performed using degenerate oligonucleotides containing NNK or NNS codons to diversify the required positions in the dAb to be affinity matured. Assembly PCR was then used to generate a full length diversified insert. The insert was digested with *Sal* I and *Not* I and used in a ligation reaction with pDOM4 for mutagenesis of multiple residues and pDOM5 for mutagenesis of single residues. The pDOM5 vector is a pUC119-based expression vector where protein expression is driven by the LacZ promoter. A GAS1 leader sequence (see WO 2005/093074) ensures secretion of isolated, soluble dAbs into the periplasm and culture supernatant of *E. coli*. dAbs are cloned SalI/NotI in this vector, which appends a myc tag at the C-terminus of the dAb. This protocol using *SalI* and *Not I* results in inclusion of an ST amino acid sequence at the N-terminus.

The ligation produced by either method was then used to transform *E. coli* strain TB1 by electroporation and the transformed cells plated on 2xTY agar containing 15 μg/ml tetracycline, yielding library sizes of $>5\times10^7$ clones.

The error-prone libraries had the following average mutation rate and size: DOM7h-11 (2.5 mutations per dAb), size:6.1 x 10^8 , DOM7h-14 (2.9 mutations per dAb) , size:5.4 x 10^8.

Each CDR library has four amino acid diversity. Two libraries were generated for each of CDRs 1 and 3, and one library for CDR2. The positions diversified within each library are as follows (amino acids based on VK dummy DPK9 sequence):

	Library size	
	DOM7h-11	DOM7h-14
1 – Q27, S28, S30, S31 (CDR1)	8.8 x 10^7	5.8 x 10^7
2 – S30, S31, Y32, N34 (CDR1)	4.6 x 10^8	4.2 x 10^8
3 – Y49, A50, A51, S53 (CDR2)	3.9 x 10^8	2.4 x 10^8
4 – Q89, S91, Y92, S93 (CDR3)	1.8 x 10^8	2.5 x 10^8
5 – Y92, Y93, T94, N96 (CDR3)	4.0 x 10^8	3.3 x 10^8

Example 2: Selection strategies:

Three phage selection strategies were adopted for Vκ AlbudAb™ (anti-serum albumin dAb) affinity maturation:

1) Selections against HSA only:

Three rounds of selection against HSA were carried out. The error prone libraries and each CDR library were selected as an individual pool in all rounds. The first round of selection was performed against HSA passively coated onto an immunotube at 1mg/ml. Round 2 was performed against 100nM HSA and round 3 against 10nM (CDR selections) or 20 or 100nM (Error prone selections) HSA, both

as soluble selections followed by a fourth round of selection with the error prone libraries against 1.5 nM HSA as a soluble selection. The error prone libraries were eluted with 0.1M glycine pH 2.0 before neutralisation with 1M Tris pH 8.0 and the CDR libraries were eluted with 1mg/ml trypsin before infection into log phase TG1 cells. The third round of each selection was subcloned into pDOM5 for screening. Soluble selections used biotinylated HSA.

2) Trypsin selections against HSA:

In order to select dAbs with increased protease resistance compared to the parental clone and with potentially improved biophysical properties, trypsin was used in phage selections (see WO2008149143). Four rounds of selection were preformed against HSA. The first round of selection of error prone libraries was performed against passively coated HSA at 1mg/ml without trypsin; the second round against passively coated HSA at 1mg/ml with 20µg/ml trypsin for 1hour at 37°C; the third round selection was performed by soluble selection using biotinylated HSA against 100 nM HSA with 20 µg/ml or 100 µg/ml trypsin for 1hour at 37°C. The final round of selection was performed by soluble selection using biotinylated HSA against 100nM HSA with 100 µg/ml trypsin overnight at 37°C.

3) Cross-over selections against HSA (round 1) and RSA (rounds 2-4):

The first round selection was carried out against 1mg/ml passively coated HSA or 1 µM HSA (soluble selection), followed by a further three rounds of soluble selections against biotinylated RSA at concentrations of 1 µM for round 1, 100nm for round 2 and 20nM, 10nM or 1nM for round 3.

Screening strategy and affinity determination:

In each case after selection a pool of phage DNA from the appropriate round of selection is prepared using a QIAfilter midiprep kit (Qiagen), the DNA is digested using the restriction enzymes SalI and NotI and the enriched V genes are ligated into the corresponding sites in pDOM5 the soluble expression vector which expresses the dAb with a myc tag (see PCT/EP2008/067789). The ligated DNA is used to electro-transform *E. coli* HB 2151 cells which are then grown overnight on agar plates containing the antibiotic carbenicillin. The resulting colonies are individually assessed for antigen binding. In each case at least 96 clones were tested for binding to HSA, CSA (*Cynomlgus* monkey Serum Albumin), MSA (mouse serum albumin) and RSA by BIAcore™ (surface plasmon resonance). MSA antigen was obtained from Sigma (essentially fatty acid free, ~99% (agarose gel electrophoresis), lyophilized powder Cat. No. A3559) and CSA was purified from *Cynomolgus* serum albumin using prometic blue resin (Amersham). Soluble dAb fragments were produced in bacterial culture in ONEX culture media (Novagen) overnight at 37°C in 96 well plates. The culture supernatant containing soluble dAb was centrifuged and analysed by BIAcore for binding to high density HSA, CSA, MSA and RSA CM5 chips. Clones were found to bind to all these species of serum albumin by off-rate screening. The clones were sequenced revealing unique dAb sequences.

The minimum identity to parent (at the amino acid level) of the clones selected was 97.2% (DOM7h-11-3: 97.2%, DOM7h-11-12: 98.2%, DOM7h11-15: 96.3%, DOM7h-11-18: 98.2%, DOM7h-11-19: 97.2%)

The minimum identity to parent (at the amino acid level) of the clones selected was 96.3% (DOM7h-14-10: 96.3%, DOM7h-14-18: 96.3%, DOM7h-14-19: 98.2%, DOM7h-14-28: 99.1%, DOM7h-14-36: 97.2%)

Unique dAbs were expressed as bacterial supernatants in 2.5L shake flasks in Onex media at 30°C for 48hrs at 250rpm. dAbs were purified from the culture media by absorption to protein L agarose followed by elution with 10mM glycine pH2.0. Binding

to HSA, CSA, MSA and RSA by BIAcore was confirmed using purified protein at 3 concentrations 1μM, 500nM and 50nM. To determine the binding affinity (K_D) of the AlbudAbs to each serum albumin; purified dAbs were analysed by BIAcore over albumin concentration range from 5000nM to 39nM (5000nM, 2500nM, 1250nM, 625nM, 312nM, 156nM, 78nM, 39nM).

Table 6

AlbudAb	**Affinity (K_D) to SA (nM)**	**Kd**	**Ka**
	Rat		
DOM7h-14	60	2.095E-01	4.00E+06
DOM7h-14-10	4	9.640E-03	4.57E+06
DOM7h-14-18	410	2.275E-01	5.60E+05
DOM 7h-14-19	890	2.870E-01	3.20E+05
DOM 7h-14-28	45 (140)	7.0E-02 (1.141e-1)	2.10E+06 (8.3e5)
DOM 7h-14-36	30 (6120)	2.9E-02 (5.54e-2)	1.55E+06 (9e3)
DOM 7h-11	2100	1.00E-01	4.80E+04
DOM 7h-11-3	10000 (88000)	(7.18e-1)	(8.11e3)
DOM 7h-11-12	200	5.22E-01	2.76E+06
DOM 7h-11-15	20	2.10E-02	1.10E+06
DOM 7h-11-18	80 (29000)	6.0E-02 (3.7e-1)	1.64E+06 (1.3e4)
DOM 7h-11-19	28 (17000)	9.1e-02	9.80E+05

		(1.4e-1)	(8.1e3)
	Cyno		
DOM 7h-14	66	9.65E-02	1.50E+06
DOM 7h-14-10	9	1.15E-02	1.60E+06
DOM 7h-14-18	180	1.05E-01	6.30E+5
DOM 7h-14-19	225	1.56E-01	7.00E+05
DOM 7h-14-28	66 (136)	1.3E-01 (1.34e-1)	2.50E+06 (9.8e5)
DOM 7h-14-36	35 (7830)	1.9E-02 (1.1e-1)	9.80E+06 (1.43e4)
DOM 7h-11	1000	6.82E-01	8.00E+05
DOM 7h-11-3	670 (200)	9.6E-02 (1.5e-1)	2.90E+05 (7.26e5)
DOM 7h-11-12	≥6000		
DOM 7h-11-15	3	5.57E-03	5.80E+06
DOM 7h-11-18	10000 (65000)	1.36 (4.8e-1)	2.25E+05 (7.3e3)
DOM 7h-11-19	≥10000 (375000)	(6.2e-1)	(1.7e3)
	Mouse		
DOM 7h-14	12	4.82E-02	4.10E+06
DOM 7h-14-10	30	3.41E-02	1.29E+06
DOM 7h-14-18	65	9.24E-02	2.28E+06
DOM 7h-14-19	60	5.76E-02	1.16E+06
DOM 7h-14-28	26 (31)	3.4E-02 (7.15e-2)	1.60E+06 (2.28e6)

DOM 7h-14-36	35 (33)	2.3E-02 (7.06e-2)	8.70E+05 (2.11e6)
DOM 7h-11	5000	9.00E-01	
DOM 7h-11-3	≥10000 (36000)	(6.12e-1)	(1.67e4)
DOM 7h-11-12	130	1.89E-01	1.53E+06
DOM 7h-11-15	10	9.40E-03	1.10E+06
DOM 7h-11-18	150 (1600)	2.4E-02 (6.23e-2)	4.40E+05 (4e4)
DOM 7h-11-19	100 (18000)	3.7E-02 (8.8e-2)	1.40E+06 (4.9e3)
	Human		
DOM 7h-14	33	4.17E-02	1.43E+06
DOM 7h-14-10	12	1.39E-02	1.50E+06
DOM 7h-14-18	280	3.39E-02	1.89E+05
DOM 7h-14-19	70	5.25E-02	8.26E+05
DOM 7h-14-28	30 (8260)	3.3E-02 (5.6e-2)	1.24E+06 (6.78e3)
DOM 7h-14-36	28 (1260)	2.4E-02 (6.7e-2)	1.23E+06 (5.4e4)
DOM 7h-11	2800	6.41E-01	7.00E+05
DOM 7h-11-3	32 (130)	1.6E-02 (2.35e-2)	6.50E+05 (1.86e5)
DOM 7h-11-12	350	4.13E-01	1.26E+06
DOM 7h-11-15	1	1.84E-03	2.00E+06
DOM 7h-11-18	36 (32000)	5.1E-02	3.40E+06

		(2.7e-1)	(8.39e3)
DOM 7h-11-19	65 (38000)	1.1E-01 (2.09e-1)	1.80E+06 (5.4e3)

*: values in brackets were derived from a second, independent SPR experiment.

All DOM7h-14 derived variants are cross-reactive to mouse, rat, human and cyno serum albumin. DOM7h-14-10 has improved affinity to rat, cyno and human serum albumin compared to parent. DOM7h-14-28 has an improved affinity to RSA. DOM7h-14-36 has an improved affinity to RSA, CSA and MSA.

DOM7h-11-3 has improved affinity to CSA and HSA. DOM7h-11-12 has improved affinity to RSA, MSA and HSA. DOM7h-11-15 has improved affinity to RSA, MSA, CSA and HSA. DOM7h-11-18 and DOM7h-11-19 have improved affinity to RSA, MSA and HSA.

Example 3: Origins of key DOM7h-11 lineage clones:

DOM7h-11-3: From affinity maturation performed against HSA using the CDR2 library (Y49, A50, A51, S53), round 3 output 10nM HSA

DOM7h-11-12: From affinity maturation performed against HSA using the error prone library, round 3 outputs (100nM, HSA) with 100ug/ml trypsin.

DOM7h-11-15: From cross-over selections performed against HSA as round 1 followed by additional 3 rounds of selections against RSA using the CDR2 library (Y49, A50, A51, S53) at round 3 selection with 1nM of RSA.

DOM7h-11-18 From cross-over selections performed against HSA as round 1 followed by additional 3 rounds of selections against RSA using the error prone library, round 3 output at 20nM of RSA

DOM7h-11-19 From cross-over selections performed against HSA as round 1 followed by additional 3 rounds of selections against RSA using the error prone library, round 3 output at 5nM of RSA

Table 7: CDR sequences (according to Kabat; ref. as above)

AlbudAb	CDR		
	CDR1	CDR2	CDR3
DPK9 Vk dummy	SQSISSYLN (SEQ ID NO: 335)	YAASSLQS (SEQ ID NO: 336)	QQSYSTPNT (SEQ ID NO: 337)
DOM7h-11	SRFIGTTLS (SEQ ID NO: 338)	WFGSRLQS (SEQ ID NO: 339)	AQAGTHPTT (SEQ ID NO: 340)
DOM7h-11-12	SRFIGTMLS (SEQ ID NO: 341)	LFGSRLQS (SEQ ID NO: 342)	AQAGTHPTT (SEQ ID NO: 343)
DOM 7h-11-15	SRFIGTMLS (SEQ ID NO: 344)	LAFSRLQS (SEQ ID NO: 345)	AQAGTHPTT (SEQ ID NO: 346)
DOM 7h-11-18	SRFIGTMLS (SEQ ID NO: 347)	WFGSRLQS (SEQ ID NO: 348)	AQAGTHPTT (SEQ ID NO: 349)
DOM 7h-11-19	SRFIGTMLS (SEQ ID NO: 350)	LFGSRLQS (SEQ ID NO: 351)	AQTGTHPTT (SEQ ID NO: 352)
DOM 7h-11-3	SRFIGTTLS (SEQ ID NO: 353)	LWFSRLQS (SEQ ID NO: 354)	AQAGTHPTT (SEQ ID NO: 355)

Example 4: Origins of key DOM7h-14 lineage clones:

DOM7h-14-19: From affinity maturation performed against HSA using the error prone library, round 3 outputs (100nM, HSA) with 100ug/ml trypsin.

DOM7h-14-10, DOM7h-14-18, DOM7h-14-28, DOM7h-14-36: From affinity maturation performed against HSA using CDR3 library (Y92, Y93, T94, N96), round 3 output.

Table 8: CDR sequences (according to Kabat; ref. as above)

AlbudAb	CDR		
	CDR1	CDR2	CDR3
DPK9 Vk dummy	SQSISSYLN (SEQ ID NO: 335)	YAASSLQS (SEQ ID NO: 336)	QQSYSTPNT (SEQ ID NO: 337)
DOM 7h-14	SQWIGSQLS (SEQ ID NO: 356)	MWRSSLQS (SEQ ID NO: 357)	AQGAALPRT (SEQ ID NO: 358)
DOM 7h-14-10	SQWIGSQLS (SEQ ID NO: 359)	MWRSSLQS (SEQ ID NO: 360)	AQGLRHPKT (SEQ ID NO: 361)
DOM 7h-14-18	SQWIGSQLS (SEQ ID NO: 362)	MWRSSLQS (SEQ ID NO: 363)	AQGLMKPMT (SEQ ID NO: 364)
DOM 7h-14-19	SQWIGSQLS (SEQ ID NO: 365)	MWRSSLQS (SEQ ID NO: 366)	AQGAALPRT (SEQ ID NO: 367)
DOM 7h-14-28	SQWIGSQLS (SEQ ID NO: 368)	MWRSSLQS (SEQ ID NO: 369)	AQGAALPKT (SEQ ID NO: 370)
DOM 7h-14-36	SQWIGSQLS (SEQ ID NO: 371)	MWRSSLQS (SEQ ID NO: 372)	AQGFKKPRT (SEQ ID NO: 373)

Example 5: Expression and Biophysical Characterisation:

The routine bacterial expression level in 2.5L shake flasks was determined following culture in Onex media at 30°C for 48hrs at 250rpm. The biophysical characteristics were determined by SEC MALLS and DSC.

SEC MALLS (size exclusion chromatography with multi-angle-LASER-light-scattering) is a non-invasive technique for the characterizing of macromolecules in

solution. Briefly, proteins (at concentration of 1mg/mL in buffer Dulbecco's PBS at 0.5 ml/min are separated according to their hydrodynamic properties by size exclusion chromatography (column: TSK3000 from TOSOH Biosciences; S200 from Pharmacia). Following separation, the propensity of the protein to scatter light is measured using a multi-angle-LASER-light-scattering (MALLS) detector. The intensity of the scattered light while protein passes through the detector is measured as a function of angle. This measurement taken together with the protein concentration determined using the refractive index (RI) detector allows calculation of the molar mass using appropriate equations (integral part of the analysis software Astra v.5.3.4.12).

DSC (Differential Scanning Calorimetry): briefly, the protein is heated at a constant rate of 180 °C/hrs (at 1mg/mL in PBS) and a detectable heat change associated with thermal denaturation measured. The transition midpoint ($_{app}T_m$) is determined, which is described as the temperature where 50% of the protein is in its native conformation and the other 50% is denatured. Here, DSC determined the apparent transition midpoint (appTm) as most of the proteins examined do not fully refold. The higher the Tm, the more stable the molecule. Unfolding curves were analysed by non-2-state equations. The software package used was Origin® v7.0383.

Table 9

AlbudAb	Biophysical parameters	
	SEC MALLS	DSC Tm(°C)
DOM7h-14	M	60
DOM 7h-14-10	M	59
DOM 7h-14-18	M	58
DOM 7h-14-19	M	59
DOM 7h-14-28	M	58.3/60.2
DOM 7h-14-36	M	59.2

DOM 7h-11	M	66.9-72.2
DOM 7h-11-3	M (95%)*	66.6/70.5
DOM 7h-11-12	M (<2%D)	71.7
DOM 7h-11-15	M (<5%D)	58.5-60.5
DOM 7h-11-18	M (98%)	58.9/65.8
DOM 7h-11-19	M	71.8/76.6

* in one other trial, monomer was primarily seen by SEC MALLS, although lower than 95%

We observed expression levels for all clones in Table 9 in the range from 15 to 119mg/L in *E coli*.

For DOM7h-14 and DOM7h-11 variants, favorable biophysical parameters (monomeric in solution as determined by SEC MALLs and appTm of >55°C as determined by DSC) and expression levels were maintained during affinity maturation. Monomeric state is advantageous because it avoids dimerisation and the risk of products that may cross-link targets such as cell-surface receptors.

Example 6: Determination of serum half life in rat, mouse and *Cynomolgus* monkey

AlbudAbs DOM7h-14-10, DOM7h-14-18, DOM7h-14-19, DOM7h-11, DOM7h11-12 and DOM7h-11-15 were cloned into the pDOM5 vector. For each AlbudAb™, 20-50mg quantities were expressed in E. coli and purified from bacterial culture supernatant using protein L affinity resin and eluted with 100mM glycine pH2. The proteins were concentred to greater than 1mg/ml, buffer exchanged into PBS and endotoxin depleted using using Q spin columns (Vivascience). For Rat pharmacokinetic (PK) analysis, AlbudAbs were dosed as single i.v injections at 2.5mg/kg using 3 rats per

compound. Serum samples were taken at 0.16, 1, 4, 12, 24, 48, 72, 120, 168hrs. Analysis of serum levels was by anti-myc ELISA as per the method described below.

For Mouse PK, DOM7h-11, DOM7h11-12 and DOM7h-11-15 were dosed as single i.v injections at 2.5mg/kg per dose group of 3 subjects and serum samples taken at 10mins; 1h; 8h; 24h; 48h; 72h, 96h. Analysis of serum levels was by anti-myc ELISA as per the method described below.

For *Cynomolgus* monkey PK DOM7h-14-10 and DOM7h-11-15 were dosed as single i.v injections at 2.5mg/kg into 3 female *Cynomolgus* monkeys per dose group and serum samples taken at 0.083, 0.25, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 192, 288, 336, 504hrs. Analysis of serum levels was by anti-myc ELISA as per the method described below.

Anti-myc ELISA method

The AlbudAb concentration in serum was measured by anti- myc ELISA. Briefly, goat anti- myc polyclonal antibody (1:500; Abcam, catalogue number ab9132) was coated overnight onto Nunc 96-well Maxisorp plates and blocked with 5% BSA/PBS + 1% tween. Serum samples were added at a range of dilutions alongside a standard at known concentrations. Bound myc-tagged AlbudAb was then detected using a rabbit polyclonal anti-Vk (1:1000; in-house reagent, bleeds were pooled and protein A purified before use) followed by an anti-rabbit IgG HRP antibody (1:10,000; Sigma, catalogue number A2074). Plates were washed between each stage of the assay with 3 x PBS+0.1% Tween20 followed by 3 x PBS. TMB (SureBlue TMB 1-Component Microwell Peroxidase Substrate, KPL, catalogue number 52-00-00) was added after the last wash and was allowed to develop. This was stopped with 1M HCl and the signal was then measured using absorbance at 450nm.

From the raw ELISA data, the concentration of unknown samples was established by interpolation against the standard curve taking into account dilution factors. The mean

concentration result from each time point was determined from replicate values and entered into WinNonLin analysis package (eg version 5.1 (available from Pharsight Corp., Mountain View, CA94040, USA). The data was fitted using a non-compartmental model, where PK parameters were estimated by the software to give terminal half-lives. Dosing information and time points were selected to reflect the terminal phase of each PK profile.

Table 10: Single AlbudAb™ PK

Species	AlbudAb	Albumin K_D (nM)	PK parameters			
			AUC h x µg/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
Rat	**DOM7h-14***	60				
	DOM7h-14-10	4	2134.6	1.2	42.1	71.2
	DOM7h-14-18	410	617.3	4.1	38.4	228.1
	DOM 7h-14-19	890	632.6	4.1	36.3	213.3
	DOM 7h-11	2100	320.1	7.8	23.3	263.9
	DOM 7h-11-12	200	398.7	6.4	35.5	321.2
	DOM 7h-11-15	20	843.4	3.0	30.3	130.7
mouse	**DOM 7h-11**	5000	304.7	8.2	18.3	216.8
	DOM 7h-11-12	130	646.6	3.9	43.9	244.8
	DOM 7h-11-15	10	499.2	5.0	33.7	243.4
Cyno	**DOM 7h-14***	66			217.5	
	DOM 7h-14-10	9	6174.6	0.4	200.8	117.8

	DOM 7h-11*	3300			135.1	
	DOM 7h-11-15	3	4195	0.6	198.1	170.3

* Historical data

Pharmacokinetic parameters derived from rat, mouse and cynomolgus monkey studies were fitted using a non-compartmental model. Key: AUC: Area under the curve from dosing time extrapolated to infinity; CL: clearance; t1/2: is the time during which the blood concentration is halved; Vz: volume of distribution based on the terminal phase.

DOM7h-11 12 and DOM7h-11-15 have an improved AUC and t1/2 in rat and mouse compared to parent. DOM7h-11-15 also has an improved AUC and t1/2 in cyno compared to parent. This improvement in AUC/t1/2 correlates with an improved in vitro KD to serum albumin.

Example 7: AlbudAb™ IFN fusions

Cloning and expression

As well as single AlbudAbs, the affinity matured Vk Albudabs were linked to Interferon alpha 2b (IFNα2b) to determine whether a useful PK of the AlbudAb was maintained as a fusion protein.

Interferon alpha 2b amino acid sequence:

CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIP VLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTET PLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRS KE (SEQ ID NO:374)

Interferon alpha 2b nucleotide sequence:

TGTGATCTGCCTCAAACCCACAGCCTGGGTAGCAGGAGGACCTTGATGCTC
CTGGCACAGATGAGGAGAATCTCTCTTTTCTCCTGCTTGAAGGACAGACATG
ACTTTGGATTTCCCCAGGAGGAGTTTGGCAACCAGTTCCAAAAGGCTGAAA
CCATCCCTGTCCTCCATGAGATGATCCAGCAGATCTTCAATCTCTTCAGCAC
AAAGGACTCATCTGCTGCTTGGGATGAGACCCTCCTAGACAAATTCTACACT
GAACTCTACCAGCAGCTGAATGACCTGGAAGCCTGTGTGATACAGGGGGTG
GGGGTGACAGAGACTCCCCTGATGAAGGAGGACTCCATTCTGGCTGTGAGG
AAATACTTCCAAAGAATCACTCTCTATCTGAAAGAGAAGAAATACAGCCCT
TGTGCCTGGGAGGTTGTCAGAGCAGAAATCATGAGATCTTTTTCTTTGTCAA
CAAACTTGCAAGAAAGTTTAAGAAGTAAGGAA (SEQ ID NO:375)

IFNa2b was linked to the AlbudAb via a TVAAPS linker region (see WO2007085814). The constructs were cloned by SOE-PCR (single overlap extension according to the method of Horton *et al.* Gene, 77, p61 (1989)). PCR amplification of the AlbudAb and IFN sequences were carried out separately using primers with a ~15 base pair overlap at the TVAAPS linker region. The primers used are as follows:-

IFNα2b SOE fragment 5'	GCCCGGATCCACCGGCTGTGATCTG (SEQ ID NO:376)
IFNα2b SOE fragment 3'	GGAGGATGGAGACTGGGTCATCTGGATGTC (SEQ ID NO:377)
Vk SOE fragment 5'	GACATCCAGATGACCCAGTCTCCATCCTCC (SEQ ID NO:378)
Vk SOE fragment 3' to also introduce a myc tag	GCGCAAGCTTTTATTAATTCAGATCCTCTTC TGAGATGAGTTTTTGTTCTGCGGCCGCCCGT TTGATTTCCACCTTGGTCCC (SEQ ID NO:379)

The fragments were purified separately and subsequently assembled in a SOE (single overlap extension PCR extension) reaction using only the flanking primers.

IFNα2b SOE fragment 5'	GCCCGGATCCACCGGCTGTGATCTG (SEQ ID NO:380)
Vk SOE fragment 3' to also introduce a myc tag	GCGCAAGCTTTTATTAATTCAGATCCTCTTC TGAGATGAGTTTTTGTTCTGCGGCCGCCCGT TTGATTTCCACCTTGGTCCC (SEQ ID NO:381)

The assembled PCR product was digested using the restriction enzymes BamHI and HindIII and the gene ligated into the corresponding sites in the pDOM50, a mammalian expression vector which is a pTT5 derivative with an N-terminal V-J2-C mouse IgG secretory leader sequence to facilitate expression into the cell media.

Leader sequence (amino acid):
METDTLLLWVLLLWVPGSTG (SEQ ID NO:382)

Leader sequence (nucleotide):
ATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTGCTGTGGGTGCCCGGA TCCACCGGGC (SEQ ID NO:383)

Plasmid DNA was prepared using QIAfilter megaprep (Qiagen). 1µg DNA/ml was transfected with 293-Fectin into HEK293E cells and grown in serum free media. The protein is expressed in culture for 5 days and purified from culture supernatant using protein L affinity resin and eluted with 100mM glycine pH2. The proteins were concentred to greater than 1mg/ml, buffer exchanged into PBS and endotoxin depleted using Q spin columns (Vivascience).

Table 11: Interferon alpha 2b-AlbudAb sequences with and without myc-tag (as amino acid- and nucleotide sequence)

The Interferon alpha 2b is N-terminal to the AlbudAb in the following fusions.

	aa + myc	**nt + myc**	**aa no tag**	**nt no tag**
DMS7321	CDLPQTHSLGSRRT	TGCGACTTGCC	CDLPQTHSLG	TGCGACTTGCC
(IFNα2b-	LMLLAQMRRISLFS	ACAGACACAT	SRRTLMLLA	ACAGACACAT
DOM7h-	CLKDRHDFGFPQE	AGTTTGGGATC	QMRRISLFSC	AGTTTGGGATC
14)	EFGNQFQKAETIPV	AAGAAGAACA	LKDRHDFGFP	AAGAAGAACA
	LHEMIQQIFNLFST	TTGATGTTATT	QEEFGNQFQ	TTGATGTTATT
	KDSSAAWDETLLD	AGCACAAATG	KAETIPVLHE	AGCACAAATG
	KFYTELYQQLNDL	CGTAGAATTTC	MIQQIFNLFS	CGTAGAATTTC
	EACVIQGVGVTETP	TTTGTTCTCTT	TKDSSAAWD	TTTGTTCTCTT
	LMKEDSILAVRKY	GTCTAAAGGAC	ETLLDKFYTE	GTCTAAAGGA
	FQRITLYLKEKKYS	CGTCACGACTT	LYQQLNDLE	CCGTCACGACT
	PCAWEVVRAEIMR	CGGATTCCCTC	ACVIQGVGV	TCGGATTCCCT
	SFSLSTNLQESLRS	AGGAAGAGTTT	TETPLMKEDS	CAGGAAGAGT
	KETVAAPSDIQMT	GGAAACCAATT	ILAVRKYFQR	TTGGAAACCA
	QSPSSLSASVGDRV	CCAAAAAGCA	ITLYLKEKKY	ATTCCAAAAA
	TITCRASQWIGSQL	GAAACTATTCC	SPCAWEVVR	GCAGAAACTA
	SWYQQKPGKAPKL	TGTCTTGCACG	AEIMRSFSLS	TTCCTGTCTTG
	LIMWRSSLQSGVPS	AAATGATCCAG	TNLQESLRSK	CACGAAATGA
	RFSGSGSGTDFTLT	CAAATATTCAA	ETVAAPSDIQ	TCCAGCAAATA
	ISSLQPEDFATYYC	TTTGTTTTCTA	MTQSPSSLSA	TTCAATTTGTT
	AQGAALPRTFGQG	CAAAGGACTC	SVGDRVTITC	TTCTACAAAGG
	TKVEIKR	ATCAGCCGCTT	RASQWIGSQL	ACTCATCAGCC
	AAAEQKLISEEDL	GGGATGAAAC	SWYQQKPGK	GCTTGGGATGA
	N* (SEQ ID NO:384)	TCTGTTAGATA	APKLLIMWR	AACTCTGTTAG
		AATTCTACACT	SSLQSGVPSR	ATAAATTCTAC
		GAACTATATCA	FSGSGSGTDF	ACTGAACTATA
		ACAACTGAAC	TLTISSLQPED	TCAACAACTGA
		GATCTAGAGGC	FATYYCAQG	ACGATCTAGA
		TTGCGTTATTC	AALPRTFGQ	GGCTTGCGTTA

		AGGGTGTAGG	GTKVEIKR	TTCAGGGTGTA
		AGTTACTGAAA	(SEQ ID	GGAGTTACTGA
		CTCCCCTAATG	NO:386)	AACTCCCCTAA
		AAAGAAGATT		TGAAAGAAGA
		CAATTCTAGCC		TTCAATTCTAG
		GTTAGAAAATA		CCGTTAGAAA
		CTTTCAGCGTA		ATACTTTCAGC
		TCACATTGTAT		GTATCACATTG
		TTAAAGGAAA		TATTTAAAGGA
		AGAAATACTCC		AAAGAAATAC
		CCATGTGCATG		TCCCCATGTGC
		GGAGGTGGTTA		ATGGGAGGTG
		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG
		TCTCTCTTTCT		GTCCTTCTCTC
		ACGAATTTGCA		TTTCTACGAAT
		AGAATCTTTGA		TTGCAAGAATC
		GATCTAAGGA		TTTGAGATCTA
		AACCGTCGCTG		AGGAAACCGT
		CTCCATCTGAC		CGCTGCTCCAT
		ATCCAGATGAC		CTGACATCCAG
		CCAGTCTCCAT		ATGACCCAGTC
		CCTCCCTGTCT		TCCATCCTCCC
		GCATCTGTAGG		TGTCTGCATCT
		AGACCGTGTCA		GTAGGAGACC
		CCATCACTTGC		GTGTCACCATC
		CGGGCAAGTC		ACTTGCCGGGC
		AGTGGATTGGG		AAGTCAGTGG
		TCTCAGTTATC		ATTGGGTCTCA
		TTGGTACCAGC		GTTATCTTGGT

		AGAAACCAGG GAAAGCCCCTA AGCTCCTGATC ATGTGGCGTTC CTCGTTGCAAA GTGGGGTCCCA TCACGTTTCAG TGGCAGTGGAT CTGGGACAGAT TTCACTCTCAC CATCAGCAGTC TGCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTGCG GCGTTGCCTAG GACGTTCGGCC AAGGGACCAA GGTGGAAATC AAACGG**GCGG CCGCAGAACA AAAACTCATC TCAGAAGAGG ATCTGAATTA A** (SEQ ID NO:385)		ACCAGCAGAA ACCAGGGAAA GCCCCTAAGCT CCTGATCATGT GGCGTTCCTCG TTGCAAAGTGG GGTCCCATCAC GTTTCAGTGGC AGTGGATCTGG GACAGATTTCA CTCTCACCATC AGCAGTCTGCA ACCTGAAGATT TTGCTACGTAC TACTGTGCTCA GGGTGCGGCG TTGCCTAGGAC GTTCGGCCAAG GGACCAAGGT GGAAATCAAA CGG (SEQ ID NO:387)
DMS732 (IFNα2b-DOM7h-14-10)	CDLPQTHSLGSRRT LMLLAQMRRISLFS CLKDRHDFGFPQE EFGNQFQKAETIPV	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA	CDLPQTHSLG SRRTLMLLA QMRRISLFSC LKDRHDFGFP	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA

	LHEMIQQIFNLFST	TTGATGTTATT	QEEFGNQFQ	TTGATGTTATT
	FDSSAAWDETLLD	AGCACAAATG	LAETIPVLHE	AGCACAAATG
	KFYTELYQQLNDL	CGTAGAATTTC	MIQQIFNLFS	CGTAGAATTTC
	EACVIQGVGVTETP	TTTGTTCTCTT	TKDSSAAWD	TTTGTTCTCTT
	LMKEDSILAVRKY	GTCTAAAGGAC	ETLLDLFYTE	GTCTAAAGGA
	FQRITLYLLEIKYS	CGTCACGACTT	LYQQLNDLE	CCGTCACGACT
	PCAWEVVRAEIMR	CGGATTCCCTC	ACVIQGVGV	TCGGATTCCCT
	SFSLSTNLQESLPS	AGGAAGAGTTT	TETPLMKEDS	CAGGAAGAGT
	KETVAAPSDIQMT	GGAAACCAATT	ILAVRKYFQR	TTGGAAACCA
	QSPSSLSASVGDRV	CCAAAAAGCA	ITLYLLEIKY	ATTCCAAAAA
	TITCRASQWIGSQL	GAAACTATTCC	SPCAWEVVR	GCAGAAACTA
	SWYQQKPGKAPKL	TGTCTTGCACG	AEIMRSFSLS	TTCCTGTCTTG
	LIMWRSSLQSGVPS	AAATGATCCAG	TNLQESLPSK	CACGAAATGA
	RFSGSGSGTDFTLT	CAAATATTCAA	ETVAAPSDIQ	TCCAGCAAATA
	ISSLQPEDFATYYC	TTTGTTTTCTA	MTQSPSSLSA	TTCAATTTGTT
	AQGLRHPKTFGQG	CAAAGGACTC	SVGDRVTITC	TTCTACAAAGG
	TKVEIKR	ATCAGCCGCTT	RASQWIGSQL	ACTCATCAGCC
	AAAEQKLISEEDL	GGGATGAAAC	SWYQQKPGK	GCTTGGGATGA
	N* (SEQ ID NO:388)	TCTGTTAGATA	APKLLIMWR	AACTCTGTTAG
		AATTCTACACT	SSLQSGVPSR	ATAAATTCTAC
		GAACTATATCA	FSGSGSGTDF	ACTGAACTATA
		ACAACTGAAC	TLTISSLQPED	TCAACAACTGA
		GATCTAGAGGC	FATYYCAQG	ACGATCTAGA
		TTGCGTTATTC	LRHPKTFGQ	GGCTTGCGTTA
		AGGGTGTAGG	GTKVEIKR	TTCAGGGTGTA
		AGTTACTGAAA	(SEQ ID	GGAGTTACTGA
		CTCCCCTAATG	NO:390)	AACTCCCCTAA
		AAAGAAGATT		TGAAAGAAGA
		CAATTCTAGCC		TTCAATTCTAG
		GTTAGAAAATA		CCGTTAGAAA

		CTTTCAGCGTA		ATACTTTCAGC
		TCACATTGTAT		GTATCACATTG
		TTAAAGGAAA		TATTTAAAGGA
		AGAAATACTCC		AAAGAAATAC
		CCATGTGCATG		TCCCCATGTGC
		GGAGGTGGTTA		ATGGGAGGTG
		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG
		TCTCTCTTTCT		GTCCTTCTCTC
		ACGAATTTGCA		TTTCTACGAAT
		AGAATCTTTGA		TTGCAAGAATC
		GATCTAAGGA		TTTGAGATCTA
		AACCGTCGCTG		AGGAAACCGT
		CTCCATCTGAC		CGCTGCTCCAT
		ATCCAGATGAC		CTGACATCCAG
		CCAGTCTCCAT		ATGACCCAGTC
		CCTCCCTGTCT		TCCATCCTCCC
		GCATCTGTAGG		TGTCTGCATCT
		AGACCGTGTCA		GTAGGAGACC
		CCATCACTTGC		GTGTCACCATC
		CGGGCAAGTC		ACTTGCCGGGC
		AGTGGATTGGG		AAGTCAGTGG
		TCTCAGTTATC		ATTGGGTCTCA
		TTGGTACCAGC		GTTATCTTGGT
		AGAAACCAGG		ACCAGCAGAA
		GAAAGCCCCTA		ACCAGGGAAA
		AGCTCCTGATC		GCCCCTAAGCT
		ATGTGGCGTTC		CCTGATCATGT
		CTCGTTGCAAA		GGCGTTCCTCG
		GTGGGGTCCCA		TTGCAAAGTGG

		TCACGTTTCAG TGGCAGTGGAT CTGGGACAGAT TTCACTCTCAC CATCAGCAGTC TGCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTTTG AGGCATCCTAA GACGTTCGGCC AAGGGACCAA GGTGGAAATC AAACGG**GCGG CCGCAGAACA AAAACTCATC TCAGAAGAGG ATCTGAATTA A** (SEQ ID NO:389)		GGTCCCATCAC GTTTCAGTGGC AGTGGATCTGG GACAGATTTCA CTCTCACCATC AGCAGTCTGCA ACCTGAAGATT TTGCTACGTAC TACTGTGCTCA GGGTTTGAGGC ATCCTAAGACG TTCGGCCAAGG GACCAAGGTG GAAATCAAAC GG (SEQ ID NO:391)
DMS7323 (IFNα2b-DOM7h-14-18)	CDLPQTHSLGSRRT LMLLAQMRRISLFS CLKDRHDFGFPQE EFGNQFQKAETIPV LHEMIQQIFNLFST KDSSAAWDETLLD KFYTELYQQLNDL EACVIQGVGVTETP LMKEDSILAVRKY FQRITLYLKEKKYS	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG CGTAGAATTTC TTTGTTCTCTT GTCTAAAGGAC CGTCACGACTT	CDLPQTHSLG SRRTLMLLA QMRRISLFSC LKDRHDFGFP QEEFGNQFQ KAETIPVLHE MIQQIFNLFS TKDSSAAWD ETLLDKFYTE LYQQLNDLE	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG CGTAGAATTTC TTTGTTCTCTT GTCTAAAGGA CCGTCACGACT

	PCAWEVVRAEIMR	CGGATTCCCTC	ACVIQGVGV	TCGGATTCCCT
	SFSLSTNLQESLRS	AGGAAGAGTTT	TETPLMKEDS	CAGGAAGAGT
	KETVAAPSDIQMT	GGAAACCAATT	ILAVRKYFQR	TTGGAAACCA
	QSPSSLSASVGDRV	CCAAAAAGCA	ITLYLKEKKY	ATTCCAAAAA
	TITCRASQWIGSQL	GAAACTATTCC	SPCAWEVVR	GCAGAAACTA
	SWYQQKPGKAPKL	TGTCTTGCACG	AEIMRSFSLS	TTCCTGTCTTG
	LIMWRSSLQSGVPS	AAATGATCCAG	TNLQESLRSK	CACGAAATGA
	RFSGSGSGTDFTLT	CAAATATTCAA	ETVAAPSDIQ	TCCAGCAAATA
	ISSLQPEDFATYYC	TTTGTTTTCTA	MTQSPSSLSA	TTCAATTTGTT
	AQGLMKPMTFGQ	CAAAGGACTC	SVGDRVTITC	TTCTACAAAGG
	GTKVEIKR**AAAEQ**	ATCAGCCGCTT	RASQWIGSQL	ACTCATCAGCC
	KLISEEDLN* (SEQ	GGGATGAAAC	SWYQQKPGK	GCTTGGGATGA
	ID NO:392)	TCTGTTAGATA	APKLLIMWR	AACTCTGTTAG
		AATTCTACACT	SSLQSGVPSR	ATAAATTCTAC
		GAACTATATCA	FSGSGSGTDF	ACTGAACTATA
		ACAACTGAAC	TLTISSLQPED	TCAACAACTGA
		GATCTAGAGGC	FATYYCAQG	ACGATCTAGA
		TTGCGTTATTC	LMKPMTFGQ	GGCTTGCGTTA
		AGGGTGTAGG	GTKVEIKR	TTCAGGGTGTA
		AGTTACTGAAA	(SEQ ID	GGAGTTACTGA
		CTCCCCTAATG	NO:394)	AACTCCCCTAA
		AAAGAAGATT		TGAAAGAAGA
		CAATTCTAGCC		TTCAATTCTAG
		GTTAGAAAATA		CCGTTAGAAA
		CTTTCAGCGTA		ATACTTTCAGC
		TCACATTGTAT		GTATCACATTG
		TTAAAGGAAA		TATTTAAAGGA
		AGAAATACTCC		AAAGAAATAC
		CCATGTGCATG		TCCCCATGTGC
		GGAGGTGGTTA		ATGGGAGGTG

		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG
		TCTCTCTTTCT		GTCCTTCTCTC
		ACGAATTTGCA		TTTCTACGAAT
		AGAATCTTTGA		TTGCAAGAATC
		GATCTAAGGA		TTTGAGATCTA
		AACCGTCGCTG		AGGAAACCGT
		CTCCATCTGAC		CGCTGCTCCAT
		ATCCAGATGAC		CTGACATCCAG
		CCAGTCTCCAT		ATGACCCAGTC
		CCTCCCTGTCT		TCCATCCTCCC
		GCATCTGTAGG		TGTCTGCATCT
		AGACCGTGTCA		GTAGGAGACC
		CCATCACTTGC		GTGTCACCATC
		CGGGCAAGTC		ACTTGCCGGGC
		AGTGGATTGGG		AAGTCAGTGG
		TCTCAGTTATC		ATTGGGTCTCA
		TTGGTACCAGC		GTTATCTTGGT
		AGAAACCAGG		ACCAGCAGAA
		GAAAGCCCCTA		ACCAGGGAAA
		AGCTCCTGATC		GCCCCTAAGCT
		ATGTGGCGTTC		CCTGATCATGT
		CTCGTTGCAAA		GGCGTTCCTCG
		GTGGGGTCCCA		TTGCAAAGTGG
		TCACGTTTCAG		GGTCCCATCAC
		TGGCAGTGGAT		GTTTCAGTGGC
		CTGGGACAGAT		AGTGGATCTGG
		TTCACTCTCAC		GACAGATTTCA
		CATCAGCAGTC		CTCTCACCATC
		TGCAACCTGAA		AGCAGTCTGCA

		GATTTTGCTAC GTACTACTGTG CTCAGGGTCTT ATGAAGCCTAT GACGTTCGGCC AAGGGACCAA GGTGGAAATC AAACGG**GCGG CCGCAGAACA AAAACTCATC TCAGAAGAGG ATCTGAATTA A** (SEQ ID NO:393)		ACCTGAAGATT TTGCTACGTAC TACTGTGCTCA GGGTCTTATGA AGCCTATGACG TTCGGCCAAGG GACCAAGGTG GAAATCAAAC GG (SEQ ID NO:395)
DMS7324 (IFNα2b-DOM7h-14-19)	CDLPQTHSLGSRRT LMLLAQMRRISLFS CLKDRHDFGFPQE EFGNQFQKAETIPV LHEMIQQIFNLFST KDSSAAWDETLLD KFYTELYQQLNDL EACVIQGVGVTETP LMKEDSILAVRKY FQRITLYLKEKKYS PCAWEVVRAEIMR SFSLSTNLQESLRS KETVAAPSDIQMT QSPSSLSASVGDRV TISCRASQWIGSQL SWYQQKPGEAPKL	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG CGTAGAATTTC TTTGTTCTCTT GTCTAAAGGAC CGTCACGACTT CGGATTCCCTC AGGAAGAGTTT GGAAACCAATT CCAAAAAGCA GAAACTATTCC TGTCTTGCACG	CDLPQTHSLG SRRTLMLLA QMRRISLFSC LKDRHDFGFP QEEFGNQFQ KAETIPVLHE MIQQIFNLFS TKDSSAAWD ETLLDKFYTE LYQQLNDLE ACVIQGVGV TETPLMKEDS ILAVRKYFQR ITLYLKEKKY SPCAWEVVR AEIMRSFSLS	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG CGTAGAATTTC TTTGTTCTCTT GTCTAAAGGA CCGTCACGACT TCGGATTCCCT CAGGAAGAGT TTGGAAACCA ATTCCAAAAA GCAGAAACTA TTCCTGTCTTG

	LIMWRSSLQSGVPS	AAATGATCCAG	TNLQESLRSI:	CACGAAATGA
	RFSGSGSGTDFTLT	CAAATATTCAA	ETVAAPSDIQ	TCCAGCAAATA
	ISSLQPEDFATYYC	TTTGTTTTCTA	MTQSPSSLSA	TTCAATTTGTT
	AQGAALPRTFGQG	CAAAGGACTC	SVGDRVTISC	TTCTACAAAGG
	TKVEIKR	ATCAGCCGCTT	RASQWIGSQL	ACTCATCAGCC
	AAAEQKLISEEDL	GGGATGAAAC	SWYQQKPGE	GCTTGGGATGA
	N* (SEQ ID NO:396)	TCTGTTAGATA	APKLLIMWR	AACTCTGTTAG
		AATTCTACACT	SSLQSGVPSR	ATAAATTCTAC
		GAACTATATCA	FSGSGSGTDF	ACTGAACTATA
		ACAACTGAAC	TLTISSLQPED	TCAACAACTGA
		GATCTAGAGGC	FATYYCAQG	ACGATCTAGA
		TTGCGTTATTC	AALPRTFGQ	GGCTTGCGTTA
		AGGGTGTAGG	GTKVEIKR	TTCAGGGTGTA
		AGTTACTGAAA	(SEQ ID	GGAGTTACTGA
		CTCCCCTAATG	NO:398)	AACTCCCCTAA
		AAAGAAGATT		TGAAAGAAGA
		CAATTCTAGCC		TTCAATTCTAG
		GTTAGAAAATA		CCGTTAGAAA
		CTTTCAGCGTA		ATACTTTCAGC
		TCACATTGTAT		GTATCACATTG
		TTAAAGGAAA		TATTTAAAGGA
		AGAAATACTCC		AAAGAAATAC
		CCATGTGCATG		TCCCCATGTGC
		GGAGGTGGTTA		ATGGGAGGTG
		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG
		TCTCTCTTTCT		GTCCTTCTCTC
		ACGAATTTGCA		TTTCTACGAAT
		AGAATCTTTGA		TTGCAAGAATC
		GATCTAAGGA		TTTGAGATCTA

		AACCGTCGCTG		AGGAAACCGT
		CTCCATCTGAC		CGCTGCTCCAT
		ATCCAGATGAC		CTGACATCCAG
		CCAGTcTCCAT		ATGACCCAGTc
		CCTCCCTGTCT		TCCATCCTCCC
		GCATCTGTAGG		TGTCTGCATCT
		AGACCGTGTCA		GTAGGAGACC
		CCATCTCTTGC		GTGTCACCATC
		CGGGCAAGTC		TCTTGCCGGGC
		AGTGGATTGGG		AAGTCAGTGG
		TCTCAGTTATC		ATTGGGTCTCA
		TTGGTACCAGC		GTTATCTTGGT
		AGAAACCAGG		ACCAGCAGAA
		GGAAGCCCCTA		ACCAGGGGAA
		AGCTCCTGATC		GCCCCTAAGCT
		ATGTGGCGTTC		CCTGATCATGT
		CTCGTTGCAAA		GGCGTTCCTCG
		GTGGGGTCCCA		TTGCAAAGTGG
		TCACGTTTCAG		GGTCCCATCAC
		TGGCAGTGGAT		GTTTCAGTGGC
		CTGGGACAGAT		AGTGGATCTGG
		TTCACTCTCAC		GACAGATTTCA
		CATCAGCAGTC		CTCTCACCATC
		TGCAACCTGAA		AGCAGTCTGCA
		GATTTTGCTAC		ACCTGAAGATT
		GTACTACTGTG		TTGCTACGTAC
		CTCAGGGTGCG		TACTGTGCTCA
		GCGTTGCCTAG		GGGTGCGGCG
		GACGTTCGGCC		TTGCCTAGGAC
		AAGGGACCAA		GTTCGGCCAAG

		GGTGGAAATC AAACGG**GCGG CCGCAGAACA AAAACTCATC TCAGAAGAGG ATCTGAATTA A** (SEQ ID NO:397)		GGACCAAGGT GGAAATCAAA CGG (SEQ ID NO:399)
DMS7325 (IFNα2b-DOM7h-11)	CDLPQTHSLGSRRT LMLLAQMRRISLFS CLRDRHDFGFPQE EFGNQFQKAETIPV LHEMIQQIFNLFST KDSSAAWDETLLD KFYTELYQQLNDL EACVIQGVGVTETP LMKEDSILAVRKY FQRITLYLKEKKYS PCAWEVVRAEIMR SFSLSTNLQESLRS KETVAAPSDIQMT QSPSSLSASVGDRV TITCRASRPIGTTLS WYQQKPGKAPKLL IWFGSRLQSGVPSR FSGSGSGTDFTLTIS SLQPEDFATYYCA QAGTHPTTFGQGT KVEIKR **AAAEQKLISEEDL**	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG CGTAGAATTTC TTTGTTCTCTT GTCTAAAGGAC CGTCACGACTT CGGATTCCCTC AGGAAGAGTTT GGAAACCAATT CCAAAAAGCA GAAACTATTCC TGTCTTGCACG AAATGATCCAG CAAATATTCAA TTTGTTTTCTA CAAAGGACTC ATCAGCCGCTT GGGATGAAAC	CDLPQTHSLG SRRTLMLLA QMRRISLFSC LKDRHDFGFP QEEFGNQFQ KAETIPVLHE MIQQIFNLFS TKDSSAAWD ETLLDKFYTE LYQQLNDLE ACVIQGVGV TETPLMKEDS ILAVRKYFQR ITLYLKEKKY SPCAWEVVR AEIMRSFSLS TNLQESLRSK ETVAAPSDIQ MTQSPSSLSA SVGDRVTITC RASRPIGTTL SWYQQKPGK	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG CGTAGAATTTC TTTGTTCTCTT GTCTAAAGGA CCGTCACGACT TCGGATTCCCT CAGGAAGAGT TTGGAAACCA ATTCCAAAAA GCAGAAACTA TTCCTGTCTTG CACGAAATGA TCCAGCAAATA TTCAATTTGTT TTCTACAAAGG ACTCATCAGCC GCTTGGGATGA

	N* (SEQ ID NO:400)	TCTGTTAGATA	APKLLIWFGS	AACTCTGTTAG
		AATTCTACACT	RLQSGVPSRF	ATAAATTCTAC
		GAACTATATCA	SGSGSGTDFT	ACTGAACTATA
		ACAACTGAAC	LTISSLQPEDF	TCAACAACTGA
		GATCTAGAGGC	ATYYCAQAG	ACGATCTAGA
		TTGCGTTATTC	THPTTFGQGT	GGCTTGCGTTA
		AGGGTGTAGG	KVEIKR (SEQ	TTCAGGGTGTA
		AGTTACTGAAA	ID NO:402)	GGAGTTACTGA
		CTCCCCTAATG		AACTCCCCTAA
		AAAGAAGATT		TGAAAGAAGA
		CAATTCTAGCC		TTCAATTCTAG
		GTTAGAAAATA		CCGTTAGAAA
		CTTTCAGCGTA		ATACTTTCAGC
		TCACATTGTAT		GTATCACATTG
		TTAAAGGAAA		TATTTAAAGGA
		AGAAATACTCC		AAAGAAATAC
		CCATGTGCATG		TCCCCATGTGC
		GGAGGTGGTTA		ATGGGAGGTG
		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG
		TCTCTCTTTCT		GTCCTTCTCTC
		ACGAATTTGCA		TTTCTACGAAT
		AGAATCTTTGA		TTGCAAGAATC
		GATCTAAGGA		TTTGAGATCTA
		AACCGTCGCTG		AGGAAACCGT
		CTCCATCTGAC		CGCTGCTCCAT
		ATCCAGATGAC		CTGACATCCAG
		CCAGTCTCCAT		ATGACCCAGTC
		CCTCCCTGTCT		TCCATCCTCCC
		GCATCTGTAGG		TGTCTGCATCT

		AGACCGTGTCA		GTAGGAGACC
		CCATCACTTGC		GTGTCACCATC
		CGGGCAAGTC		ACTTGCCGGGC
		GTCCGATTGGG		AAGTCGTCCGA
		ACGACGTTAAG		TTGGGACGAC
		TTGGTACCAGC		GTTAAGTTGGT
		AGAAACCAGG		ACCAGCAGAA
		GAAAGCCCCTA		ACCAGGGAAA
		AGCTCCTGATC		GCCCCTAAGCT
		TGGTTTGGTTC		CCTGATCTGGT
		CCGGTTGCAAA		TTGGTTCCCGG
		GTGGGGTCCCA		TTGCAAAGTGG
		TCACGTTTCAG		GGTCCCATCAC
		TGGCAGTGGAT		GTTTCAGTGGC
		CTGGGACAGAT		AGTGGATCTGG
		TTCACTCTCAC		GACAGATTTCA
		CATCAGCAGTC		CTCTCACCATC
		TGCAACCTGAA		AGCAGTCTGCA
		GATTTTGCTAC		ACCTGAAGATT
		GTACTACTGTG		TTGCTACGTAC
		CGCAGGCTGG		TACTGTGCGCA
		GACGCATCCTA		GGCTGGGACG
		CGACGTTCGGC		CATCCTACGAC
		CAAGGGACCA		GTTCGGCCAAG
		AGGTGGAAAT		GGACCAAGGT
		CAAACGG**GCG**		GGAAATCAAA
		GCCGCAGAAC		CGG (SEQ ID
		AAAAACTCAT		NO:403)
		CTCAGAAGAG		
		GATCTGAATT		

		AA (SEQ ID NO:401)		
DMS7326 (IFNα2b-DOM7h-11-12)	CDLPQTHSLGSRRT	TGCGACTTGCC	CDLPQTHSLG	TGCGACTTGCC
	LMLLAQMRRISLFS	ACAGACACAT	SRRTLMLLA	ACAGACACAT
	CLKDRHDFGFPQE	AGTTTGGGATC	QMRRISLFSC	AGTTTGGGATC
	EFGNQFQKAETIPV	AAGAAGAACA	LKDRHDFGFP	AAGAAGAACA
	LHEMIQQIFNLFST	TTGATGTTATT	QEEFGNQFQ	TTGATGTTATT
	KDSSAAWDETLLD	AGCACAAATG	KAETIPVLHE	AGCACAAATG
	KFYTELYQQLNDL	CGTAGAATTTC	MIQQIFNLFS	CGTAGAATTTC
	EACVIQGVGVTETP	TTTGTTCTCTT	TKDSSAAWD	TTTGTTCTCTT
	LMKEDSILAVRKY	GTCTAAAGGAC	ETLLDKFYTE	GTCTAAAGGA
	FQRITLYLKEKKYS	CGTCACGACTT	LYQQLNDLE	CCGTCACGACT
	PCAWEVVRAEIMR	CGGATTCCCTC	ACVIQGVGV	TCGGATTCCCT
	SFSLSTNLQESLRS	AGGAAGAGTTT	TETPLMKEDS	CAGGAAGAGT
	KETVAAPSDIQMT	GGAAACCAATT	ILAVRKYFQR	TTGGAAACCA
	QSPSSLSASVGDRV	CCAAAAAGCA	ITLYLKEKKY	ATTCCAAAAA
	TITCRASRPIGTML	GAAACTATTCC	SPCAWEVVR	GCAGAAACTA
	SWYQQKPGKAPKL	TGTCTTGCACG	AEIMRSFSLS	TTCCTGTCTTG
	LILFGSRLQSGVPS	AAATGATCCAG	TNLQESLRSK	CACGAAATGA
	RFSGSGSGTDFTLT	CAAATATTCAA	ETVAAPSDIQ	TCCAGCAAATA
	ISSLQPEDFATYYC	TTTGTTTTCTA	MTQSPSSLSA	TTCAATTTGTT
	AQAGTHPTTFGQG	CAAAGGACTC	SVGDRVTITC	TTCTACAAAGG
	TKVEIKR	ATCAGCCGCTT	RASRPIGTML	ACTCATCAGCC
	AAAEQKLISEEDL	GGGATGAAAC	SWYQQKPGK	GCTTGGGATGA
	N* (SEQ ID NO:404)	TCTGTTAGATA	APKLLILFGS	AACTCTGTTAG
		AATTCTACACT	RLQSGVPSRF	ATAAATTCTAC
		GAACTATATCA	SGSGSGTDFT	ACTGAACTATA
		ACAACTGAAC	LTISSLQPEDF	TCAACAACTGA
		GATCTAGAGGC	ATYYCAQAG	ACGATCTAGA
		TTGCGTTATTC	THPTTFGQGT	GGCTTGCGTTA

		AGGGTGTAGG	EVEIER (SEQ	TTCAGGGTGTA
		AGTTACTGAAA	ID NO:406)	GGAGTTACTGA
		CTCCCCTAATG		AACTCCCCTAA
		AAAGAAGATT		TGAAAGAAGA
		CAATTCTAGCC		TTCAATTCTAG
		GTTAGAAAATA		CCGTTAGAAA
		CTTTCAGCGTA		ATACTTTCAGC
		TCACATTGTAT		GTATCACATTG
		TTAAAGGAAA		TATTTAAAGGA
		AGAAATACTCC		AAAGAAATAC
		CCATGTGCATG		TCCCCATGTGC
		GGAGGTGGTTA		ATGGGAGGTG
		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG
		TCTCTCTTTCT		GTCCTTCTCTC
		ACGAATTTGCA		TTTCTACGAAT
		AGAATCTTTGA		TTGCAAGAATC
		GATCTAAGGA		TTTGAGATCTA
		AACCGTCGCTG		AGGAAACCGT
		CTCCATCTGAC		CGCTGCTCCAT
		ATCCAGATGAC		CTGACATCCAG
		CCAGTCTCCAT		ATGACCCAGTC
		CCTCCCTGTCT		TCCATCCTCCC
		GCATCTGTAGG		TGTCTGCATCT
		AGACCGTGTCA		GTAGGAGACC
		CCATCACTTGC		GTGTCACCATC
		CGGGCAAGTC		ACTTGCCGGGC
		GTCCGATTGGG		AAGTCGTCCGA
		ACGATGTTAAG		TTGGGACGATG
		TTGGTACCAGC		TTAAGTTGGTA

		AGAAACCAGG GAAAGCCCCTA AGCTCCTGATC TTGTTTGGTTC CCGGTTGCAAA GTGGGGTCCCA TCACGTTTCAG TGGCAGTGGAT CTGGGACAGAT TTCACTCTCAC CATCAGCAGTC TGCAACCTGAA GATTTTGCTAC GTACTACTGTG CGCAGGCTGG GACGCATCCTA CGACGTTCGGC CAAGGGACCA AGGTGGAAAT CAAACGG**GCG GCCGCAGAAC AAAAACTCAT CTCAGAAGAG GATCTGAATT AA** (SEQ ID NO:405		CCAGCAGAAA CCAGGGAAAG CCCCTAAGCTC CTGATCTTGTT TGGTTCCCGGT TGCAAAGTGG GGTCCCATCAC GTTTCAGTGGC AGTGGATCTGG GACAGATTTCA CTCTCACCATC AGCAGTCTGCA ACCTGAAGATT TTGCTACGTAC TACTGTGCGCA GGCTGGGACG CATCCTACGAC GTTCGGCCAAG GGACCAAGGT GGAAATCAAA CGG (SEQ ID NO:407)
DMS7327 (IFNα2b-DOM7h-11-15)	CDLPQTHSLGSRRT LMLLAQMRRISLFS CLKDRHDFGFPQE EFGNQFQKAETIPV	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA	CDLPQTHSLG SRRTLMLLA QMRRISLFSC LKDRHDFGFP	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA

	LHEMIQQIFNLFST	TTGATGTTATT	QEEFGNQFQ	TTGATGTTATT
	KDSSAAWDETLLD	AGCACAAATG	KAETIPVLHE	AGCACAAATG
	KFYTELYQQLNDL	CGTAGAATTTC	MIQQIFNLFS	CGTAGAATTTC
	EACVIQGVGVTETP	TTTGTTCTCTT	TKDSSAAWD	TTTGTTCTCTT
	LMKEDSILAVFKY	GTCTAAAGGAC	ETLLDKFYTE	GTCTAAAGGA
	FQRITLYLKEKKYS	CGTCACGACTT	LYQQLNDLE	CCGTCACGACT
	PCAWEVVRAEIMR	CGGATTCCCTC	ACVIQGVGV	TCGGATTCCCT
	SFSLSTNLQESLRS	AGGAAGAGTTT	TETPLMKEDS	CAGGAAGAGT
	KETVAAPSDIQMT	GGAAACCAATT	ILAVFKYFQR	TTGGAAACCA
	QSPSSLSASVGDRV	CCAAAAAGCA	ITLYLKEKKY	ATTCCAAAAA
	TITCRASRPIGTML	GAAACTATTCC	SPCAWEVVR	GCAGAAACTA
	SWYQQKPGKAPKL	TGTCTTGCACG	AEIMRSFSLS	TTCCTGTCTTG
	LILAFSRLQSGVPS	AAATGATCCAG	TNLQESLRSI	CACGAAATGA
	RFSGSGSGTDFTLT	CAAATATTCAA	ETVAAPSDIQ	TCCAGCAAATA
	ISSLQPEDFATYYC	TTTGTTTTCTA	MTQSPSSLSA	TTCAATTTGTT
	AQAGTHPTTFGQG	CAAAGGACTC	SVGDRVTITC	TTCTACAAAGG
	TKVEIKR	ATCAGCCGCTT	RASRPIGTML	ACTCATCAGCC
	AAAEQKLISEEDL	GGGATGAAAC	SWYQQKPGK	GCTTGGGATGA
	N* (SEQ ID NO:408)	TCTGTTAGATA	APKLLILAFS	AACTCTGTTAG
		AATTCTACACT	RLQSGVPSRF	ATAAATTCTAC
		GAACTATATCA	SGSGSGTDFT	ACTGAACTATA
		ACAACTGAAC	LTISSLQPEDF	TCAACAACTGA
		GATCTAGAGGC	ATYYCAQAG	ACGATCTAGA
		TTGCGTTATTC	THPTTFGQGT	GGCTTGCGTTA
		AGGGTGTAGG	KVEIKR (SEQ	TTCAGGGTGTA
		AGTTACTGAAA	ID NO:410)	GGAGTTACTGA
		CTCCCCTAATG		AACTCCCCTAA
		AAAGAAGATT		TGAAAGAAGA
		CAATTCTAGCC		TTCAATTCTAG
		GTTAGAAAATA		CCGTTAGAAA

		CTTTCAGCGTA		ATACTTTCAGC
		TCACATTGTAT		GTATCACATTG
		TTAAAGGAAA		TATTTAAAGGA
		AGAAATACTCC		AAAGAAATAC
		CCATGTGCATG		TCCCCATGTGC
		GGAGGTGGTTA		ATGGGAGGTG
		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG
		TCTCTCTTTCT		GTCCTTCTCTC
		ACGAATTTGCA		TTTCTACGAAT
		AGAATCTTTGA		TTGCAAGAATC
		GATCTAAGGA		TTTGAGATCTA
		AACCGTCGCTG		AGGAAACCGT
		CTCCATCTGAC		CGCTGCTCCAT
		ATCCAGATGAC		CTGACATCCAG
		CCAGTCTCCAT		ATGACCCAGTC
		CCTCCCTGTCT		TCCATCCTCCC
		GCATCTGTAGG		TGTCTGCATCT
		AGACCGTGTCA		GTAGGAGACC
		CCATCACTTGC		GTGTCACCATC
		CGGGCAAGTC		ACTTGCCGGGC
		GTCCGATTGGG		AAGTCGTCCGA
		ACGATGTTAAG		TTGGGACGATG
		TTGGTACCAGC		TTAAGTTGGTA
		AGAAACCAGG		CCAGCAGAAA
		GAAAGCCCCTA		CCAGGGAAAG
		AGCTCCTGATC		CCCCTAAGCTC
		CTTGCTTTTTC		CTGATCCTTGC
		CCGTTTGCAAA		TTTTTCCCGTT
		GTGGGGTCCCA		TGCAAAGTGG

		TCACGTTTCAG TGGCAGTGGAT CTGGGACAGAT TTCACTCTCAC CATCAGCAGTC TGCAACCTGAA GATTTTGCTAC GTACTACTGCG CGCAGGCTGG GACGCATCCTA CGACGTTCGGC CAAGGGACCA AGGTGGAAAT CAAACGG**GCG** **GCCGCAGAAC** **AAAAACTCAT** **CTCAGAAGAG** **GATCTGAATT** **AA** (SEQ ID NO:409)		GGTCCCATCAC GTTTCAGTGGC AGTGGATCTGG GACAGATTTCA CTCTCACCATC AGCAGTCTGCA ACCTGAAGATT TTGCTACGTAC TACTGCGCGCA GGCTGGGACG CATCCTACGAC GTTCGGCCAAG GGACCAAGGT GGAAATCAAA CGG (SEQ ID NO:411)

The amino acid and nucleotide sequences highlighted in bold represents the cloning site and MYC tag. * represents the stop codon at the end of the gene.

Affinity Determination and Biophysical Characterisation:

To determine the binding affinity (K_D) of the AlbudAb-IFNα2b fusion proteins to each serum albumin; purified fusion proteins were analysed by BIAcore over albumin (immobilised by primary-amine coupling onto CM5 chips; BIAcore) using fusion protein concentrations from 5000nM to 39nM (5000nM, 2500nM, 1250nM, 625nM, 312nM, 156nM, 78nM, 39nM) in HBS-EP BIAcore buffer.

Table 12: Affinity to SA

AlbudAb	Fusion	Affinity to SA (nM)	Kd	Ka
		Rat		
DOM7h-14	IFNα2b	350	4.500E-02	1.28E+05
DOM7h-14-10	IFNα2b	16	4.970E-03	5.90E+05
DOM 7h-14-18	IFNα2b	780	2.127E-01	5.80E+05
DOM 7h-14-19	IFNα2b	1900	1.206E-01	7.96E+04
DOM 7h-11	IFNα2b	6000	7.500E-01	nd
DOM 7h-11-12	IFNα2b	1700	3.100E-01	1.30E+05
DOM 7h-11-15	IFNα2b	200	1.660E-02	1.50E+05
		Cyno		
DOM 7h-14	IFNα2b	60	1.32E-02	5.0E+05
DOM 7h-14-10	IFNα2b	19	7.05E-03	4.50E+05
DOM 7h-14-18	IFNα2b	no binding	no binding	no binding
DOM 7h-14-19	IFNα2b	520	8.47E-02	2.73E+05
DOM 7h-11	IFNα2b	3300	3.59E-01	1.20E+05
DOM 7h-11-12	IFNα2b	630	3.45E-01	7.00E+05
DOM 7h-11-15	IFNα2b	15	4.86E-03	3.60E+05
		Mouse		
DOM 7h-14	IFNα2b	240	3.21E-02	1.50E+06
DOM 7h-14-10	IFNα2b	60	3.45E-02	6.86E+05
DOM 7h-14-18	IFNα2b	180	1.50E-01	9.84E+05

DOM 7h-14-19	IFNα2b	490	4.03E-02	1.19E+05
DOM 7h-11	IFNα2b	6000	1.55E-01	nd
DOM 7h-11-12	IFNα2b	150	9.49E-02	6.30E+05
DOM 7h-11-15	IFNα2b	28	6.69E-03	2.80E+05
		Human		
DOM 7h-14	IFNα2b	244	2.21E-02	9.89E+04
DOM 7h-14-10	IFNα2b	32	6.58E-03	3.48E+05
DOM 7h-14-18	IFNα2b	470	2.75E-01	6.15E+05
DOM 7h-14-19	IFNα2b	350	4.19E-02	1.55E+05
DOM 7h-11	IFNα2b	670	2.02E-01	7.00E+05
DOM 7h-11-12	IFNα2b	500	1.66E-01	3.90E+05
DOM 7h-11-15	IFNα2b	10	1.87E-03	3.50E+05

When IFNα2b is linked to the AlbudAb variants, in all cases the affinity of AlbudAb binding to serum albumin is reduced. DOM7h-14-10 and DOM7-11-15 retain improved binding affinity to serum albumin across species compared to parent. DOM7h-11-12 also shows improved binding affinity to serum albumin across species compared to parent.

Table 13: Biophysical Characterisation

Biophysical Characterisation was carried out by SEC MALLS and DSC as described above for the single AlbudAbs.

AlbudAb	Fusion	DMS number	Biophysical parameters

			SEC MALLS	DSC Tm(°C)
DOM 7h-14	IFNα2b	DMS7321	M/D	58-65
DOM 7h-14-10	IFNα2b	DMS7322	M/D	55-65
DOM 7h-14-18	IFNα2b	DMS7323	M/D	55-65
DOM 7h-14-19	IFNα2b	DMS7324	M/D	59-66
DOM 7h-11	IFNα2b	DMS7325	M/D	65.8-66.2
DOM 7h-11-12	IFNα2b	DMS7326	M/D	67-67.3
DOM 7h-11-15	IFNα2b	DMS7327	M/D	56.3-66.2

M/D indicates a monomer/dimer equilibrium as detected by SEC MALLS

We observed expression for all clones in Tabale 13 in the range of 17.5 to 54 mg/L in HEK293.

For IFNα2b-DOM7h-14 and IFNα2b-DOM7h-11 variants, favorable biophysical parameters and expression levels were maintained during affinity maturation.

PK Determination for AlbudAb-IFNα2bfusions

AlbudAbs IFNα2b fusions DMS7321 (IFNα2b-DOM7h-14) DMS7322 (IFNα2b-DOM7h-14-10) DMS7323 (IFNα2b-DOM7h-14-18), DMS7324 (IFNα2b-DOM7h-14-19), DMS7325 (IFNα2b-DOM7h-11), DMS7326 (IFNα2b-DOM7h-11-12), DMS7327 (IFNα2b-DOM7h-11-15) were expressed with the myc tag at 20-50mg quantities in HEK293 cells and purified from culture supernatant using protein L affinity resin and eluted with 100mM glycine pH2. The proteins were concentrated to greater than 1mg/ml, buffer exchanged into Dulbecco's PBS and endotoxin depleted using Q spin columns (Vivascience).

For Rat PK, IFN-AlbudAbs were dosed as single i.v injections at 2.0mg/kg using 3 rats per compound. Serum samples were taken at 0.16, 1, 4, 8, 24, 48, 72, 120, 168hrs. Analysis of serum levels was by EASY ELISA according to manufacturers instructions (GE Healthcare, catalogue number RPN5960).

For Mouse PK, DMS7322 (IFN2b-DOM7h-14-10) DMS7325 (IFN2b-DOM7h-11), DMS7326 (IFN2b-DOM7h-11-12), DMS7327 (IFN2b-DOM7h-11-15) all with myc tags were dosed as single i.v injections at 2.0mg/kg per dose group of 3 subjects and serum samples taken at 10mins; 1h; 8h; 24h; 48h; 72h; 96h. Analysis of serum levels was by EASY ELISA according to manufacturers instructions (GE Healthcare, catalogue number RPN5960).

Table 14:

Species	AlbudAb	Fusion	Albumin K_D (nM)	PK parameters			
				AUC h x ug/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
Rat	**7h-14**	IFNα2b	350	832.1	2.4	27	94.5
	7h-14-10	IFNα2b	16	1380.7	1.5	35.8	75.2
	7h-14-18	IFNα2b	780	691.2	2.9	22.4	93.7
	7h-14-19	IFNα2b	1900	969.4	2.2	25	78.7

	7h-11	IFNα2b	6000	327.9	6.5	11	101.9
	7h-11-12	IFNα2b	1700	747.1	2.8	25.8	104.7
	7h-11-15	IFNα2b	200	1118.7	1.8	39.5	103.6
mouse	**7h-14**	IFNα2b	240	761.2	2.6	30.4	115.3
	7h-14-10	IFNα2b	60	750.5	2.7	30.9	118.6
	7h-11	IFNα2b	6000	493.9	4.0	8.8	51.2
	7h-11-12	IFNα2b	150	439.6	4.5	21.5	140.9
	7h-11-15	IFNα2b	28	971.8	2.1	33.6	99.6

Pharmacokinetic parameters derived from rat and mouse studies were fitted using a non-compartmental model. Key: AUC: Area under the curve from dosing time extrapolated to infinity; CL: clearance; t1/2: is the time during which the blood concentration is halved; Vz: volume of distribution based on the terminal phase.

IFNα2b –AlbudAbs were tested in rat and mouse. For all IFNα2b -DOM7h-11 variant fusion proteins in both rat and mouse, t1/2 is improved compared to parent. The improvement in t1/2 correlates with the improved in vitro K_D to serum albumin. For IFNα2b-DOM7h-14-10 variants, the improvement in *in vitro* K_D to serum albumin also correlated to an improvement in t1/2 in rat.

All IFNα2b -AlbudAb fusion proteins exhibit a 5 to 10-fold decrease in the binding to RSA compared to the single AlbudAb. This effect is more pronounced (i.e. 10-fold) for the DOM7h-14 series than the DOM7h-11 series (only 5-fold decrease).

Example 8: Further AlbudAb fusions with proteins, peptides and NCEs.

Various AlbudAbs fused to other chemical entities namely domain antibodies (dAbs), peptides and NCEs were tested. The results are shown in table 15.

Table 15:

Species	AlbudAb	Fusion	Albumin K_D (nM)	PK parameters			
				AUC h x ug/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
Rat	DOM7h-14	Exendin-4	2400	18	57.1	11	901.9
	DOM7h-14-10	Exendin-4	19	43.6	23.1	22.1	740.3
	DOM7h-14-18	Exendin-4	16000	16.9	75.7	9.4	1002.5
	DOM7h-14-19	Exendin-4	17000	31.4	32.5	11.9	556.7
	DOM7h-11	Exendin-4	24000	6.1	168	7.1	1684.1
	DOM7h-11-12	Exendin-4	1400	24.2	59.9	13	1068.7
	DOM7h-11-15	Exendin-4	130	36.3	27.6	19.3	765.7
	DOM7h14-10	NCE-GGGGSC	62				
	DOM7h14-10	NCE-TVAAPSC	35				
Human	DOM7h-14	NCE	204				
mouse	DOM7h-11	DOM1m-		234	10.7	4.7	72.5

		21-23					
	DOM7h-11-12	DOM1m-21-23		755	3.3	18	86.2
	DOM7h-11-15	DOM1m-21-23		1008	2.5	17.4	62.4

Key: DOM1m-21-23 is an anti-TNFR1 dAb, Exendin-4 is a peptide (a GLP-1 agonist) of 39 amino acids length. NCE, NCE-GGGGSC and NCE-TVAAPSC are described below.

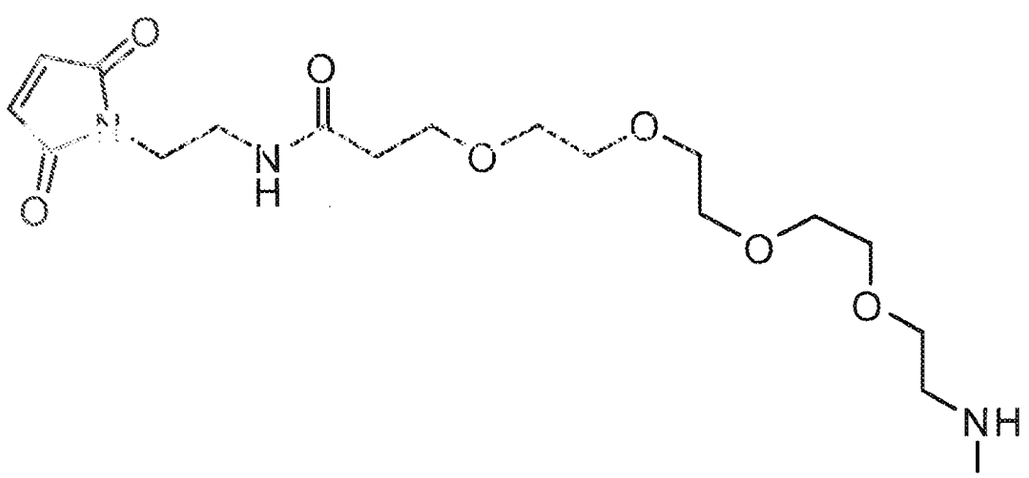
Previously we have described the use of genetic fusions with an albumin-binding dAb (AlbudAb) to extend the PK half-life of anti-TNFR1 dAbs in vivo (see, eg, WO04003019, WO2006038027, WO2008149148). Reference is made to the protocols in these PCT applications. In the table above, DOM1m-21-23 is an anti-mouse TNFR1 dAb.

To produce genetic fusions of exendin-4 or with DOM7h-14 (or other AlbudAb) which binds serum albumin, the exendin-4-linker-AlbudAb sequence was cloned into the pTT-5 vector (obtainable from CNRC, Canada). In each case the exendin-4 was at the 5' end of the construct and the dAb at the 3' end. The linker was a $(G_4S)_3$ linker. Endotoxin-free DNA was prepared in E.coli using alkaline lysis (using the endotoxin-free plasmid Giga kit, obtainable from Qiagen CA) and used to transfect HEK293E cells (obtainable from CNRC, Canada). Transfection was into 250ml/flask of HEK293E cells at $1.75x10^6$ cells/ml using 333ul of 293fectin (Invotrogen) and 250ug of DNA per flask and expression was at 30°C for 5 days. The supernatant was harvested by centrifugation and purification was by affinity purification on protein L. Protein was batch bound to the resin, packed on a column and washed with 10 column volumes of PBS. Protein was eluted with 50ml of 0.1M glycine pH2 and neatralised with Tris pH8.. Protein of the expected size was identified on an SDS-PAGE gel.

NCE Albudab fusions:

A new chemical entity (NCE) AlbudAb fusion was tested. The NCE, a small molecule ADAMTS-4 inhibitor was synthesised with a PEG linker (PEG 4 linker (ie 4 PEG molecules before the maleimide) and a maleimide group for conjugation to the AlbudAb. Conjugation of the NCE to the AlbudAb is via an engineered cystine residue at amino acid position R108C, or following a 5 amino acid (GGGGSC) or 6 amino acid (TVAAPSC) spacer engineered at the end of the AlbudAb. Briefly, the AlbudAb was reduced with TCEP (Pierce, Catalogue Number 77720), desalted using a PD10 column (GE healthcare) into 25mM Bis-Tris, 5mM EDTA, 10% (v/v) glycerol pH6.5. A 5 fold molar excess of maleimide activated NCE was added in DMSO not to exceed 10% (V/V) final concentration. The reaction was incubated over night at room temperature and dialysed extensively into 20mM Tris pH7.4

PEG linker:



Sequences:

DOM7h-14 R108C:

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSL QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKC (SEQ ID NO:412)

Nucleotide:
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC GTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTG GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTC CTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGAC AGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTAC TACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCCAAGGGACCAAG GTGGAAATCAAATGC (SEQ ID NO:413)

See table 5 for the sequences of DOM7h-14-10/TVAAPSC and DOM7h-14-10/GGGGSC (ie, DOM7h-14-10/G4SC).

NCE-AlbudAbs DOM7h-14-10 GGGGSC and DOM7h14-10 TVAAPSC, exhibit a 5 to 10 fold decrease in *in vitro* affinity (K_D) to RSA as determined by BIAcore when fused to the chemical entity. PK data are not available for these molecules yet.

dAb-Albudab fusion: the 2 DOM7h-11 AlbudAbs with the highest affinity to RSA experience a 2-fold decrease in affinity to RSA as on BIAcore when fused to a therapeutic domain antibody (DOM1m-21-23) compared to the unfused AlbudAb. The DOM7h-11 clone shows a micromolar K_D when fused (2.8uM) as well as when unfused (~5uM).

Exendin 4-AlbudAb fusion: the effect of fusing the AlbudAbs to a peptide on the binding ability to RSA is about 10-fold, apart from DOM7h-14-10, which only shows a 4-fold decrease in binding. The effect, however, is more pronounced for the DOM7h-14 series (except DOM7h-14-10) than it appears to be for the DOM7h-11 series.

For all the above data, the T1/2 of the fusion increased with improved affinity to the species' SA.

We generally classify Albudab-therapeutics as being therapeutically amenable (for treatment and/or prophylaxis of diseases, conditions or indications) when the AlbudAb-drug fusions show an affinity range (K_D) of from 0.1 nM to 10 mM for serum albumin binding.

We define the therapeutic ranges of AlbudAbs and AlbudAb fusions (Protein-AlbudAbs for example IFNa2b-DOM7h-14-10; Peptide-AlbudAbs for example Exendin-4-DOM7h-14-10; dAb-AlbudAbs for example DOM1m21-23-DOM7h11-15; NCE-AlbudAb for example ADAMTS-4-DOM7h-14-10) as follows: Affinity (K_D) ranges that are useful for therapy of chronic or acute conditions, diseases or indictions are shown. Also shown are affinity ranges marked as "intermediate". AlbudAbs and fusions in this range have utility for chronic or acute diseases, conditions or indications. In this way, the affinity of the AlbudAb or fusion for serum albumin can be tailored or chosen according to the disease, condition or indication to be addressed. As described above, the invention provides AlbudAbs with affinities that allow for each AlbudAb to be categorised as "high affinity", "medium affinity" or "low affinity", thus enabling the skilled person to select the appropriate AlbudAb of the invention according to the therapy at hand. See Figure 2.

Example 9: DOM7h-11-15^{S12P} Sequences

Amino Acid Sequence of DOM7h-11-15^{S12P}

DIQMTQSPSSLPASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR
(SEQ ID NO: 414)

An aspect of the invention provides a nucleic acid comprising the nucleotide sequence of DOM7h-11-15^{S12P} or a nucleotide sequence that is at least 80% identical to said selected sequence. DOM7h-11-15^{S12P} was produced using the following nucleic acid sequence (the underlined C denotes the change (versus the nucleic acid encoding DOM7h-11-15) leading to a proline at position 12):-

GACATCCAGATGACCCAGTCTCCATCCTCCCTGCCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC
CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACT
ACTGCGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCAAGGGACCAAGG
TGGAAATCAAACGG (SEQ ID NO: 415)

DOM7h-11-15^{S12P} was constructed by using DOM7h-11-15 as a template in a PCR where a primer was used to introduce the S12P mutation. The primer sequence is:-

GCAACAGCGTCGACGGACATCCAGATGACCCAGTCTCCATCCTCCCTGCCTG
CATCTGTAGG (SEQ ID NO: 416).

An alternative aspect of the invention provides a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 415 or a nucleotide sequence that is at least 80% identical to said selected sequence. In one embodiment, DOM7h-11-15^{S12P} is encoded by, and expressed from, a vector that contains a linker region and a C-terminal sequence encoding a protein or peptide drug or a single variable domain or other antibody fragment to make the in-line protein fusion product. The linker, in one embodiment, comprises the amino acid sequence TVA, eg, TVAAPS. Other aspects of the invention are a vector comprising the nucleic acid; and an isolated host cell comprising the vector. The invention also provides a method of treating or preventing a disease or disorder in a patient, comprising administering at least one dose of DOM7h-11-15^{S12P} to said patient.

CLAIMS:

1. An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14 (DOM7h-14 as shown in figure 1), wherein the variant comprises at least one mutation in CDR3 region 92 to 96 (position numbering according to Kabat) compared to DOM7h-14, and wherein the variant has from 1 to 8 changes compared to the amino acid sequence of DOM7h-14.

2. The variant of claim 1, wherein the variant comprises a AQG(X1)(X2)(X3)P(X4)T motif, wherein A is at position 89 (according to Kabat), and at least one of (X1) to (X4) represents an amino acid change compared to the sequence of DOM7h-14.

3. The variant of claim 1 or 2, wherein the variant comprises a mutation at each of positions 92, 93 and 94 and optionally position 96 (numbering according to Kabat) compared to DOM7h-14.

4. The variant of claim 3, wherein the variant comprises one or more amino acid residues selected from

Position 92 = L or F,
Position 93 = R, M or K,
Position 94 = H or K, and
Position 96 = K or M (numbering according to Kabat).

5. The variant of claim 1 or 2, the variant comprises a Lys or Met at position 96 (numbering according to Kabat) compared to DOM7h-14.

6. The variant of claim 5, wherein the variant comprises one or more amino acid residues selected from

Position 92 = L or F,
Position 93 = R, M or K, and
Position 94 = H or K (numbering according to Kabat).

7. The variant of claim 1, wherein the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-14-10 (SEQ ID NO: 1), DOM7h-14-18 (SEQ ID NO: 2), DOM7h-14-28 (SEQ ID NO: 4) and DOM7h-14-36 (SEQ ID NO: 5) or has up to 4 changes compared to the selected amino acid sequence, wherein the variant comprises at least one mutation in CDR3 region 92 to 96 (position numbering according to Kabat) compared to DOM7h-14.

8. An anti-serum albumin (SA) binding moiety comprising CDR3 of a selected variant of any preceding claim.

9. The binding moiety of claim 8, comprising CDR1 of the selected variant or an amino acid sequence that is at least 50% identical to CDR1 of the selected variant.

10. The binding moiety of claim 8 or 9, comprising CDR2 of the selected variant or an amino acid sequence that is at least 50% identical to CDR2 of the selected variant.

11. An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises a Ser at position 22 and a Glu at position 42 (numbering according to Kabat) compared to DOM7h-14, and wherein the variant has from 0 to 4 further changes compared to the amino acid sequence of DOM7h-14.

12. The variant of claim 11, wherein the variant comprises an amino acid sequence that is identical to the amino acid sequence of DOM7h-14-19 (SEQ ID NO: 3) or has up to 4 changes compared to the amino acid sequence of DOM7h-14-19, wherein the variant comprises a Ser at position 22 and a Glu at position 42 (numbering according to Kabat) compared to DOM7h-14.

13. The variant or binding moiety of any preceding claim, wherein the variant or binding moiety comprises a binding site that specifically binds human SA with a dissociation constant (KD) of from about 0.1 to about 10000 nM, optionally from about 1 to about 6000 nM, as determined by surface plasmon resonance.

14. The variant or binding moiety of any preceding claim, wherein the variant or binding moiety comprises a binding site that specifically binds human SA with an off-rate constant (K_d) of from about 1.5×10^{-4} to about 0.1 sec^{-1}, optionally from about 3×10^{-4} to about 0.1 sec^{-1} as determined by surface plasmon resonance.

15. The variant or binding moiety of any preceding claim, wherein the variant or binding moiety comprises a binding site that specifically binds human SA with an on-rate constant (K_a) of from about 2×10^6 to about 1×10^4 $M^{-1}sec^{-1}$, optionally from about 1×10^6 to about 2×10^4 $M^{-1}sec^{-1}$ as determined by surface plasmon resonance.

16. The variant or binding moiety of any preceding claim, wherein the variant or binding moiety comprises a binding site that specifically binds *Cynomolgus* monkey SA with a dissociation constant (KD) of from about 0.1 to about 10000 nM, optionally from about 1 to about 6000 nM, as determined by surface plasmon resonance.

17. The variant or binding moiety of any preceding claim, wherein the variant or binding moiety comprises a binding site that specifically binds *Cynomolgus*

monkey SA with an off-rate constant (K_d) of from about 1.5 x 10^{-4} to about 0.1 sec^{-1} , optionally from about 3 x 10^{-4} to about 0.1 sec^{-1} as determined by surface plasmon resonance.

18. The variant or binding moiety of any preceding claim, wherein the variant or binding moiety comprises a binding site that specifically binds *Cynomolgus* monkey SA with an on-rate constant (K_a) of from about 2 x 10^6 to about 1 x 10^4 $M^{-1}sec^{-1}$, optionally from about 1 x 10^6 to about 5 x 10^3 $M^{-1}sec^{-1}$ as determined by surface plasmon resonance.

19. A multispecific ligand comprising an anti-SA variant or binding moiety of any preceding claim and a binding moiety that specifically binds a target antigen other than SA.

20. An anti-SA variant single variable domain or moiety of any one of claims 1 to 18, wherein the variable domain or moiety is conjugated to a drug (optionally an NCE drug), optionally wherein the variable domain or moiety is DOM7h-14-10 (SEQ ID NO: 1).

21. A fusion protein comprising a polypeptide or peptide drug fused to a variant or moiety according to any one of claims 1 to 18, optionally wherein the variant or moiety is DOM7h-14-10 (SEQ ID NO: 1).

22. A composition comprising a variant, moiety, fusion protein or ligand of any preceding claim and a pharmaceutically acceptable diluent, carrier, excipient or vehicle.

23. A nucleic acid comprising a nucleotide sequence encoding a variant or moiety according to any one of claims 1 to 18 or a multispecific ligand of claim 20 or

fusion protein of claim 21.

24. A nucleic acid comprising the nucleotide sequence of a DOM7h-14 variant selected from the nucleotide sequence of DOM7h-14-10 (SEQ ID NO: 1), DOM7h-14-18 (SEQ ID NO: 2), DOM7h-14-28 (SEQ ID NO: 4), DOM7h-14-36 (SEQ ID NO: 5) or DOM7h-14-19 (SEQ ID NO: 3) or a nucleotide sequence that is at least 80% identical to said selected sequence.

25. A vector comprising the nucleic acid of claim 23 or 24.

26. An isolated host cell comprising the vector of claim 25.

27. A method of treating or preventing a disease or disorder in a patient, comprising administering at least one dose of a variant or moiety according to any one of claims 1 to 18 to said patient.

DOM7h-14-18	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-36	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	85	'	'	'	'	90	'	'	'	'	95	'	'	'	'	100
DOM7h-14	E	D	F	A	T	Y	Y	C	**A**	**Q**	**G**	**A**	**A**	**L**	**P**	**R**	**T**	F	G	Q
DOM7h-14-10	.	.	.	.	.	.	.	.	.	.	.	**L**	**R**	**H**	.	**K**	.	.	.	.
DOM7h-14-18	.	.	.	.	.	.	.	.	.	.	.	**L**	**M**	**K**	.	**M**	.	.	.	.
DOM7h-14-19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**K**	.	.	.	.
DOM7h-14-36	.	.	.	.	.	.	.	.	.	.	.	**F**	**K**	**K**	.	.	.	.	.	.

Kabat Residue	'	'	'	'	105	'	'	'
DOM7h-14	G	T	K	V	E	I	K	R
DOM7h-14-10	.	.	.	.	.	.	.	.
DOM7h-14-18	.	.	.	.	.	.	.	.
DOM7h-14-19	.	.	.	.	.	.	.	.
DOM7h-14-28	.	.	.	.	.	.	.	.
DOM7h-14-36	.	.	.	.	.	.	.	.

Figure 1B

human	kinetics based on DOM7h-14 and DOM7h-11 lineage (ranges supported by data)		
	overall range		
	KD: 1 to 10000		
	Kd:1.5e-4 to 0.1 ; Ka:2e6 to 1e4		
therapeutic ranges	chronic	intermediate	acute
	high affinity	medium affinity	low affinity
	KD: 0.1-400	KD: 400-2000	KD: 2000-10000
	Kd:1.5e-4 to 8e-3 ; Ka:1e6 to 5e4	Kd: 8e-3 to 0.08 ; Ka: 2e4 to 5e4	Kd:0.08 to 0.1 ; Ka: 5e4 to 1e4
optional ranges	KD: 1-200	KD: 400-1500	KD: 2000-6000
	Kd:3e-4 to 2e-3; Ka: 1e6 to 5e4	Kd:8e-3 to 0.08; Ka: 2e4 to 6e4	Kd:0.08 to 0.1 ; Ka: 5e4 to 2e4
Examples	DOM7h-11-15, DOM7h-14, DOM7h-14-10, DOM7h-14-18, DOM7h-14-19, DOM7h-11-18, DOM7h-11-19 DMS7321, DMS7322; DMS7324, DMS7327	DMS7325, DMS7326; DMS7323	DOM7h-11

Figure 2A

Cyno				
		overall range		
		KD: 1 to 10000		
		Kd:1.5e-4 to 0.1 ; Ka:2e6 to 1e4		
therapeutic ranges	chronic	intermediate	acute	
	high affinity	medium affinity	low affinity	
	KD: 0.1-400	KD: 400-2000	KD: 2000-10000	
	Kd:1.5e-4 to 8e-3 ; Ka:2e6 to 2e4	Kd: 8e-3 to 0.08 ; Ka: 2e4 to 5e4	Kd:0.08 to 0.1 ; Ka: 5e4 to 1e4	
optional ranges	KD: 1-200	KD: 400-1500	KD: 2000-6000	
	Kd:3e-4 to 2e-3; Ka: 1e6 to 1e4	Kd:2e-3 to 0.05; Ka: 2e4 to 1e4	Kd:0.08 to 0.1 ; Ka: 5e4 to 2e4	
Examples	DMS7327; DOM7h-11-15; DOM7h-14; DOM7h-14-10; DOM7h-14-18; DOM7h-14-19, DOM7h-14-28, DOM7h-14-36 DMS7321; DMS7322	DOM7h-11; DMS7326; DMS7324;	DOM7h11-12, DOM7h-11-18 DMS7325	

Figure 2B

Rat			
	overall range		
	KD: 1 to 10000		
	Kd: 2e-3 to 0.15 ; Ka: 2e6 to 1e4		
therapeutic ranges	chronic	intermediate	acute
	high affinity	medium affinity	low affinity
	KD: 1-300	KD: 300-2000	KD: 2000-10000
	Kd:2e-3 to 5e-2 ; Ka:2e6 to 2e5	Kd:5e-2 to 0.09 ; Ka:2e5 to 4.5e4	Kd:0.09 to 0.15 ; Ka: 4.5e4 to 1.5e4
optional ranges	KD: 20-200	KD: 400-1800	KD: 2000-6000
	Kd:9e-3 to 2e-2 ; Ka: 1e6 to 1e5	Kd: 4e-2 to 0.09; Ka:1e5 to 5e4	Kd: 0.1 to 0.14 ; Ka: 5e4 to 3e4
Examples	DOM7h-11-15; DOM7h-11-12; DOM7h-11-18, DOM7h-11-19, DOM7h-14-28, DOM7h-14-36, DOM7h-14 DMS7327; DMS7322	DOM7h-14-18; DOM7h-14-19; DMS7321; DMS7323, DMS7324, DMS7326;,	DMS7325; DOM7h-11;

Figure 2C

Mouse			
	overall range		
	KD: 1 to 10000		
	Kd: 2e-3 to 0.15 ; Ka: 2e6 to 1e4		
therapeutic ranges	chronic	intermediate	acute
	high affinity	medium affinity	low affinity
	KD: 1-100	KD: 100-2000	KD: 2000-10000
	Kd:2e-3 to 1e-2 ; Ka:2e6 to 1e5	Kd:1e-2 to 0.07 ; Ka: 1e5 to 3e4	Kd: 0.08 to 0.15; Ka: 4e4 to 1.5e4
optional ranges	KD: 1 to 80	KD: 120-2000	KD: 4000-10000
	Kd:2e-3 to 1e-2 ; Ka: 2e6 to 1.5e5	Kd: 9e-3 to 0.07 ; Ka: 1.3e5 to 3e4	Kd:0.1 to 0.15 ; Ka: 2.5e4 to 1.5e4
Examples	DOM7h-11-15;; DOM7h-14; DOM7h-14-10, DOM7h-14-18, DOM7h-14-19, DOM7h-11-18, DOM7h-11-19, DOM7h-14-28, DOM7h-14-36 DMS7322, DMS7327	DMS7321; DMS7323; DMS7324; DOM7h-11-12; DMS7326	DMS7325; DOM7h-11

Figure 2D

DB63557 WO - Sequence Listing

SEQUENCE LISTING

<110> Elena DE ANGELIS
Carolyn ENEVER
Haiqun LIU
Oliver SCHON

<120> IMPROVED ANTI-SERUM ALBUMIN BINDING VARIANTS

<130> DB63557 WO

<140> PCT/EP2010/052007
<141> 2010-02-17

<150> 61/153746
<151> 2009-02-19

<150> 61/163990
<151> 2010-03-27

<160> 10

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 1

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5				10						15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Trp	Ile	Gly	Ser	Gln
			20					25					30		
Leu	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35					40					45			
Met	Trp	Arg	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Ala	Gln	Gly	Leu	Arg	His	Pro	Lys
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg				
			100					105							

<210> 2
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 2

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5				10						15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Trp	Ile	Gly	Ser	Gln
			20					25					30		
Leu	Ser	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35					40					45			
Met	Trp	Arg	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Ala	Gln	Gly	Leu	Met	Lys	Pro	Met
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg				
			100					105							

<210> 3
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 3
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln
            20   25   30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Glu Ala Pro Lys Leu Leu Ile
        35   40   45
Met Trp Arg Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Gly Ala Ala Leu Pro Arg
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100   105

<210> 4
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 4
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln
            20   25   30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Met Trp Arg Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Gly Ala Ala Leu Pro Lys
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100   105

<210> 5
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 5
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln
            20   25   30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Met Trp Arg Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Gly Phe Lys Lys Pro Arg
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100   105

<210> 6
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 6
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gggcaagtca gtggattggg tctcagttat cttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatcatgtgg cgttcctcgt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgtgctcag ggttttgaggc atcctaagac gttcggccaa 300
gggaccaagg tggaaatcaa acgg 324

<210> 7
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 7
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gggcaagtca gtggattggg tctcagttat cttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatcatgtgg cgttcctcgt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgtgctcag ggtcttatga agcctatgac gttcggccaa 300
gggaccaagg tggaaatcaa acgg 324

<210> 8
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 8
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcttttgcc gggcaagtca gtggattggg tctcagttat cttggtacca gcagaaacca 120
ggggaagccc ctaagctcct gatcatgtgg cgttcctcgt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgtgctcag ggtgcggcgt tgcctaggac gttcggccaa 300
gggaccaagg tggaaatcaa acgg 324

<210> 9
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 9
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gggcaagtca gtggattggg tctcagttat cttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatcatgtgg cgttcctcgt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacatacta ctgtgctcag ggtgcggcgt tgcctaagac gttcggccaa 300
gggaccaagg tggaaatcaa acgg 324

<210> 10
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 10
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60

atcacttgcc gggcaagtca gtggattggg tctcagttat cttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatcatgtgg cgttcctcgt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgtgctcag ggttttaaga agcctcggac gttcggccaa 300
gggaccaagg tggaaatcaa acgg 324

<210> 11
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 11
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gln Tyr
20 25 30
Arg Met His Trp Val Arg Gln Ala Pro Gly Lys Ser Leu Glu Trp Val
35 40 45
Ser Ser Ile Asp Thr Arg Gly Ser Ser Thr Tyr Tyr Ala Asp Pro Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Ala Val Thr Met Phe Ser Pro Phe Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 12
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 12
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ala Asp Tyr
20 25 30
Gly Met Arg Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ser Ile Thr Arg Thr Gly Arg Val Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Trp Arg Asn Arg His Gly Glu Tyr Leu Ala Asp Phe Asp Tyr
100 105 110
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 13
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 13
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Met Arg Tyr
20 25 30
Arg Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35 40 45
Ser Ser Ile Asp Ser Asn Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Asp Arg Thr Glu Arg Ser Pro Val Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 14
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 14
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Asp Tyr
20 25 30
Glu Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ser Ile Ser Glu Ser Gly Thr Thr Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Arg Arg Phe Ser Ala Ser Thr Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 15
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 15
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Tyr Thr Gly His Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 16
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 16
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Tyr Thr Gly Arg Trp Glu Pro Tyr Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 17
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 17
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 18
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 18
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 19
<211> 119

<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 19
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 20
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 20
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Met Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 21
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 21
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Gly Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Asp Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
115

<210> 22
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 22
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Tyr Thr Gly Arg Trp Glu Pro Phe Asp His Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 23
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 23
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp His Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 24
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 24
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 25
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 25
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 26
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 26
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp His Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 27
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 27
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 28
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 28

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asn Thr Gly Asp His Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 29
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 29

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Gly Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Asp Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 30
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 30
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Gly Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Asp Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp His Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 31
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 31
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 32
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 32
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 33
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 33
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Lys Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 34
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 34
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 35
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 35
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 36
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 36
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 37
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 37
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asn Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 38
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 38
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 39
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 39
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Ser Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Asp Asn Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 40
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 40
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ile Thr Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Gln Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 41
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 41
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Gly Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 42
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 42
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 43
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 43
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 44
<211> 119

<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 44
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 45
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 45
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Lys Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 46
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 46
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Glu Arg Arg Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
115

<210> 47
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 47
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Asn Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Tyr Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Thr Ser
115

<210> 48
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 48
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 49
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 49
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Lys Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 50
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 50
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 51
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 51
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 52
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 52
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 53
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 53
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Val Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 54
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 54
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Lys Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 55
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 55
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 56
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 56
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 57
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 57
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 58
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 58
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 59
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 59
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Lys Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 60
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 60
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

```
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 61
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 61

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 62
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 62

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 63
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 63

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
```

35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ala Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 64
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 64
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ala Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Lys Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 65
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 65
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ala Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 66
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 66
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 67
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 67
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 68
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 68
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Phe
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 69
<211> 119

<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 69
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 70
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 70
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 71
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 71
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
        115

<210> 72
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 72
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Pro Asp Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 73
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 73
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Pro Asp Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 74
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 74
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Pro Asp Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 75
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 75
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Pro Asp Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 76
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 76
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Pro Asp Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 77
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 77
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Pro Asp Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 78
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 78
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
35 40 45
Ser Gln Ile Ser Ala Trp Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 79
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 79
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Gly Gly Gln Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 80
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 80
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Ser Gly Tyr Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 81
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 81
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Gly Gly Thr Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 82
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 82
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Lys Gly Thr Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 83
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 83
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35   40   45
Ser Gln Ile Ser Glu Thr Gly Arg Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 84
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 84
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Asn Asn Thr Gly Ser Thr Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 85
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 85
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 86
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 86
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 87
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 87
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 88
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 88
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

```
        35                  40                  45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 89
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 89

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 90
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 90

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Thr His Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 91
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 91
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Arg Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 92
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 92
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Leu Asn Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 93
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 93
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 94
<211> 119

<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 94
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Arg Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 95
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 95
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Arg Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 96
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 96
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Val Tyr Thr Gly Arg Trp Val Ser Phe Glu Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
115

<210> 97
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 97
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Leu Tyr Thr Gly Arg Trp Val Ser Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 98
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 98
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Val Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 99
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 99
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Leu Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 100
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 100
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asn Thr Ala Asp Arg Arg Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 101
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 101
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Arg Tyr Tyr Ala Asp Ala Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 102
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 102
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Arg Tyr Tyr Ala His Ala Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 103
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 103
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asn Thr Ala Asp Arg Arg Tyr Tyr Ala Asp Ala Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 104
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 104
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala His Ala Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 105
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 105
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Arg Tyr Tyr Ala His Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 106
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 106
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asn Thr Ala Asp Arg Arg Tyr Tyr Ala His Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 107
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 107
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Val Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 108
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 108
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 109
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 109
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 110
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 110
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

```
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 111
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 111

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 112
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 112

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ser His Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 113
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 113

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
```

35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Thr His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 114
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 114
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Thr Asp Ala Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 115
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 115
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 116
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 116
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 117
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 117
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 118
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 118
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 119
<211> 119

<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 119
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 120
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 120
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 121
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 121
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
115

<210> 122
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 122
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asp Thr Gly Asp Arg Arg Tyr Tyr Asp His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 123
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 123
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ala Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 124
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 124
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Gly Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 125
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 125
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Ala Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 126
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 126
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Gly Pro Phe Gln Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 127
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 127
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Gln Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 128
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 128
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 129
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 129
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Gln Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 130
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 130
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Gln Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 131
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 131
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 132
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 132
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 133
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 133
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 134
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 134
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 135
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 135
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 136
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 136
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 137
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 137
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 138
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 138
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

```
        35                  40                  45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ser His Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 139
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 139

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ser His Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 140
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 140

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Thr His Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 141
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 141
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Thr His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 142
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 142
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 143
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 143
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 144
<211> 119

<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 144
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 145
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 145
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 146
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 146
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
115

<210> 147
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 147
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 148
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 148
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ala Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 149
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 149
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Arg Tyr Tyr Ala His Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 150
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 150
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Arg Tyr Tyr Ala His Ala Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 151
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 151
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Arg Tyr Tyr Ala His Ala Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 152
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 152
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Arg Tyr Tyr Asp His Ala Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 153
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 153

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Arg Tyr Tyr Asp His Ala Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 154
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 154

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Arg Tyr Tyr Asp His Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115
```

<210> 155
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 155
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Arg Tyr Tyr Asp Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Thr Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 156
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 156
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 157
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 157
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Tyr Thr Gly Arg Trp Glu Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 158
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 158
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 159
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 159
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttatg aggtatagga tgcattgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcatcg attgattcta atggttctag tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaagatcgt 300
acggagcgtt cgccggtttt tgactactgg ggtcagggaa ccctggtcac cgtctcgagc 360

<210> 160
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 160
gaggtgcagc tgttggagtc tgggggaggc ttggtgcagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt gattatgaga tgcattgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcatct attagtgaga gtggtacgac gacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaacgtcgt 300
ttttctgctt ctacgtttga ctactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 161
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 161
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 300

ggtcattggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 162
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 162
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 300
ggtcgttggg agccttatga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 163
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 163
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 300
ggtcgttggg agcctttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 164
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 164
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 300
ggtcgttggg agcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 165
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 165
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 166
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 166

gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 167
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 167
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tgggatgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttga ctactggggt cagggaaccc tggtcacagt ctcgagc 357

<210> 168
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 168
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccata tcccgcgaca attccaagaa cacgctgtat 240
atgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 169
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 169
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttggt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg atctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 170
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 170
gaggtgcagc tgttggagtc aggggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 300
ggtcgttggg agcctttga ccactggggt cagggggaccc tggtcaccgt ctcgagc 357

<210> 171
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 171
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 172
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 172
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 173
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 173
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 174
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 174
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 175
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 175
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tgggatgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcacagt ctcgagc 357

<210> 176
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 176
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tgggatgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcgaata cgggtgatca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttga ctactggggt cagggaaccc tggtcacagt ctcgagc 357

<210> 177
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 177
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttggt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg atctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 178
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 178
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttggt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg atctagagtg ggtctcacag atttcgaata cgggtgatca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 179
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 179
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 180
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 180
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60

tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 181
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 181
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcggactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga agccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 182
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 182
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 183
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 183
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 184
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 184
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggcat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 185
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 185
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttaa ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 186
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 186
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 187
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 187
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa ctcgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg tgcctttga caactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 188
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 188
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttatt acgtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttca gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 189
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 189
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttggt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcggactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 190
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 190
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaagac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 191
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 191
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 192
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 192
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 193
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 193
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttaa gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 194
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 194
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttagt aagtattcga tggggtgggt ccgccaggct 120

ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgagcg tagatactac 180
gcagactcag tgaagggccg gttcaccatc tcccgcgaca atcccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg agcctttga atactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 195
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 195
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aactattcga tgggggtggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcggactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttatga gtactggggt cagggaaccc tggtcaccgt cacgagc 357

<210> 196
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 196
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tgggggtggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgata attccaagaa cacactgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 197
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 197
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tgggggtggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga agccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 198
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 198
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tgggggtggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 199
<211> 357
<212> DNA
<213> Artificial Sequence

<220>

<223> Derived from a Human Germline sequence.

<400> 199
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 200
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 200
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 201
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 201
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc ggtatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 202
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 202
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga agccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 203
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 203
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 204

<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 204
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 205
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 205
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 206
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 206
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 207
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 207
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggcc 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga agcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 208
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 208
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180

gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 209
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 209
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 210
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 210
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 211
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 211
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 212
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 212
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga agcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 213
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 213
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttTGTT aagtattcga tggggtgggt ccgccaggcc 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaagac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgcctttTGA gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 214
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 214
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttTGTT aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggccttttGA gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 215
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 215
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttTGTT aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttGA gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 216
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 216
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttTTTG aagttttcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttGA gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 217
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 217
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttTTTG aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttGA gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 218
<211> 357

<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 218
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 219
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 219
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttg aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 220
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 220
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggcat attactgtgc gatatatacg 300
ggtcggtggc ccgactttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 221
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 221
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggcat attactgtgc gatatatacg 300
ggtcggtggc ccgactttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 222
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 222
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggc ccgactttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 223
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 223
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggc ccgactttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 224
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 224
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggc ccgactttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 225
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 225
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggc ccgactttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 226
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 226
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tgggatgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcggcct ggggtgacag gacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 227
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 227
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcggacg gcggtcagag gacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 228
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 228
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tgggatgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcggact ccggttaccg cacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 229
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 229
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtccagagtg ggtctcacag atttcggacg ggggtacgcg gacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 230
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 230
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tgggatgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcggaca agggtacgcg cacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 231
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 231
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tgggatgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcggaga ccggtcgcag gacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 232
<211> 357
<212> DNA

<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 232
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attaacaata cgggttcgac cacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 233
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 233
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtccagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 234
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 234
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtccagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 235
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 235
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 236
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 236
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300

ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 237
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 237
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 238
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 238
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
acacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 239
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 239
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg cagatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 240
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 240
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attttgaata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 241
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 241

gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 242
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 242
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 243
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 243
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 244
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 244
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc ggtatatact 300
gggcgttggg tgtcttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 245
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 245
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gctatatact 300
gggcgttggg tgtcttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 246
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 246
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gtttaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc ggtatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 247
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 247
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gctatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 248
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 248
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata ctgctgatcg tagatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 249
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 249
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 250
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 250
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcgg cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggcgatcg tagatactac 180
gcacacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 251
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 251
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata ctgctgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttTGT ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 252
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 252
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcacacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttTGT ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 253
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 253
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tagatactac 180
gcacacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttTGT ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 254
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 254
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cggctgatcg tagatactac 180
gcacacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttTGT ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 255
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 255
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60

tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgtgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 256
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 256
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 257
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 257
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 258
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 258
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 259
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 259
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 260
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 260
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttTGTT aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
tcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 261
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 261
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttTGTT aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
acacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 262
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 262
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttTGTT aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
acagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttTGT ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 263
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 263
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttTTTC aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 264
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 264
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttTTTG aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 265
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 265
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 266
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 266
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 267
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 267
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgcctc 60
tcctgtgcag cctccggatt cacctttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatcactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg aacctttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 268
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 268
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 269
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 269
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttttc aagtattcga tggggtgggt ccgccaggct 120

ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 270
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 270
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata cgggtgatcg tagatactac 180
gatcactctg tgaagggccg gttcactatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 271
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 271
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata cgggtgatcg tagatactac 180
gatgacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 272
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 272
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg ggcctttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 273
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 273
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg tgcctttgc ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 274
<211> 357
<212> DNA
<213> Artificial Sequence

<220>

<223> Derived from a Human Germline sequence.

<400> 274
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg gacctttta gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 275
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 275
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttca gtactggggt cagggaactc tggtcaccgt ctcgagc 357

<210> 276
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 276
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 277
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 277
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg cgccttttca gtactggggt cagggaactc tggtcaccgt ctcgagc 357

<210> 278
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 278
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg tgcctttca gtactggggt cagggcaccc tggtcaccgt ctcgagc 357

<210> 279

<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 279
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ccggtgatcg tagatactac 180
gatcactctg tgaagggccg gttcactatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 280
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 280
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttttg aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 281
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 281
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 282
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 282
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttttg aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 283
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 283
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180

gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 284
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 284
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 285
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 285
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttg aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 286
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 286
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttg aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
tcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 287
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 287
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
tcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 288
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 288
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttttTC aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
acacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 289
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 289
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttttTG aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
acacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 290
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 290
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttttTC aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 291
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 291
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttttTG aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 292
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 292
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttttTG aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ccggtgatcg tagatactac 180
gatcactctg tgaagggccg gttcactatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 293
<211> 357

<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 293
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ccggtgatcg tagatactac 180
gatcactctg tgaagggccg gttcactatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 294
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 294
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgcgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 295
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 295
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 296
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 296
gaggtgcagc tgttggagtc tgggggaggc ttggtgcagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 297
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 297
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tacatactac 180
gatcacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 298
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 298
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 299
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 299
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180
gcacacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 300
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 300
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac 180
gcacacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 301
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 301
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180
gatcacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 302
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 302
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac 180
gatcacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt caggggaccc tggtcaccgt ctcgagc 357

<210> 303
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 303
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 304
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 304
gaggtgcagc tgctggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180
gatgacgcgg tgaagggccg gttcaccatc acccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 305
<211> 163
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 305
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1   5   10   15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20   25   30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    50   55   60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
65   70   75   80
Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln Gln Lys Pro Gly
                85   90   95
Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser Leu Gln Ser Gly
            100   105   110
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        115   120   125
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala
    130   135   140
Gln Gly Ala Ala Leu Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu
145   150   155   160
Ile Lys Arg

<210> 306
<211> 489

<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 306
catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60
ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120
ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180
cagtctccat cctccctgtc tgcatctgta ggagaccgtg tcaccatcac ttgccgggca 240
agtcagtgga ttgggtctca gttatcttgg taccagcaga aaccagggaa agccctaag 300
ctcctgatca tgtggcgttc ctcgttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg 420
tactactgtg ctcagggtgc ggcgttgcct aggacgttcg gccaagggac caaggtggaa 480
atcaaacgg 489

<210> 307
<211> 163
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 307
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1   5   10   15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20   25   30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    50   55   60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
65   70   75   80
Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln Gln Lys Pro Gly
                85   90   95
Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser Leu Gln Ser Gly
            100   105   110
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        115   120   125
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala
    130   135   140
Gln Gly Leu Arg His Pro Lys Thr Phe Gly Gln Gly Thr Lys Val Glu
145   150   155   160
Ile Lys Arg

<210> 308
<211> 489
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 308
catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60
ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120
ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180
cagtctccat cctccctgtc tgcatctgta ggagaccgtg tcaccatcac ttgccgggca 240
agtcagtgga ttgggtctca gttatcttgg taccagcaga aaccagggaa agccctaag 300
ctcctgatca tgtggcgttc ctcgttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg 420
tactactgtg ctcagggttt gaggcatcct aagacgttcg gccaagggac caaggtggaa 480
atcaaacgg 489

<210> 309
<211> 163
<212> PRT
<213> Artificial Sequence

<220>

<223> Derived from a Human Germline sequence.

<400> 309
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1   5   10   15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20   25   30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    50   55   60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
65   70   75   80
Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln Gln Lys Pro Gly
                85   90   95
Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser Leu Gln Ser Gly
            100   105   110
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        115   120   125
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala
    130   135   140
Gln Gly Leu Met Lys Pro Met Thr Phe Gly Gln Gly Thr Lys Val Glu
145   150   155   160
Ile Lys Arg

<210> 310
<211> 489
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 310
catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60
ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120
ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180
cagtctccat cctccctgtc tgcatctgta ggagaccgtg tcaccatcac ttgccgggca 240
agtcagtgga ttgggtctca gttatcttgg taccagcaga aaccagggaa agcccctaag 300
ctcctgatca tgtggcgttc ctcgttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg 420
tactactgtg ctcagggtct tatgaagcct atgacgttcg gccaagggac caaggtggaa 480
atcaaacgg   489

<210> 311
<211> 163
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 311
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1   5   10   15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20   25   30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    50   55   60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Ser Cys Arg Ala
65   70   75   80
Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln Gln Lys Pro Gly
                85   90   95
Glu Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser Leu Gln Ser Gly
            100   105   110
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        115   120   125
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala
    130   135   140
Gln Gly Ala Ala Leu Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu
145   150   155   160

Ile Lys Arg

<210> 312
<211> 489
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 312
catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60
ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120
ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180
cagtctccat cctccctgtc tgcatctgta ggagaccgtg tcaccatctc ttgccgggca 240
agtcagtgga ttgggtctca gttatcttgg taccagcaga aaccagggga agccccctaag 300
ctcctgatca tgtggcgttc ctcgttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg 420
tactactgtg ctcagggtgc ggcgttgcct aggacgttcg gccaagggac caaggtggaa 480
atcaaacgg 489

<210> 313
<211> 163
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 313
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1   5   10   15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20   25   30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    50   55   60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
65   70   75   80
Ser Arg Pro Ile Gly Thr Thr Leu Ser Trp Tyr Gln Gln Lys Pro Gly
                85   90   95
Lys Ala Pro Lys Leu Leu Ile Trp Phe Gly Ser Arg Leu Gln Ser Gly
            100   105   110
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        115   120   125
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala
    130   135   140
Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly Thr Lys Val Glu
145   150   155   160
Ile Lys Arg

<210> 314
<211> 489
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 314
catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60
ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120
ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180
cagtctccat cctccctgtc tgcatctgta ggagaccgtg tcaccatcac ttgccgggca 240
agtcgtccga ttgggacgac gttaagttgg taccagcaga aaccagggaa agccccctaag 300
ctcctgatct ggttttggttc ccggttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg 420
tactactgtg cgcaggctgg gacgcatcct acgacgttcg gccaagggac caaggtggaa 480
atcaaacgg 489

<210> 315
<211> 163
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 315
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1   5   10   15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20   25   30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    50   55   60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
65   70   75   80
Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln Gln Lys Pro Gly
                85   90   95
Lys Ala Pro Lys Leu Leu Ile Leu Phe Gly Ser Arg Leu Gln Ser Gly
            100   105   110
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        115   120   125
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala
    130   135   140
Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly Thr Lys Val Glu
145   150   155   160
Ile Lys Arg

<210> 316
<211> 489
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 316
catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60
ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120
ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180
cagtctccat cctccctgtc tgcatctgta ggagaccgtg tcaccatcac ttgccgggca 240
agtcgtccga ttgggacgat gttaagttgg taccagcaga aaccagggaa agcccctaag 300
ctcctgatct tgtttggttc ccggttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg 420
tactactgtg cgcaggctgg gacgcatcct acgacgttcg gccaagggac caaggtggaa 480
atcaaacgg 489

<210> 317
<211> 163
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 317
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1   5   10   15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20   25   30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    50   55   60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
65   70   75   80
Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln Gln Lys Pro Gly
                85   90   95
Lys Ala Pro Lys Leu Leu Ile Leu Ala Phe Ser Arg Leu Gln Ser Gly
            100   105   110

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
115 120 125
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala
130 135 140
Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly Thr Lys Val Glu
145 150 155 160
Ile Lys Arg

<210> 318
<211> 489
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 318
catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60
ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120
ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180
cagtctccat cctccctgtc tgcatctgta ggagaccgtg tcaccatcac ttgccgggca 240
agtcgtccga ttgggacgat gttaagttgg taccagcaga aaccagggaa agcccctaag 300
ctcctgatcc ttgcttttc ccgtttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg 420
tactactgcg cgcaggctgg gacgcatcct acgacgttcg gccaagggac caaggtggaa 480
atcaaacgg 489

<210> 319
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 319
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln
20 25 30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Met Trp Arg Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Gly Leu Arg His Pro Lys
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Gly Gly Gly Gly
100 105 110
Ser Cys

<210> 320
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 320
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gggcaagtca gtggattggg tctcagttat cttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatcatgtgg cgttcctcgt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgtgctcag ggtttgaggc atcctaagac gttcggccaa 300
gggaccaagg tggaaatcaa acggggtggc ggaggggggtt cctgt 345

<210> 321
<211> 115
<212> PRT

<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 321
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln
            20   25   30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Met Trp Arg Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Gly Leu Arg His Pro Lys
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100   105   110
Pro Ser Cys
        115

<210> 322
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 322
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gggcaagtca gtggattggg tctcagttat cttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatcatgtgg cgttcctcgt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgtgctcag ggtttgaggc atcctaagac gttcggccaa 300
gggaccaagg tggaaatcaa acggaccgtc gctgctccat cttgt   345

<210> 323
<211> 235
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 323
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
            20   25   30
Ser Met Gly Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Arg Ile Asp Ser Tyr Gly Arg Gly Thr Tyr Tyr Glu Asp Pro Val
    50   55   60
Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Ile Ser Gln Phe Gly Ser Asn Ala Phe Asp Tyr Trp Gly Gln
            100   105   110
Gly Thr Gln Val Thr Val Ser Ser Ala Ser Thr Ser Gly Pro Ser Asp
        115   120   125
Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
    130   135   140
Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Thr Leu
145   150   155   160
Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Trp
                165   170   175
Phe Gly Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
            180   185   190
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
        195   200   205

Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr
210 215 220
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
225 230 235

<210> 324
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 324
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
20 25 30
Ser Met Gly Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Arg Ile Asp Ser Tyr Gly Arg Gly Thr Tyr Tyr Glu Asp Pro Val
50 55 60
Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Ile Ser Gln Phe Gly Ser Asn Ala Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Gln Val Thr Val Ser Ser Ala Ser Thr Ser Gly Pro Ser Asp
115 120 125
Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
130 135 140
Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Thr Leu
145 150 155 160
Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Trp
165 170 175
Phe Gly Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
180 185 190
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
195 200 205
Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr
210 215 220
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln
225 230 235 240
Lys Leu Ile Ser Glu Glu Asp Leu Asn
245

<210> 325
<211> 705
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 325
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttaat aggtatagta tgggtggct ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacgg attgattctt atggtcgtgg tacatactac 180
gaagaccccg tgaagggccg gttcagcatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgccgtat attactgtgc gaaaatttct 300
cagtttgggt caaatgcgtt tgactactgg ggtcagggaa cccaggtcac cgtctcgagc 360
gctagcacca gtggtccatc ggacatccag atgacccagt ctccatcctc cctgtctgca 420
tctgtaggag accgtgtcac catcacttgc cgggcaagtc gtccgattgg gacgacgtta 480
agttggtacc agcagaaacc agggaaagcc cctaagctcc tgatctggtt tggttcccgg 540
ttgcaaagtg gggtcccatc acgtttcagt ggcagtggat ctgggacaga tttcactctc 600
accatcagca gtctgcaacc tgaagatttt gctacgtact actgtgcgca ggctgggacg 660
catcctacga cgttcggcca agggaccaag gtggaaatca aacgg 705

<210> 326
<211> 750
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 326
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttaat aggtatagta tggggtggct ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacgg attgattctt atggtcgtgg tacatactac 180
gaagaccccg tgaagggccg gttcagcatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgccgtat attactgtgc gaaaatttct 300
cagtttgggt caaatgcgtt tgactactgg ggtcagggaa cccaggtcac cgtctcgagc 360
gctagcacca gtggtccatc ggacatccag atgacccagt ctccatcctc cctgtctgca 420
tctgtaggag accgtgtcac catcacttgc cgggcaagtc gtccgattgg gacgacgtta 480
agttggtacc agcagaaacc agggaaagcc cctaagctcc tgatctggtt tggttcccgg 540
ttgcaaagtg gggtcccatc acgtttcagt ggcagtggat ctgggacaga tttcactctc 600
accatcagca gtctgcaacc tgaagatttt gctacgtact actgtgcgca ggctgggacg 660
catcctacga cgttcggcca agggaccaag gtggaaatca aacgggcggc cgcagaacaa 720
aaactcatct cagaagagga tctgaattaa 750

<210> 327
<211> 235
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 327
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
            20   25   30
Ser Met Gly Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Arg Ile Asp Ser Tyr Gly Arg Gly Thr Tyr Tyr Glu Asp Pro Val
    50   55   60
Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Ile Ser Gln Phe Gly Ser Asn Ala Phe Asp Tyr Trp Gly Gln
            100   105   110
Gly Thr Gln Val Thr Val Ser Ser Ala Ser Thr Ser Gly Pro Ser Asp
        115   120   125
Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
    130   135   140
Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu
145   150   155   160
Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu
                165   170   175
Phe Gly Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
            180   185   190
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
        195   200   205
Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr
    210   215   220
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
225   230   235

<210> 328
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 328
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
            20   25   30
Ser Met Gly Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ser Arg Ile Asp Ser Tyr Gly Arg Gly Thr Tyr Tyr Glu Asp Pro Val
50 55 60
Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Ile Ser Gln Phe Gly Ser Asn Ala Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Gln Val Thr Val Ser Ser Ala Ser Thr Ser Gly Pro Ser Asp
115 120 125
Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
130 135 140
Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu
145 150 155 160
Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu
165 170 175
Phe Gly Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
180 185 190
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
195 200 205
Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr
210 215 220
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln
225 230 235 240
Lys Leu Ile Ser Glu Glu Asp Leu Asn
245

<210> 329
<211> 705
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 329
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttaat aggtatagta tggggtggct ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacgg attgattctt atggtcgtgg tacatactac 180
gaagaccccg tgaagggccg gttcagcatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgccgtat attactgtgc gaaaatttct 300
cagtttgggt caaatgcgtt tgactactgg ggtcagggaa cccaggtcac cgtctcgagc 360
gctagcacca gtggtccatc ggacatccag atgacccagt ctccatcctc cctgtctgca 420
tctgtaggag accgtgtcac catcacttgc cgggcaagtc gtccgattgg gacgatgtta 480
agttggtacc agcagaaacc agggaaagcc cctaagctcc tgatcttgtt tggttcccgg 540
ttgcaaagtg gggtcccatc acgtttcagt ggcagtggat ctgggacaga tttcactctc 600
accatcagca gtctgcaacc tgaagatttt gctacgtact actgtgcgca ggctgggacg 660
catcctacga cgttcggcca agggaccaag gtggaaatca aacgg 705

<210> 330
<211> 750
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 330
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt cacctttaat aggtatagta tggggtggct ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacgg attgattctt atggtcgtgg tacatactac 180
gaagaccccg tgaagggccg gttcagcatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgccgtat attactgtgc gaaaatttct 300
cagtttgggt caaatgcgtt tgactactgg ggtcagggaa cccaggtcac cgtctcgagc 360
gctagcacca gtggtccatc ggacatccag atgacccagt ctccatcctc cctgtctgca 420
tctgtaggag accgtgtcac catcacttgc cgggcaagtc gtccgattgg gacgatgtta 480
agttggtacc agcagaaacc agggaaagcc cctaagctcc tgatcttgtt tggttcccgg 540
ttgcaaagtg gggtcccatc acgtttcagt ggcagtggat ctgggacaga tttcactctc 600
accatcagca gtctgcaacc tgaagatttt gctacgtact actgtgcgca ggctgggacg 660
catcctacga cgttcggcca agggaccaag gtggaaatca aacgggcggc cgcagaacaa 720
aaactcatct cagaagagga tctgaattaa 750

<210> 331
<211> 235

<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 331
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
            20   25   30
Ser Met Gly Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Arg Ile Asp Ser Tyr Gly Arg Gly Thr Tyr Tyr Glu Asp Pro Val
    50   55   60
Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Ile Ser Gln Phe Gly Ser Asn Ala Phe Asp Tyr Trp Gly Gln
            100   105   110
Gly Thr Gln Val Thr Val Ser Ser Ala Ser Thr Ser Gly Pro Ser Asp
        115   120   125
Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
    130   135   140
Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu
145   150   155   160
Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu
                165   170   175
Ala Phe Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
            180   185   190
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
        195   200   205
Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr
    210   215   220
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
225   230   235

<210> 332
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 332
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
            20   25   30
Ser Met Gly Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Arg Ile Asp Ser Tyr Gly Arg Gly Thr Tyr Tyr Glu Asp Pro Val
    50   55   60
Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Ile Ser Gln Phe Gly Ser Asn Ala Phe Asp Tyr Trp Gly Gln
            100   105   110
Gly Thr Gln Val Thr Val Ser Ser Ala Ser Thr Ser Gly Pro Ser Asp
        115   120   125
Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
    130   135   140
Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu
145   150   155   160
Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu
                165   170   175
Ala Phe Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
            180   185   190
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
        195   200   205
Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr

210 215 220
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln
225 230 235 240
Lys Leu Ile Ser Glu Glu Asp Leu Asn
245

<210> 333
<211> 705
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 333
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttTAAT aggtatagta tgggGTGGCT ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacgg attgattctt atggtcgtgg tacatactac 180
gaagacccCG tgaagggccg gttcagcatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgccgtat attactgtgc gaaaatttct 300
cagtttgggt caaatgcgtt tgactactgg ggtcagggaa cccaggtcac cgtctcgagc 360
gctagcacca gtggtccatc ggacatccag atgacccagt ctccatcctc cctgtctgca 420
tctgtaggag accgtgtcac catcacttgc cgggcaagtc gtccgattgg gacgatgtta 480
agttggtacc agcagaaacc agggaaagcc cctaagctcc tgatccttgc tttttcccgt 540
ttgcaaagtg gggtcccatc acgtttcagt ggcagtggat ctgggacaga tttcactctc 600
accatcagca gtctgcaacc tgaagatttt gctacgtact actgcgcgca ggctgggacg 660
catcctacga cgttcggcca agggaccaag gtggaaatca aacgg 705

<210> 334
<211> 750
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 334
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttTAAT aggtatagta tgggGTGGCT ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacgg attgattctt atggtcgtgg tacatactac 180
gaagacccCG tgaagggccg gttcagcatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgccgtat attactgtgc gaaaatttct 300
cagtttgggt caaatgcgtt tgactactgg ggtcagggaa cccaggtcac cgtctcgagc 360
gctagcacca gtggtccatc ggacatccag atgacccagt ctccatcctc cctgtctgca 420
tctgtaggag accgtgtcac catcacttgc cgggcaagtc gtccgattgg gacgatgtta 480
agttggtacc agcagaaacc agggaaagcc cctaagctcc tgatccttgc tttttcccgt 540
ttgcaaagtg gggtcccatc acgtttcagt ggcagtggat ctgggacaga tttcactctc 600
accatcagca gtctgcaacc tgaagatttt gctacgtact actgcgcgca ggctgggacg 660
catcctacga cgttcggcca agggaccaag gtggaaatca aacgggcggc cgcagaacaa 720
aaactcatct cagaagagga tctgaattaa 750

<210> 335
<211> 9
<212> PRT
<213> Homo Sapiens

<400> 335
Ser Gln Ser Ile Ser Ser Tyr Leu Asn
1 5

<210> 336
<211> 8
<212> PRT
<213> Homo Sapiens

<400> 336
Tyr Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 337

<211> 9
<212> PRT
<213> Homo Sapiens

<400> 337
Gln Gln Ser Tyr Ser Thr Pro Asn Thr
 1   5

<210> 338
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 338
Ser Arg Pro Ile Gly Thr Thr Leu Ser
 1   5

<210> 339
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 339
Trp Phe Gly Ser Arg Leu Gln Ser
 1   5

<210> 340
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 340
Ala Gln Ala Gly Thr His Pro Thr Thr
 1   5

<210> 341
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 341
Ser Arg Pro Ile Gly Thr Met Leu Ser
 1   5

<210> 342
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 342
Leu Phe Gly Ser Arg Leu Gln Ser
 1   5

<210> 343
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 343
Ala Gln Ala Gly Thr His Pro Thr Thr
 1   5

<210> 344
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 344
Ser Arg Pro Ile Gly Thr Met Leu Ser
 1   5

<210> 345
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 345
Leu Ala Phe Ser Arg Leu Gln Ser
 1   5

<210> 346
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 346
Ala Gln Ala Gly Thr His Pro Thr Thr
 1   5

<210> 347
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 347
Ser Arg Pro Ile Gly Thr Met Leu Ser
 1   5

<210> 348
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 348
Trp Phe Gly Ser Arg Leu Gln Ser

1 5

<210> 349
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 349
Ala Gln Ala Gly Thr His Pro Thr Thr
1 5

<210> 350
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 350
Ser Arg Pro Ile Gly Thr Met Leu Ser
1 5

<210> 351
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 351
Leu Phe Gly Ser Arg Leu Gln Ser
1 5

<210> 352
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 352
Ala Gln Thr Gly Thr His Pro Thr Thr
1 5

<210> 353
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 353
Ser Arg Pro Ile Gly Thr Thr Leu Ser
1 5

<210> 354
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 354
Leu Trp Phe Ser Arg Leu Gln Ser
1 5

<210> 355
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 355
Ala Gln Ala Gly Thr His Pro Thr Thr
1 5

<210> 356
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 356
Ser Gln Trp Ile Gly Ser Gln Leu Ser
1 5

<210> 357
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 357
Met Trp Arg Ser Ser Leu Gln Ser
1 5

<210> 358
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 358
Ala Gln Gly Ala Ala Leu Pro Arg Thr
1 5

<210> 359
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 359
Ser Gln Trp Ile Gly Ser Gln Leu Ser
1 5

<210> 360
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 360
Met Trp Arg Ser Ser Leu Gln Ser
 1   5

<210> 361
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 361
Ala Gln Gly Leu Arg His Pro Lys Thr
 1   5

<210> 362
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 362
Ser Gln Trp Ile Gly Ser Gln Leu Ser
 1   5

<210> 363
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 363
Met Trp Arg Ser Ser Leu Gln Ser
 1   5

<210> 364
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 364
Ala Gln Gly Leu Met Lys Pro Met Thr
 1   5

<210> 365
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 365
Ser Gln Trp Ile Gly Ser Gln Leu Ser
 1   5

<210> 366

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

<220>
<223> Derived from a Human Germline sequence.

<400> 366
Met Trp Arg Ser Ser Leu Gln Ser
 1   5

<210> 367
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 367
Ala Gln Gly Ala Ala Leu Pro Arg Thr
 1   5

<210> 368
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 368
Ser Gln Trp Ile Gly Ser Gln Leu Ser
 1   5

<210> 369
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 369
Met Trp Arg Ser Ser Leu Gln Ser
 1   5

<210> 370
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 370
Ala Gln Gly Ala Ala Leu Pro Lys Thr
 1   5

<210> 371
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 371
Ser Gln Trp Ile Gly Ser Gln Leu Ser
 1   5

<210> 372
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 372
Met Trp Arg Ser Ser Leu Gln Ser
 1   5

<210> 373
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 373
Ala Gln Gly Phe Lys Lys Pro Arg Thr
 1   5

<210> 374
<211> 165
<212> PRT
<213> Homo Sapiens

<400> 374
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160
Leu Arg Ser Lys Glu
                165

<210> 375
<211> 495
<212> DNA
<213> Homo Sapiens

<400> 375
tgtgatctgc ctcaaaccca cagcctgggt agcaggagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360
aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480
ttaagaagta aggaa   495

<210> 376
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 376
gcccggatcc accggctgtg atctg 25

<210> 377
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 377
ggaggatgga gactgggtca tctggatgtc 30

<210> 378
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 378
gacatccaga tgacccagtc tccatcctcc 30

<210> 379
<211> 82
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 379
gcgcaagctt ttattaattc agatcctctt ctgagatgag tttttgttct gcggccgccc 60
gtttgatttc caccttggtc cc 82

<210> 380
<211> 56
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 380
gcccggatcc accggctgtg atctggcgca agcttttatt aattcagatc ctcttc 56

<210> 381
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 381
tgagatgagt ttttgttctg cggccgcccg tttgatttcc accttggtcc c 51

<210> 382
<211> 1
<212> PRT
<213> Murine

<400> 382

Gly
 1

<210> 383
<211> 61
<212> DNA
<213> Murine

<400> 383
atggagaccg acaccctgct gctgtgggtg ctgctgctgt gggtgcccgg atccaccggg 60
c 61

<210> 384
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 384
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165   170   175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180   185   190
Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln
        195   200   205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser
    210   215   220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225   230   235   240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245   250   255
Tyr Tyr Cys Ala Gln Gly Ala Ala Leu Pro Arg Thr Phe Gly Gln Gly
            260   265   270
Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser
        275   280   285
Glu Glu Asp Leu Asn
    290

<210> 385
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 385
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180

```
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccagggaaag ccctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtgcgg cgttgcctag gacgttcggc caagggacca aggtggaaat caaacgggcg 840
gccgcagaac aaaaactcat ctcagaagag gatctgaatt aa                    882
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<210> 386
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 386

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Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1               5                  10                  15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165                 170                 175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180                 185                 190
Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln
        195                 200                 205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser
    210                 215                 220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225                 230                 235                 240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245                 250                 255
Tyr Tyr Cys Ala Gln Gly Ala Ala Leu Pro Arg Thr Phe Gly Gln Gly
            260                 265                 270
Thr Lys Val Glu Ile Lys Arg
        275
```

<210> 387
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 387

```
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
```

aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccagggaaag cccctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtgcgg cgttgcctag gacgttcggc caagggacca aggtggaaat caaacgg 837

<210> 388
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 388
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
165 170 175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
180 185 190
Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln
195 200 205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser
210 215 220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225 230 235 240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
245 250 255
Tyr Tyr Cys Ala Gln Gly Leu Arg His Pro Lys Thr Phe Gly Gln Gly
260 265 270
Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser
275 280 285
Glu Glu Asp Leu Asn
290

<210> 389
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 389
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480

ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccagggaaag cccctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtttga ggcatcctaa gacgttcggc caagggacca aggtggaaat caaacgggcg 840
gccgcagaac aaaaactcat ctcagaagag gatctgaatt aa 882

<210> 390
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 390

Cys	Asp	Leu	Pro	Gln	Thr	His	Ser	Leu	Gly	Ser	Arg	Arg	Thr	Leu	Met
1				5				10						15	
Leu	Leu	Ala	Gln	Met	Arg	Arg	Ile	Ser	Leu	Phe	Ser	Cys	Leu	Lys	Asp
			20					25					30		
Arg	His	Asp	Phe	Gly	Phe	Pro	Gln	Glu	Glu	Phe	Gly	Asn	Gln	Phe	Gln
		35					40					45			
Lys	Ala	Glu	Thr	Ile	Pro	Val	Leu	His	Glu	Met	Ile	Gln	Gln	Ile	Phe
	50					55					60				
Asn	Leu	Phe	Ser	Thr	Lys	Asp	Ser	Ser	Ala	Ala	Trp	Asp	Glu	Thr	Leu
65					70					75					80
Leu	Asp	Lys	Phe	Tyr	Thr	Glu	Leu	Tyr	Gln	Gln	Leu	Asn	Asp	Leu	Glu
				85					90					95	
Ala	Cys	Val	Ile	Gln	Gly	Val	Gly	Val	Thr	Glu	Thr	Pro	Leu	Met	Lys
			100					105					110		
Glu	Asp	Ser	Ile	Leu	Ala	Val	Arg	Lys	Tyr	Phe	Gln	Arg	Ile	Thr	Leu
		115					120					125			
Tyr	Leu	Lys	Glu	Lys	Lys	Tyr	Ser	Pro	Cys	Ala	Trp	Glu	Val	Val	Arg
	130					135					140				
Ala	Glu	Ile	Met	Arg	Ser	Phe	Ser	Leu	Ser	Thr	Asn	Leu	Gln	Glu	Ser
145					150					155					160
Leu	Arg	Ser	Lys	Glu	Thr	Val	Ala	Ala	Pro	Ser	Asp	Ile	Gln	Met	Thr
				165					170					175	
Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	Ile
			180					185					190		
Thr	Cys	Arg	Ala	Ser	Gln	Trp	Ile	Gly	Ser	Gln	Leu	Ser	Trp	Tyr	Gln
		195					200					205			
Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	Met	Trp	Arg	Ser	Ser
	210					215					220				
Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr
225					230					235					240
Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Thr
				245					250					255	
Tyr	Tyr	Cys	Ala	Gln	Gly	Leu	Arg	His	Pro	Lys	Thr	Phe	Gly	Gln	Gly
			260					265					270		
Thr	Lys	Val	Glu	Ile	Lys	Arg									
		275													

<210> 391
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 391
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactcccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccagggaaag cccctaagct cctgatcatg 660

tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtttga ggcatcctaa gacgttcggc caagggacca aggtggaaat caaacgg 837

<210> 392
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 392
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165   170   175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180   185   190
Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln
        195   200   205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser
    210   215   220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225   230   235   240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245   250   255
Tyr Tyr Cys Ala Gln Gly Leu Met Lys Pro Met Thr Phe Gly Gln Gly
            260   265   270
Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser
        275   280   285
Glu Glu Asp Leu Asn
    290

<210> 393
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 393
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccagggaaag cccctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780

cagggtctta tgaagcctat gacgttcggc caagggacca aggtggaaat caaacgggcg 840
gccgcagaac aaaaactcat ctcagaagag gatctgaatt aa 882

<210> 394
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 394

Cys	Asp	Leu	Pro	Gln	Thr	His	Ser	Leu	Gly	Ser	Arg	Arg	Thr	Leu	Met
1				5				10						15	
Leu	Leu	Ala	Gln	Met	Arg	Arg	Ile	Ser	Leu	Phe	Ser	Cys	Leu	Lys	Asp
			20					25					30		
Arg	His	Asp	Phe	Gly	Phe	Pro	Gln	Glu	Glu	Phe	Gly	Asn	Gln	Phe	Gln
		35					40					45			
Lys	Ala	Glu	Thr	Ile	Pro	Val	Leu	His	Glu	Met	Ile	Gln	Gln	Ile	Phe
	50					55					60				
Asn	Leu	Phe	Ser	Thr	Lys	Asp	Ser	Ser	Ala	Ala	Trp	Asp	Glu	Thr	Leu
65					70					75					80
Leu	Asp	Lys	Phe	Tyr	Thr	Glu	Leu	Tyr	Gln	Gln	Leu	Asn	Asp	Leu	Glu
				85					90					95	
Ala	Cys	Val	Ile	Gln	Gly	Val	Gly	Val	Thr	Glu	Thr	Pro	Leu	Met	Lys
			100					105					110		
Glu	Asp	Ser	Ile	Leu	Ala	Val	Arg	Lys	Tyr	Phe	Gln	Arg	Ile	Thr	Leu
		115					120					125			
Tyr	Leu	Lys	Glu	Lys	Lys	Tyr	Ser	Pro	Cys	Ala	Trp	Glu	Val	Val	Arg
	130					135					140				
Ala	Glu	Ile	Met	Arg	Ser	Phe	Ser	Leu	Ser	Thr	Asn	Leu	Gln	Glu	Ser
145					150					155					160
Leu	Arg	Ser	Lys	Glu	Thr	Val	Ala	Ala	Pro	Ser	Asp	Ile	Gln	Met	Thr
				165					170					175	
Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	Ile
			180					185					190		
Thr	Cys	Arg	Ala	Ser	Gln	Trp	Ile	Gly	Ser	Gln	Leu	Ser	Trp	Tyr	Gln
		195					200					205			
Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	Met	Trp	Arg	Ser	Ser
	210					215					220				
Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr
225					230					235					240
Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Thr
				245					250					255	
Tyr	Tyr	Cys	Ala	Gln	Gly	Leu	Met	Lys	Pro	Met	Thr	Phe	Gly	Gln	Gly
			260					265					270		
Thr	Lys	Val	Glu	Ile	Lys	Arg									
		275													

<210> 395
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 395
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attcgctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactcgccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccagggaaag cgcctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtctta tgaagcctat gacgttcggc caagggacca aggtggaaat caaacgg 837

<210> 396

<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 396

```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1               5                  10                  15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165                 170                 175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180                 185                 190
Ser Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln
        195                 200                 205
Gln Lys Pro Gly Glu Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser
    210                 215                 220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225                 230                 235                 240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245                 250                 255
Tyr Tyr Cys Ala Gln Gly Ala Ala Leu Pro Arg Thr Phe Gly Gln Gly
            260                 265                 270
Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser
        275                 280                 285
Glu Glu Asp Leu Asn
    290
```

<210> 397
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 397

```
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatctctt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccaggggaag cccctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtgcgg cgttgcctag gacgttcggc caagggacca aggtggaaat caaacgggcg 840
gccgcagaac aaaaactcat ctcagaagag gatctgaatt aa                    882
```

<210> 398
<211> 279

<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 398

```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1               5                  10                  15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165                 170                 175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180                 185                 190
Ser Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln
        195                 200                 205
Gln Lys Pro Gly Glu Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser
    210                 215                 220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225                 230                 235                 240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245                 250                 255
Tyr Tyr Cys Ala Gln Gly Ala Ala Leu Pro Arg Thr Phe Gly Gln Gly
            260                 265                 270
Thr Lys Val Glu Ile Lys Arg
        275
```

<210> 399
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 399

```
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactcccctа atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatctctt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccaggggaag cccctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtgcgg cgttgcctag gacgttcggc caagggacca aggtggaaat caaacgg    837
```

<210> 400
<211> 293
<212> PRT
<213> Artificial Sequence

<220>

<223> Derived from a Human Germline sequence.

<400> 400
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165   170   175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180   185   190
Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Thr Leu Ser Trp Tyr Gln
        195   200   205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Trp Phe Gly Ser Arg
    210   215   220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225   230   235   240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245   250   255
Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly
            260   265   270
Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser
        275   280   285
Glu Glu Asp Leu Asn
    290

<210> 401
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 401
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcgtccgatt 600
gggacgacgt taagttggta ccagcagaaa ccagggaaag cccctaagct cctgatctgg 660
tttggttccc ggttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgcg 780
caggctggga cgcatcctac gacgttcggc caagggacca aggtggaaat caaacgggcg 840
gccgcagaac aaaaactcat ctcagaagag gatctgaatt aa   882

<210> 402
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 402
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
165 170 175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
180 185 190
Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Thr Leu Ser Trp Tyr Gln
195 200 205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Trp Phe Gly Ser Arg
210 215 220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225 230 235 240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
245 250 255
Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly
260 265 270
Thr Lys Val Glu Ile Lys Arg
275

<210> 403
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 403
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactcccctа atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcgtccgatt 600
gggacgacgt taagttggta ccagcagaaa ccagggaaag ccctaagct cctgatctgg 660
tttggttccc ggttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgcg 780
caggctggga cgcatcctac gacgttcggc caagggacca aggtggaaat caaacgg 837

<210> 404
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 404
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
165 170 175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
180 185 190
Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln
195 200 205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu Phe Gly Ser Arg
210 215 220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225 230 235 240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
245 250 255
Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly
260 265 270
Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser
275 280 285
Glu Glu Asp Leu Asn
290

<210> 405
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 405
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcgtccgatt 600
gggacgatgt taagttggta ccagcagaaa ccagggaaag cccctaagct cctgatcttg 660
tttggttccc ggttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgcg 780
caggctggga cgcatcctac gacgttcggc caagggacca aggtggaaat caaacgggcg 840
gccgcagaac aaaaactcat ctcagaagag gatctgaatt aa 882

<210> 406
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 406
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp

```
          20                  25                  30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
          35                  40                  45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
      50                  55                  60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
           100                 105                 110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
          115                 120                 125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
      130                 135                 140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165                 170                 175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
           180                 185                 190
Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln
          195                 200                 205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu Phe Gly Ser Arg
      210                 215                 220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225                 230                 235                 240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245                 250                 255
Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly
           260                 265                 270
Thr Lys Val Glu Ile Lys Arg
          275
```

<210> 407
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 407

```
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactcccctа atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcgtccgatt 600
gggacgatgt taagttggta ccagcagaaa ccagggaaag cccctaagct cctgatcttg 660
tttggttccc ggttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgcg 780
caggctggga cgcatcctac gacgttcggc caagggacca aggtggaaat caaacgg    837
```

<210> 408
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 408

```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1               5                  10                  15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
           20                  25                  30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
          35                  40                  45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
```

```
    50                  55                  60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165                 170                 175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180                 185                 190
Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln
        195                 200                 205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu Ala Phe Ser Arg
    210                 215                 220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225                 230                 235                 240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245                 250                 255
Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly
            260                 265                 270
Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser
        275                 280                 285
Glu Glu Asp Leu Asn
    290
```

<210> 409
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 409

```
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcgtccgatt 600
gggacgatgt taagttggta ccagcagaaa ccagggaaag cccctaagct cctgatcctt 660
gctttttccc gtttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgcgcg 780
caggctggga cgcatcctac gacgttcggc caagggacca aggtggaaat caaacgggcg 840
gccgcagaac aaaaactcat ctcagaagag gatctgaatt aa                    882
```

<210> 410
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 410

```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1               5                  10                  15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60
```

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
165 170 175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
180 185 190
Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln
195 200 205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu Ala Phe Ser Arg
210 215 220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225 230 235 240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
245 250 255
Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly
260 265 270
Thr Lys Val Glu Ile Lys Arg
275

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<220>
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gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactcccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcgtccgatt 600
gggacgatgt taagttggta ccagcagaaa ccagggaaag ccctaagct cctgatcctt 660
gcttttctcc gtttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgcgcg 780
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<210> 412
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

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1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln
20 25 30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Met Trp Arg Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Gly Leu Arg His Pro Lys
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Cys
100 105

<210> 413
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 413
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atcacttgcc gggcaagtca gtggattggg tctcagttat cttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatcatgtgg cgttcctcgt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgtgctcag ggtttgaggc atcctaagac gttcggccaa 300
gggaccaagg tggaaatcaa atgc 324

<210> 414
<211> 108
<212> PRT
<213> Artificial Sequence

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<400> 414
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20 25 30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Leu Ala Phe Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 415
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
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atcacttgcc gggcaagtcg tccgattggg acgatgttaa gttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatccttgct ttttcccgtt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgcgcgcag gctgggacgc atcctacgac gttcggccaa 300
gggaccaagg tggaaatcaa acgg 324

<210> 416
<211> 62
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 416
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gg 62

<210> 417
<211> 360

<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

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tcctgtgcag cctccggatt cacctttagt cagtatagga tgcattgggt ccgccaggct 120
ccagggaaga gtctagagtg ggtctcaagt attgatacta ggggttcgtc tacatactac 180
gcagaccccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaagctgtg 300
acgatgtttt ctccttttt tgactactgg ggtcagggaa ccctggtcac cgtctcgagc 360

<210> 418
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<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 418
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ccagggaagg gtctagagtg ggtctcatct attacgcgga ctggtcgtgt tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatggcgg 300
aatcggcatg gtgagtatct tgctgatttt gactactggg gtcagggaac cctggtcacc 360
gtctcgagc 369

<210> 419
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<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 419
Thr Val Ala Ala Pro Ser Cys
1 5

<210> 420
<211> 6
<212> PRT
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<220>
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<400> 420
Gly Gly Gly Gly Ser Cys
1 5

VARIANTES DE UNION A ANTI-ALBÚMINA DE SUERO MEJORADAS

La invención se refiere a variantes mejoradas del dominio variable sencillo de inmunoglobulina anti-albúmina de suero DOM7h-14, así como a ligandos y fármacos conjugados que comprenden dichas variantes, composiciones, ácido nucleicos, vectores y huéspedes.

ANTECEDENTES DE LA INVENCIÓN

Los documentos WO04003019 y WO2008/096158 describen restos de unión anti-albúmina de suero (SA), tales como dominios variables sencillos de inmunoglobulina (dAbs) anti-SA, que tienen semividas terapéuticamente útiles. Estos documentos describen dAbs anti-SA así como ligandos multiespecíficos que comprenden dichos dAbs, por ejemplo, ligandos que comprenden un dAb y un dAb anti-SA que se une específicamente a un antígeno diana, tal como TNFR1. Se describen restos de unión que se unen específicamente a albúminas de suero de más de una especie, por ejemplo dAbs anti-SA de reactividad cruzada de ser humano/ratón.

Los documentos WO05118642 y WO2006/059106 describen el concepto de conjugar o asociar un resto de unión anti-SA, tal como un dominio variable sencillo de inmunoglobulina anti-SA, a un fármaco, para aumentar la semivida del fármaco. Se describen y ejemplifican proteínas, péptidos y fármacos NCE (nueva entidad química). El documento WO2006/059106 describe el uso de este concepto para aumentar la semivida de agentes insulinotrópicos, por ejemplo, hormonas incretinas tales como el péptido similar a glucagón (GLP)-1.

También se hace referencia a Holt y col, "Anti-Serum albumin domain antibodies for extending the half-lives of short lived drugs", Protein Engineering,

Design & Selection, vol 21, Nº 5, pág. 283-288, 2008.

El documento WO2008/096158 describe DOM7h-14, que es un buen dAb anti-SA. Sería deseable proporcionar dAbs mejorados que fueran variantes del DOM7h-14 y que la albúmina de suero se uniera específicamente, preferiblemente albúminas de especies humanas y no humanas, que proporcionarían utilidad en modelos animales de enfermedades así como para la terapia y/o diagnóstico en seres humanos. También sería deseable permitir la elección entre restos de unión (dAbs) anti-SA de afinidad relativamente moderada y elevada. Dichos restos podrían unirse a fármacos, eligiéndose el resto de unión anti-SA de acuerdo con la solicitud final contemplada. Esto permitiría al fármaco adaptarse mejor a las indicaciones crónicas o agudas del tratamiento y/o prevención, dependiendo de la elección del resto de unión anti-SA. También sería deseable proporcionar anti-dAbs, que sean monoméricos o sustancialmente lo sean en solución. Esto sería especialmente ventajoso cuando el dAb anti-SA está unido a un resto de unión, por ejemplo, un dAb, que se une específicamente a un receptor de la superficie celular, tal como TNFR1, con el propósito de antagonizar al receptor. El estado monomérico del dAb anti-SA es útil para reducir la posibilidad de entrecruzamiento del receptor, ya que es menos probable que se formen multímeros que puedan unirse y producir entrecruzamientos de los receptores (por ejemplo, TNFR1) en la superficie celular, aumentando de esta manera la probabilidad de agonismo de los receptores y la señalización perjudicial de los receptores.

SUMARIO DE LA INVENCIÓN

Aspectos de la presente invención resuelven estos problemas.

Con este fin, los presentes inventores descubren sorprendentemente que pueden dirigirse mutaciones beneficiosas en la región CDR3 de 92 a 96 (numeración

de las posiciones de acuerdo con Kabat) del DOM7h-14.

Por lo tanto, en un aspecto la invención proporciona una variante de dominio variable sencillo de inmunoglobulina anti-albúmina de suero (SA) de DOM7h-14, en el que la variante comprende al menos una mutación en la región CDR3 de 92 a 96 (numeración de las posiciones de acuerdo con Kabat) en comparación con DOM7h-14 y en el que la variante tiene de 1 a 8 cambios en comparación con la secuencia de aminoácidos de DOM7h-14. También se proporciona un resto de unión a anti-albúmina de suero (SA) que comprende la CDR3 de una variante de este aspecto de la invención.

Otro aspecto de la invención proporciona una variante de dominio variable sencillo de inmunoglobulina anti-albúmina de suero (SA) de DOM7h-14, en el que la variante comprende una Ser en la posición 22 y una Glu en la posición 42 (numeración de acuerdo con Kabat) en comparación con DOM7h-14 y en el que la variante tiene de 0 a 4 cambios adicionales en comparación con la secuencia de aminoácidos de DOM7h-14.

Realizaciones de cualquier aspecto de la invención proporciona variantes de DOM7h-14 con buena afinidad anti-albúmina de suero. La elección de variantes puede permitir la adaptación de la semivida de acuerdo con el entorno terapéutico y/o profiláctico deseado. Por ejemplo, en una realización, la afinidad de la variante para la albúmina de suero es relativamente alta, de manera que la variante sería útil para incluir en productos que encuentren utilidad en el tratamiento y/o prevención de enfermedades, afecciones, toxicidades crónicas o persistentes, u otras indicaciones crónicas. En una realización, la afinidad de la variante para la albúmina de suero es relativamente moderada, de manera que la variante sería útil para incluir en productos que encuentren utilidad en el tratamiento y/o prevención de enfermedades,

afecciones, toxicidades, agudas u otras indicaciones agudas. En una realización, la afinidad de la variante para la albúmina de suero es intermedia, de manera que la variante sería útil para incluir en productos que encuentren utilidad en el tratamiento y/o prevención de enfermedades, afecciones, toxicidades, agudas o crónicas u otras indicaciones agudas o crónicas.

Es concebible que una molécula con una afinidad y especificidad elevada apropiada para la albúmina de suero permaneciera en circulación el suficiente tiempo para tener el efecto terapéutico deseado (Tomlinson, *Nature Biotechnology* **22**, 521 - 522 (2004)). En este caso, una variante anti-SA de elevada afinidad permanecería en la circulación en suero coincidiendo con la de la albúmina de suero de la especie (WO2008096158). Una vez en circulación, cualquier agente terapéutico fusionado a la variante AlbudAb™ (una AlbudAb es un dAb anti-albúmina de suero o dominio variable sencillo de inmunoglobulina), ya sea NCE, péptido o proteína, sería capaz por consiguiente de actuar durante más tiempo sobre su diana y presentar un efecto terapéutico más duradero. Esto permitiría dirigir enfermedades crónicas o persistentes sin necesidad de dosis frecuentes.

Una variante con afinidad moderada (pero específica para SA) permanecería únicamente en la circulación en suero durante un tiempo corto (por ejemplo, durante algunas horas o algunos días) permitiendo la dirección específica de las dianas terapéuticas implicadas en enfermedades agudas mediante el agente terapéutico fusionado.

De este modo es posible adaptar el producto que contiene anti-SA al área de enfermedad terapéutica eligiendo una variante anti-SA con la afinidad de unión a albúmina y/o semivida en suero apropiada.

Un aspecto de la invención proporciona un ligando multiespecífico que

comprende una variante anti-SA como se ha descrito anteriormente y un resto de unión que se une específicamente a un antígeno diana distinto de SA.

Un aspecto de la invención proporciona un producto de fusión, por ejemplo, una proteína de fusión o fusión con un péptido o fármaco de NCE (nueva entidad química), que comprende un polipéptido, proteína, péptido o fármaco de NCE fusionado o conjugado (para una NCE) a cualquier variante como se ha descrito anteriormente, en el que la variante es DOM7h-14-10 (o una variante que tiene una identidad de secuencia de aminoácidos de al menos el 95, 96, 97, 98 o 99% con la secuencia de aminoácidos de DOM7h-14-10. DOM7h-14-10 produce únicamente una modesta disminución de afinidad cuando se fusiona o se conjuga con el compañero haciéndole útil en los productos de fusión.

Un aspecto de la invención proporciona una composición que comprende una variante, proteína o ligando de fusión de cualquier aspecto anterior y un diluyente, transportador, excipiente o vehículo farmacéuticamente aceptable.

Un aspecto de la invención proporciona un método de tratamiento o prevención de una enfermedad o trastorno en un paciente, que comprende administrar al menos una dosis de una variante de acuerdo con cualquier aspecto o realización de la invención a dicho paciente.

Un aspecto de la invención proporciona una fusión a polipéptido o conjugado que comprende un dAb anti-albúmina de suero como se describe en este documento (por ejemplo, DOM7h-14-10 y una incretina o agente insulinotrópico, por ejemplo, exendina-4, GLP-1(7-37), GLP-1(6-36) o cualquier incretina o agente insulinotrópico descrito en el documento WO06/059106, incorporándose explícitamente estos agentes en este documento como referencia como se describe en este documento para incluir en esta invención y en las reivindicaciones a continuación.

BREVE DESCRIPCIÓN DE LOS DIBUJOS

Figura 1: Alineamiento de la secuencia de aminoácidos para dAbs de la variante DOM7h-14. Un "." en una posición particular indica que en esa posición se encuentra el mismo amino en DOM7h-14. Las CDR se indican subrayadas y en negrita (la primera secuencia subrayada es la CDR1, la segunda secuencia subrayada es la CDR2 y la tercera secuencia subrayada es la CDR3).

Figura 2: Parámetros cinéticos de variantes de DOM7h-14. Unidades KD = nM; unidades Kd = s^{-1}; unidades Ka = M^{-1} s^{-1}. La anotación A e-B significa A x 10^{-B} y C e D significa C x 10^{D}. Se indican los intervalos cinéticos globales de diversas especies, de acuerdo con las confirmaciones de los ejemplos a continuación. También se proporcionan intervalos opcionales para usar en entornos terapéuticos particulares (indicaciones, afecciones o enfermedades agudas o crónicas e "intermedias" para usar tanto en entornos crónicos como agudos). Los dAb y productos de elevada afinidad que comprenden éstos son útiles para entornos crónicos. Los dAb y productos de afinidad media que comprenden éstos son útiles para entornos intermedios. Los dAb y productos de baja afinidad que comprenden éstos son útiles para entornos agudos. La afinidad en este aspecto es la afinidad para la albúmina de suero. Se enumeran diversos ejemplos de dAbs anti-suero y proteínas de fusión y éstos confirman los intervalos descritos. Muchos de los ejemplos tienen cinéticas favorables en seres humanos y uno o más en animales no humanos (por ejemplo, en ser humano y en mono *Cynomolgus* y/o en ratón). La elección del dAb o del producto que comprende éste puede adaptarse, de acuerdo con la invención, dependiendo del entorno (por ejemplo, crónico o agudo) a tratar terapéuticamente.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

En esta memoria descriptiva, la invención se ha descrito haciendo referencia a

realizaciones, de manera que se permite realizar una memoria descriptiva clara y concisa. Se pretende y debe apreciarse que las realizaciones puedan combinarse de diversas maneras o realizarse por separado sin alejarse de la invención.

A menos que se indique otra cosa, todos los términos técnicos y científicos usados en este documento tienen el mismo significado que el habitualmente entendido por un experto en la materia (por ejemplo, en cultivos celulares, genética molecular, química de ácidos nucleicos, técnicas de hibridación y bioquímica). Para métodos moleculares, genéticos y bioquímicos se usan técnicas convencionales (véase en líneas generales, Sambrook *y col.,* Molecular Cloning: A Laboratory Manual, 2d ed. (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. y Ausubel *y col.,* Short Protocols in Molecular Biology (1999) 4ª Ed, John Wiley & Sons, Inc. que se incorporan en este documento como referencia) y métodos químicos.

Como se usa en este documento, la expresión "antagonista del Receptor del Factor de Necrosis Tumoral I (TNFR1)" o "antagonista anti-TNFR1" o similar se refiere a un agente (por ejemplo, una molécula, un compuesto) que se une a TNFR1 y puede inhibir una (es decir, una o más) función de TNFR1. Por ejemplo, un antagonista de TNFR1 puede inhibir la unión de TNFα a TNFR1 y/o inhibir la transducción de señal mediada a través de TNFR1. Por consiguiente, con un antagonista de TNFR1 pueden inhibirse las respuestas celulares y los procedimientos mediados por TNFR1 (por ejemplo, muerte celular inducida por TNFα en un ensayo de citotoxicidad L929 convencional).

Un "paciente" es cualquier animal, por ejemplo, un mamífero, por ejemplo, un primate no humano (tal como babuino, mono *rhesus* o mono *Cynomolgus*), ratón, ser humano, conejo, rata, perro, gato o cerdo. En una realización, el paciente es un ser humano.

Como se usa en este documento, "péptido" se refiere de aproximadamente dos a aproximadamente 50 aminoácidos que están unidos entre sí mediante enlaces peptídicos.

Como se usa en este documento, "polipéptido" se refiere a al menos aproximadamente 50 aminoácidos que están unidos entre sí mediante enlaces peptídicos. Los polipéptidos generalmente comprenden estructura terciaria y plegada en los dominios funcionales.

Como se usa en este documento un anticuerpo se refiere a IgG, IgM, IgA, IgD o IgE o un fragmento (tal como un Fab, $F(ab')_2$, Fv, Fv unido por puentes disulfuro, scFv, anticuerpos multiespecíficos de conformación cerrada, scFv unido por puentes disulfuro, diacuerpo) que procede de cualquier especie que produce de manera natural un anticuerpo o creado mediante tecnología de ADN recombinante; o aislado de suero, células B, hibridomas, transfectomas, levaduras o bacterias.

Como se usa en este documento, "formato de anticuerpo" se refiere a cualquier estructura polipeptídica adecuada en la que pueden incorporarse uno o más dominios variables de anticuerpo para conferir especificidad de unión para el antígeno en la estructura. En la técnica se conoce una diversidad de formatos de anticuerpo adecuados tales como, anticuerpos quiméricos, anticuerpos humanizados, anticuerpos humanos, anticuerpos monocatenarios, anticuerpos biespecíficos, cadenas pesadas de anticuerpos, cadenas ligeras de anticuerpos, homodímeros y heterodímeros de cadenas pesadas y/o ligeras de anticuerpos, fragmentos de unión a antígeno de cualquiera de los anteriores (por ejemplo, un fragmento Fv, (por ejemplo, Fv monocatenario (scFv), Fv unido por puentes disulfuro), un fragmento Fab, un fragmento Fab', un fragmento $F(ab')_2$), un dominio variable de anticuerpo sencillo (por ejemplo, un dAb, V_H, V_{HH}, V_L) y versiones modificadas de cualquiera de los anteriores (por ejemplo, modificados por la

unión covalente de polietilenglicol u otro polímero adecuado o un V_{HH} humanizado).

La frase "dominio variable sencillo de inmunoglobulina" se refiere a un dominio variable de anticuerpo (V_H, V_{HH}, V_L) que se une específicamente a un antígeno o epítope independientemente de los diferentes dominios o regiones V. Un dominio variable sencillo de inmunoglobulina puede presentarse en un formato (por ejemplo, homo- o hetero- multimérico) con otras regiones variables o dominios variables en los que las otras regiones o dominios no necesitan la unión al antígeno mediante el dominio variable de inmunoglobulina sencillo (es decir, en el que el dominio variable sencillo de inmunoglobulina se une al antígeno independientemente de los dominios variables adicionales). Un "anticuerpo de dominio" o "dAb" es lo mismo que un "dominio variable sencillo de inmunoglobulina" como se usa el término en este documento. Un "dominio variable de inmunoglobulina sencillo" es lo mismo que un "dominio variable sencillo de inmunoglobulina" como se usa el término en este documento. Un "dominio variable de anticuerpo sencillo" o un "dominio variable sencillo de anticuerpo" es lo mismo que un "dominio variable sencillo de inmunoglobulina" como se usa el término en este documento. Un dominio variable sencillo de inmunoglobulina en una realización es un dominio variable de anticuerpo humano, pero también incluye dominios variables de anticuerpos sencillos de otras especies tales como roedores (por ejemplo, como se describe en el documento WO 00/29004, cuyo contenido se incorpora en este documento como referencia en su totalidad), tiburón nodriza y dAbs V_{HH} de *Camélidos*. Los V_{HH} de Camélidos son polipéptidos de dominio variable sencillo de inmunoglobulina que proceden de especies que incluyen camello, llama, alpaca, dromedario y guanaco, que producen de manera natural anticuerpos de cadena pesada desprovistos de cadenas ligeras. El V_{HH} puede humanizarse.

Un "dominio" es una estructura de proteína plegada que tiene una estructura

terciaria independiente del resto de la proteína. Generalmente, los dominios son responsables de las propiedades funcionales específicas de las proteínas, y en muchos casos pueden añadirse, eliminarse o transferirse a otras proteínas sin que el resto de la proteína y/o del dominio pierda la función . Un "dominio variable de anticuerpo sencillo" es un dominio polipeptídico plegado que comprende secuencias características de dominios variables de anticuerpos. Por lo tanto incluye dominios variables de anticuerpo completos y dominios variables modificados, por ejemplo, en los que uno o más bucles se han reemplazado por secuencias que no son características de dominios variables de anticuerpos, o dominios variables de anticuerpo que se han truncado o comprenden extensiones N o C-terminal, así como fragmentos plegados de dominios variables que conservan al menos la actividad y especificidad de unión del dominio de longitud completa.

En la presente solicitud, el término "prevención" y "prever" implica la administración de la composición protectora antes de la inducción de la enfermedad o afección. "Tratamiento" y "tratar" implica la administración de la composición protectora después de que comiencen a manifestarse los síntomas de la enfermedad o afección. "Supresión" o "suprimir" se refiere a la administración de la composición después de un suceso inductivo, pero antes de la aparición clínica de la enfermedad o afección.

Como se usa en este documento, el término "dosis" se refiere a la cantidad de ligando administrado a un sujeto toda al mismo tiempo (dosis unitaria) o en dos o más administraciones durante un intervalo de tiempo definido. Por ejemplo, dosis puede hacer referencia a la cantidad de ligando (por ejemplo, ligando que comprende un dominio variable sencillo de inmunoglobulina que se une al antígeno diana) administrada a un sujeto en el transcurso de un día (24 horas) (dosis diaria), dos días, una semana, dos semanas, tres semanas o uno o más meses (por ejemplo, mediante una

administración única o mediante dos o más administraciones). El intervalo entre dosis puede ser cualquier cantidad de tiempo deseada. La expresión "farmacéuticamente eficaz" cuanto se refiere a una dosis significa la cantidad suficiente de ligando, dominio o agente farmacéuticamente activo para proporcionar el efecto deseado. La cantidad que es "eficaz" variará de sujeto en sujeto, dependiendo de la edad y estado general del individuo, el fármaco o agente farmacéuticamente activo particular y similar. Por tanto, no siempre es posible especificar una cantidad "eficaz" exacta que pueda aplicarse a todos los pacientes. Sin embargo, usando experimentación rutinaria, un experto en la materia puede determinar una dosis "eficaz" apropiada en cualquier caso individual.

Para un experto en la materia serán familiares los métodos para realizar el análisis farmacocinético y para determinar la semivida del ligando (por ejemplo, dominio variable sencillo, proteína de fusión o ligando multiespecífico). Pueden encontrarse más detalles en *Kenneth, A y col*: Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists y en *Peters y col*, Pharmacokinetic analysis: A Practical Approach (1996). También se hace referencia a "Pharmacokinetics", M Gibaldi & D Perron, publicado por Marcel Dekker, 2ª Rev. edición ex. (1982), que describe parámetros farmacocinéticos tales como semividas t alfa y t beta y el área bajo la curva (AUC). Opcionalmente, todos los parámetros y los valores farmacocinéticos indicados en este documento deben interpretarse como valores en un ser humano. Opcionalmente, todos los parámetros y valores farmacocinéticos indicados en este documento deben interpretarse como valores en ratón, rata o mono *Cynomolgus*.

Las semividas ($t_{1/2}$ alfa y $t_{1/2}$ beta) y el AUC pueden determinarse a partir una curva de la concentración en suero del ligando frente al tiempo. Para realizar el modelo de la curva, puede usarse, por ejemplo, el paquete de análisis WinNonlin, por ejemplo versión 5.1 (disponible de Pharsight Corp., Mountain View, CA94040, USA). Cuando se

usan modelos de dos compartimentos, en una primera fase (la fase alfa) el ligando se distribuye principalmente en el paciente, con alguna eliminación. Una segunda fase (fase beta) es la fase en la que el ligando se ha distribuido y la concentración en suero va disminuyendo a medida que el paciente va eliminando el ligando. La semivida t alfa es la semivida de la primera fase y la semivida t beta es la semivida de la segunda fase. Por tanto, en una realización, en el contexto de la presente invención, el dominio variable, proteína de fusión o ligando tiene una semivida $t\alpha$ en el intervalo de (o de aproximadamente) 15 minutos o más. En una realización, el límite inferior del intervalo es (o aproximadamente es) 30 minutos, 45 minutos, 1 hora, 2 horas, 3 horas, 4 horas, 5 horas, 6 horas, 7 horas, 10 horas, 11 horas o 12 horas. Adicionalmente, o de manera alternativa, el dominio variable, proteína de fusión o ligando de acuerdo con la invención tendrá una semivida $t\alpha$ en el intervalo de hasta e incluyendo 12 horas (o aproximadamente 12 horas). En una realización, el límite superior del intervalo es (o aproximadamente es) 11, 10, 9, 8, 7, 6 ó 5 horas. Un ejemplo de un intervalo adecuado es (o es aproximadamente) de 1 a 6 horas, de 2 a 5 horas o de 3 a 4 horas.

En una realización, la presente invención proporciona el dominio variable, proteína de fusión o ligando de acuerdo con la invención que tiene una semivida $t\beta$ en el intervalo de (o de aproximadamente) 2,5 horas o más. En una realización, el límite inferior del intervalo es (o es aproximadamente) 3 horas, 4 horas, 5 horas, 6 horas, 7 horas, 10 horas, 11 horas o 12 horas. Adicionalmente, o de manera alternativa, la semivida $t\beta$ es (o es aproximadamente) de hasta e incluyendo 21 ó 25 días. En una realización, el límite superior del intervalo es (o es aproximadamente) 12 horas, 24 horas, 2 días, 3 días, 5 días, 10 días, 15 días, 19 días, 20 días, 21 días o 22 días. Por ejemplo, el dominio variable, proteína de fusión o ligando de acuerdo con el invención tendrá una semivida $t\beta$ en el intervalo de 12 a 60 horas (o aproximadamente de 12 a

60 horas). En una realización adicional, estará en el intervalo de 12 a 48 horas (o aproximadamente de 12 a 48 horas). Aún en otra realización adicional, estará en el intervalo de 12 a 26 horas (o aproximadamente de 12 a 26 horas).

Como una alternativa al uso de modelos de dos compartimentos, el experto en la materia estará familiarizado con el uso de modelos no compartimentales, que pueden usarse para determinar semividas terminales (en este sentido, la expresión "semivida terminal" como se usa en este documento significa una semivida terminal determinada usando modelos no compartimentales). Para realizar el modelo de la curva de esta manera, puede usarse, por ejemplo, el paquete de análisis WinNonlin, por ejemplo versión 5.1 (disponible de Pharsight Corp., Mountain View, CA94040, USA). En este ejemplo, en una realización el dominio variable sencillo, proteína de fusión o ligando tiene una semivida terminal de al menos (o de al menos aproximadamente) 8 horas, 10 horas, 12 horas, 15 horas, 28 horas, 20 horas, 1 día, 2 días, 3 días, 7 días, 14 días, 15 días, 16 días, 17 días, 18 días, 19 días, 20 días, 21 días, 22 días, 23 días, 24 días o 25 días. En una realización, el límite superior de este intervalo es (o es aproximadamente) 24 horas, 48 horas, 60 horas o 72 horas o 120 horas. Por ejemplo, la semivida terminal es (o es aproximadamente) 8 horas a 60 horas, o de 8 horas a 48 horas o de 12 horas a 120 horas, por ejemplo, en un ser humano.

Además, o como alternativa al criterio anterior, el dominio variable, proteína de fusión o ligando de acuerdo con la invención tiene un valor AUC (área bajo la curva) en el intervalo de (o de aproximadamente) 1 mg.min/ml o más. En una realización, el límite inferior del intervalo es (o es aproximadamente) 5, 10, 15, 20, 30, 100, 200 ó 300 mg.min/ml. Adicionalmente, o de manera alternativa, el dominio variable, proteína de fusión o ligando de acuerdo con la invención tiene una AUC en el intervalo de (o de aproximadamente) hasta 600 mg.min/ml o más. En una realización, el límite superior del

intervalo es (o es aproximadamente) 500, 400, 300, 200, 150, 100, 75 ó 50 mg.min/ml. Ventajosamente, el dominio variable, proteína de fusión o ligando tendrá una AUC en (o aproximadamente en) el intervalo seleccionado del grupo que consiste en: de 15 a 150 mg.min/ml, de 15 a 100 mg.min/ml, de 15 a 75 mg.min/ml y de 15 a 50 mg.min/ml.

"Resonancia de Plasmón Superficial": Pueden usarse ensayos de competición para determinar si un antígeno o epítope específico, tal como albúmina de suero humana, compite con otro antígeno o epítope, tal como albúmina de suero de mono *Cynomolgus*, para unirse a un ligando de unión a albúmina de suero descrito en este documento, tal como un dAb específico. De manera similar pueden usarse ensayos de competición para determinar si un primer ligando tal como dAb, compite con un segundo ligando tal como un dAb de unión a un antígeno o epítope diana. El término "compite" como se usa en este documento se refiere a una sustancia, tal como una molécula, compuesto, preferiblemente una proteína, que es capaz de interferir a cualquier grado con la interacción de unión especifica entre dos o más moléculas. La frase "no se inhibe de manera competitiva" significa que la sustancia, tal como una molécula, compuesto, preferiblemente una proteína, no interfiere a ningún grado cuantificable o significativo con la interacción de unión especifica entre dos o más moléculas. La interacción de unión especifica entre dos o más moléculas incluye preferiblemente la interacción de unión específica entre un dominio variable sencillo y su compañero o diana afín. La molécula interferente o competidora puede ser otro dominio variable sencillo o puede ser una molécula que sea estructuralmente y/o funcionalmente similar a un compañero o diana afín.

La expresión "resto de unión" se refiere a un dominio que se une específicamente a un antígeno o epítope independientemente de un dominio de unión a antígeno o epítope diferente. Un resto de unión puede ser un anticuerpo de dominio

(dAb) o puede ser un dominio que es un derivado de un armazón de proteína no inmunoglobulina, por ejemplo, un armazón seleccionado del grupo que consiste CTLA-4, lipocalín, SpA, un affibody, un avímero, GroEl, transferrina, GroES y fibronectina, que se une a un ligando que no es el ligando natural (en el caso de la presente invención, en el resto se une a albúmina de suero). Véase el documento WO2008/096158, que describe ejemplos de armazones de proteínas y métodos para seleccionar dominios de unión específicos a antígeno o epítope a partir de repertorios (véanse los Ejemplos 17 a 25). Estas descripciones específicas del documento WO2008/096158 se incorporan expresamente como referencia en esta memoria descriptiva y se describen explícitamente en esta y para usar con la presente invención y se contempla que puede incorporarse cualquier parte de dicha descripción en una o más reivindicaciones en este documento.

En un primer aspecto, la invención proporciona una variante de dominio variable sencilla de inmunoglobulina anti-albúmina de suero (SA) de DOM7h-14, en el que la variante comprende al menos una mutación en la región CDR3 de 92 a 96 (numeración de las posiciones de acuerdo con Kabat) en comparación con DOM7h-14 y en el que la variante tiene de 1 a 8 cambios en comparación con la secuencia de aminoácidos de DOM7h-14.

Opcionalmente, la variante comprende un motivo AQG(X1)(X2)(X3)P(X4)T, en la que A se encuentra en la posición 89 (de acuerdo con Kabat) y al menos una de (X1) a (X4) representa un cambio de aminoácido en comparación con la secuencia de DOM7h-14.

En una realización, la posición 95 (de acuerdo con Kabat) es Pro. Adicionalmente o como alternativa, en una realización la posición 98 (de acuerdo con Kabat) es Ala. Adicionalmente o como alternativa, en una realización la posición 90 (de

acuerdo con Kabat) es Gln. Adicionalmente o como alternativa, en una realización la posición 91 (de acuerdo con Kabat) es Gly. Adicionalmente o como alternativa, en una realización la posición 97 (de acuerdo con Kabat) es Thr.

En una realización, la variante comprende una mutación en cada una de las posiciones 92, 93 y 94 y opcionalmente en la posición 96 (numeración de acuerdo con Kabat) comparada con DOM7h-14.

Opcionalmente, la variante comprende uno o más restos aminoacídicos seleccionados de

Posición 92 = L o F,

Posición 93 = R, M o K,

Posición 94 = H o K, y

Posición 96 = K o M (numeración de acuerdo con Kabat)

En una realización, la variante comprende una Lys o Met en la posición 96 (numeración de acuerdo con Kabat) en comparación con DOM7h-14. En esta realización, opcionalmente la variante comprende uno o más restos aminoacídicos seleccionados de

Posición 92 = L o F,

Posición 93 = R, M o K, y

Posición 94 = H o R (numeración de acuerdo con Kabat)

En una realización, la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de un dominio variable sencillo seleccionado de DOM7h-14-10, DOM7h-14-18, DOM7h-14-28 y DOM7h-14-36 o tiene hasta 4 cambios en comparación con la secuencia de aminoácidos seleccionada, en la que la variante comprende al menos una mutación en la región CDR3 de 92 a 96 (numeración de las posiciones de acuerdo con Kabat) en comparación con DOM7h-14.

Un aspecto de la invención proporciona un resto de unión a anti albúmina de suero (SA) que comprende CDR3 o una variante de acuerdo con el primer aspecto de la invención. En una realización, el resto de unión comprende la CDR1 de la variante seleccionada o una secuencia de aminoácidos que tiene una identidad de secuencia de al menos el 50% con la variante seleccionada. Adicionalmente o como alternativa, en una realización el resto de unión a SA comprende la CDR2 de la variante seleccionada o una secuencia de aminoácidos que tiene una identidad de secuencia de al menos el 50% con la variante seleccionada.

En un aspecto adicional de la invención, se proporciona una variante de DOM7h-14 de dominio variable sencillo de inmunoglobulina anti albúmina de suero (SA), en el que la variante comprende una Ser en la posición 22 y una Glu en la posición 42 (numeración de acuerdo con Kabat) en comparación con DOM7h-14, y en la que la variante tiene de 0 a 4 cambios adicionales en comparación con DOM7h-14.En una realización la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de DOM7h-14-19 o tiene hasta 4 cambios en comparación con la secuencia de DOM7h-14-19, en la que la variante comprende una Ser en la posición 22 y una Glu en la posición 42 (numeración de acuerdo con Kabat) comparada con DOM7h-14.

En una realización, la variante o resto de unión de acuerdo con cualquier aspecto o realización de la invención comprende una más de las siguientes características cinéticas:

(a) La variante o resto comprende un sitio de unión que se une específicamente a SA humana con una constante de disociación (KD) de (o de aproximadamente) 0,1 a (o a aproximadamente) 10.000 nM, opcionalmente de (o de aproximadamente) 1 a (o a aproximadamente) 6.000 nM, determinada de

acuerdo con la resonancia de plasmón superficial;

(b) La variante o resto comprende un sitio de unión que se une específicamente a SA humana con una constante de velocidad de disociación (K_d) de (o de aproximadamente) 1,5 x 10^{-4} a (o de aproximadamente a) 0,1 s^{-1}, opcionalmente de (o de aproximadamente) 3 x 10^{-4} a (o de aproximadamente a) 0,1 s^{-1} determinada de acuerdo con la resonancia de plasmón superficial;

(c) La variante o resto comprende un sitio de unión que se une específicamente a SA humana con una constante de velocidad de asociación (K_a) de (o de aproximadamente) 2 x 10^6 a (o de aproximadamente a) 1 x 10^4 $M^{-1}s^{-1}$, opcionalmente de (o de aproximadamente) 1 x 10^6 a (o de aproximadamente a) 2 x 10^4 $M^{-1}s^{-1}$ determinada de acuerdo con la resonancia de plasmón superficial;

(d) La variante o resto comprende un sitio de unión que se une específicamente a SA de mono Cy*nomolgus* con una constante de disociación (KD) de (o de aproximadamente) 0,1 a (o a aproximadamente) 10.000 nM, opcionalmente de (o de aproximadamente) 1 a (o a aproximadamente) 6.000 nM, determinada de acuerdo con la resonancia de plasmón superficial;

(e) La variante o resto de cualquier reivindicación anterior, en la que la variante comprende un sitio de unión que se une específicamente a SA de mono Cy*nomolgus* con una constante de velocidad de disociación (K_d) de (o de aproximadamente) 1,5 x 10^{-4} a (o a aproximadamente) 0,1 s^{-1} opcionalmente de (o de aproximadamente) 3 x 10^{-4} a (o a aproximadamente) 0,1 s^{-1}, determinada de acuerdo con la resonancia de plasmón superficial;

(f) La variante o resto de cualquier reivindicación anterior, en la que la variante comprende un sitio de unión que se une específicamente a SA de mono Cy*nomolgus* con una constante de velocidad de asociación (K_a) de (o de

aproximadamente) 2×10^6 a (o a aproximadamente) 1×10^4 $M^{-1}s^{-1}$, opcionalmente de (o de aproximadamente) 1×10^6 a (o a aproximadamente) 5×10^3 $M^{-1}s^{-1}$, determinada de acuerdo con la resonancia de plasmón superficial;

(g) La variante o resto comprende un sitio de unión que se une específicamente a SA de rata con una constante de disociación (KD) de (o de aproximadamente) 1 a (o a aproximadamente) 10.000 nM, opcionalmente de (o de aproximadamente) 20 a (o a aproximadamente) 6.000 nM, determinada de acuerdo con la resonancia de plasmón superficial;

(h) La variante o resto comprende un sitio de unión que se une específicamente a SA de rata con una constante de velocidad de disociación (K_d) de (o de aproximadamente) 2×10^{-3} a (o a aproximadamente) 0,15 s^{-1}, opcionalmente de (o de aproximadamente) 9×10^{-3} a (o a aproximadamente) 0,14 s^{-1}, determinada de acuerdo con la resonancia de plasmón superficial;

(i) La variante o resto comprende un sitio de unión que se une específicamente a SA de rata con una constante de velocidad de asociación (K_a) de (o de aproximadamente) 2×10^6 a (o a aproximadamente) 1×10^4 $M^{-1}s^{-1}$, opcionalmente de (o de aproximadamente) 1×10^6 a (o a aproximadamente) 3×10^4 $M^{-1}s^{-1}$, determinada de acuerdo con la resonancia de plasmón superficial;

(j) La variante o resto comprende un sitio de unión que se une específicamente a SA de ratón con una constante de disociación (KD) de (o de aproximadamente) 1 a (o a aproximadamente) 10.000 nM , determinada de acuerdo con la resonancia de plasmón superficial;

(k) La variante o resto comprende un sitio de unión que se une específicamente a SA de ratón con una constante de velocidad de disociación (K_d) de (o de aproximadamente) 2×10^{-3} a (o a aproximadamente) 0,15 s^{-1}, determinada de

acuerdo con la resonancia de plasmón superficial; y/o

(l) La variante o resto comprende un sitio de unión que se une específicamente a SA de ratón con una constante de velocidad de asociación (K_a) de (o de aproximadamente) 2 x 10^6 a (o a aproximadamente) 1 x 10^4 $M^{-1}s^{-1}$, opcionalmente de (o de aproximadamente) 2 x 10^6 a (o a aproximadamente) 1,5 x 10^4 $M^{-1}s^{-1}$ determinada de acuerdo con la resonancia de plasmón superficial;

Opcionalmente la variante o resto tiene

I: una KD de acuerdo con (a) y (b), una K_d de acuerdo con (b) y (e) y una K_a de acuerdo con (c) y (f); o

II: una KD de acuerdo con (a) y (g), una K_d de acuerdo con (b) y (h) y una K_a de acuerdo con (c) e (i); o

III: una KD de acuerdo con (a) y (j), una K_d de acuerdo con (b) y (k) y una K_a de acuerdo con (c) y (l); o

IV: cinética de acuerdo con I y II; o

V: cinética de acuerdo con I y III; o

VI: cinética de acuerdo con I, II y III.

La invención también proporciona un ligando que comprende una variante o resto de cualquier aspecto o realización anterior de la invención. Por ejemplo, el ligando puede ser un ligando dual específico (para ejemplos de ligandos de especificidad dual, véase el documento WO04003019). En un aspecto, la invención proporciona un ligando multiespecífico que comprende una variante o resto anti-SA de cualquier aspecto o realización anterior de la invención y un resto de unión adicional que se une específicamente a un antígeno diana distinto de SA. El o cada resto de unión puede ser cualquier resto de unión que se una específicamente a una diana, por ejemplo, el resto es un anticuerpo, fragmento de anticuerpo, scFv, Fab, dAb o un resto de unión que

comprende un armazón de proteína no inmunoglobulina. Dichos restos se describen con detalle en el documento WO2008/096158 (véanse los ejemplos 17 a 25, cuya descripción se incorpora en este documento como referencia). Son ejemplos de armazones de proteínas no inmunoglobulina CTLA-4, lipocalina, proteína A estafilococal (spA), Affibody™, Avimers™, GroEL y fibronectinas.

En una realización, se proporciona un engarce entre el resto de unión anti-diana y la variante sencilla o resto anti-SA, comprendiendo el engarce la secuencia de aminoácidos AST, opcionalmente ASTSGPS, por ejemplo, en la que se usa dAbs anti-SA y anti-diana.

Engarces alternativos se describen en el documento WO200708814 (incorporado en este documento como referencia) y en el documento WO2008/096158 (véase el pasaje de la página 135, de la línea 12 a la página 140, línea 14, cuya descripción y todas las secuencias de engarces se incorporan expresamente en este documento como referencia y incluyen explícitamente en este documento y para usar con la presente invención y se contempla que cualquier parte de dicha descripción puede incorporarse en una o más de las reivindicaciones de este documento).

En una realización del ligando multiespecífico, el antígeno diana puede ser, o ser parte de, polipéptidos, proteínas o ácidos nucleicos, que pueden ser de origen natural o sintéticos. En este aspecto, el ligando de la invención puede unirse al antígeno diana y actuar como un antagonista o agonista (por ejemplo, agonista del receptor EPO). Un experto en la materia apreciará que la elección es amplia y variada. Pueden ser por ejemplo, proteínas de seres humanos o animales, citocinas, receptores de citocinas, en los que los receptores de citocinas incluyen receptores para citocinas, enzimas, co-factores para enzimas o proteínas de unión a ADN. Las citocinas y factores de crecimiento adecuados incluyen, pero preferiblemente sin limitación: ApoE, Apo-SAA,

BDNF, Cardiotropina-1, EGF, receptor de EGF, ENA-78, Eotaxina, Eotaxina-2, Exodus-2, EpoR, FGF-ácido, FGF-básico, factor 10 del crecimiento de fibroblasto, ligando FLT3, Fractalkina (CX3C), GDNF, G-CSF, GM-CSF, GF-β1, insulina, IFN-γ, IGF-I, IGF-II, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8 (72 a.a.), IL-8 (77 a.a.), IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-16, IL-17, IL-18 (IGIF), Inhibina α, Inhibina β, IP-10, factor 2 del crecimiento de queratocitos (KGF-2), KGF, Leptina, LIF, Linfotactina, sustancia inhibidora de Müllerian, factor inhibidor de colonias de monocitos, proteína atrayente de monocitos, M-CSF, MDC (67 a.a.), MDC (69 a.a.), MCP-1 (MCAF), MCP-2, MCP-3, MCP-4, MDC (67 a.a.), MDC (69 a.a.), MIG, MIP-1α, MIP-1β, MIP-3α, MIP-3β, MIP-4, factor 1 inhibidor de progenitores mieloides (MPIF-1), NAP-2, Neurturina, factor del crecimiento Nervioso, β-NGF, NT-3, NT-4, Oncostatina M, PDGF-AA, PDGF-AB, PDGF-BB, PF-4, RANTES, SDF1α, SDF1β, SCF, SCGF, factor de células madre (SCF), TARC, TGF-α, TGF-β, TGF-β2, TGF-β3, factor de necrosis tumoral (TNF), TNF-α, TNF-β, receptor I de TNF, receptor II de TNF, TNIL-1, TPO, VEGF, receptor 1 de VEGF, receptor 2 de VEGF, receptor 3 de VEGF, GCP-2, GRO/MGSA, GRO-β, GRO-γ, HCC1, 1-309, HER 1, HER 2, HER 3 y HER 4, CD4, receptores de quimioquina humana CXCR4 o CCR5, proteína no estructural de tipo 3 (NS3) del virus de la hepatitis C, TNF-alfa, IgE, IFN-gamma, MMP-12, CEA, *H. pylori*, TB, gripe, Hepatitis E, MMP-12, receptores de internalización que se sobrexpresan en determinadas células, tales como el receptor del factor del crecimiento epidérmico (EGFR), receptor de ErBb2 en células tumorales, un receptor celular internalizador, receptor de LDL, receptor de FGF2, receptor de ErbB2, receptor de transferrina, receptor de PDGF, receptor de VEGF, PsmAr, una proteína matriz extracelular, elastina, fibronectina, laminina, antitripsina-α1, inhibidor proteasa del factor tisular, PDK1, GSK1, Bad, caspasa-9, Forkhead, un antígeno de *Helicobacter pylori*, un antígeno de *Mycobacterium tuberculosis*, y un

antígeno del virus de la gripe. Deberá apreciarse de que esta enumeración no es exhaustiva.

En una realización, el ligando multiespecífico comprende una variante o resto dAb anti-SA de la invención y un resto de unión anti-TNFR1, por ejemplo, un dAb anti-TNFR1. Opcionalmente, el ligando sólo tiene un resto de unión anti-TNFR1 (por ejemplo, dAb) para reducir la posibilidad de entrecruzamiento del receptor. En una realización, la variante dAb anti-SA es DOM7h-14 10.

En una realización, el resto de unión anti-TNFR1 es DOM1h-131-206 descrito en el documento WO2008149148 (cuya secuencia de aminoácidos y nucleótidos se describe en esta solicitud PCT, incorporada expresamente en este documento como referencia así como incluida explícitamente en este documento y para usar con la presente invención y se contempla que cualquier parte de dicha descripción pueda incorporarse en una o más de las reivindicaciones en este documento). En una realización, el ligando multiespecífico comprende o consiste en la secuencia de aminoácidos de DOM1h-131-206 y la secuencia de aminoácidos de DOM7h-14-10.

En una realización, el resto de unión anti-TNFR1 o dAb es cualquiera de dicho resto o dAb descrito en la solicitud en trámite junto con la presente USSN 61/153.746, cuya descripción se incorpora en este documento como referencia. En una realización, el resto de unión anti-TNFR1 comprende una secuencia de aminoácidos que es al menos el 95% idéntica a la secuencia de aminoácidos de DOM1h-574-156, DOM1h-574-72, DOM1h-574-109, DOM1h-574-138, DOM1h-574-162 o DOM1h-574-180 o la secuencia de aminoácidos de cualquier dAb anti-TNFR1 descrita en la Tabla 3. En una realización, el ligando multiespecífico comprende o consiste en la secuencia de aminoácidos de DOM1h-574-156 y la secuencia de aminoácidos de DOM7h-14-10.

En una realización, el ligando de la invención es una proteína de fusión que

comprende una variante o resto de la invención fusionada directa o indirectamente a uno o más polipéptidos. Por ejemplo, la proteína de fusión puede ser una "fusión a fármaco" como se describe en el documento WO2005/118642 (cuya descripción se incorpora en este documento como referencia), que comprende una variante de la invención y un fármaco polipeptídico como se define en esa solicitud PCT.

Como se usa en este documento, "fármaco" se refiere a cualquier compuesto (por ejemplo, molécula orgánica pequeña, ácido nucleico, polipéptido) que puede administrarse a un individuo para producir un efecto benéfico, terapéutico o de diagnóstico mediante la unión a y/o modificando la función de una molécula diana biológica en el individuo. La molécula diana puede ser una molécula diana endógena codificada por el genoma del individuo (por ejemplo una enzima, receptor, factor de crecimiento, citocina codificada por el genoma del individuo) o una molécula diana exógena codificada por el genoma de un patógeno (por ejemplo una enzima codificada por el genoma de un virus, bacteria, hongo, nematodo u otro patógeno). Los fármacos adecuados para usar en las proteínas y conjugados de fusión comprenden una variante de dAb anti-SA de la invención se describe en el documento WO2005/118642 y en el documento WO2006/059106 (cuya descripción completa se incorpora en este documento como referencia e incluye la lista completa de fármacos específicos aunque también esta lista se escribe en este documento expresamente y se contempla que dicha incorporación proporciona una descripción de fármacos específicos para incluir en las reivindicaciones de este documento). Por ejemplo, el fármaco puede ser péptido 1 de tipo glucagón (GLP-1) o una variante, alfa interferón 2b o una variante o exendina-4 o una variante.

En una realización, la invención proporciona un conjugado de fármaco como se define y se describe en el documento WO2005/118642 y en el documento

WO2008/059106, en el que el conjugado comprende una variante o resto de la invención. En un ejemplo, el fármaco está unido de manera covalente a la variante o resto (por ejemplo, la variante o resto y el fármaco se expresan como parte de un polipéptido sencillo). De manera alternativa, en un ejemplo, el fármaco no está unido o asociado de manera covalente a la variante o resto. El fármaco puede estar unido de manera covalente o no covalente a la variante o resto de manera directa o indirecta (por ejemplo, mediante un engarce adecuado y/o mediante unión no covalente de compañeros de unión complementarios (por ejemplo, biotina y avidina)). Cuando se emplean compañeros de unión complementarios, uno de los compañeros de unión puede unirse de manera covalente al fármaco directamente o mediante un resto de engarce adecuado y el compañero de unión complementario puede unirse de manera covalente a la variante o resto directamente o mediante un resto de engarce adecuado. Cuando el fármaco es un polipéptido o péptido, la composición del fármaco puede ser una proteína de fusión, en la que el polipéptido o péptido, fármaco y el resto de unión a polipéptido son partes específicas (restos) de una cadena polipeptídica continua. Como se describe en este documento, los restos de unión al polipéptido y los restos de fármaco polipeptídicos pueden unirse directamente entre sí mediante un enlace peptídico, o unirse mediante un aminoácido, péptido o engarce polipeptídico adecuado.

Un ligando que contiene una variante (monómero) de dominio variable sencillo o resto de la invención o más de un dominio variable sencillo o resto (multímero, proteína de fusión, conjugado y ligando de especificidad dual como se define este documento) que se une específicamente a la albúmina de suero, puede comprender adicionalmente una o más entidades seleccionadas de, pero preferiblemente no limitadas, un marcador, una etiqueta, un dominio variable sencillo adicional, un dominio variable sencillo adicional un dAb, un anticuerpo, un fragmento de anticuerpo, un marcador y un fármaco.

Una o más de estas entidades puede localizarse en el extremo COOH o en el extremo N o en ambos extremos N y COOH del ligando que comprende el dominio variable sencillo o resto, (de dominio variable sencillo de inmunoglobulina o no inmunoglobulina). Una o más de estas entidades puede localizarse en el extremo COOH, o en el extremo N, o en ambos extremos N y COOH del dominio variable sencillo o resto que se une específicamente a la albúmina de suero del ligando que contiene un dominio variable sencillo (monómero) o resto o más de un dominio variable sencillo o resto (multímero, proteína de fusión, conjugado y ligando de especificidad dual como se define en este documento). Los ejemplos no limitantes de etiquetas que pueden posicionarse en uno o ambos de estos extremos incluyen una etiqueta HA, his o una myc. Las entidades, que incluyen una o más etiquetas, marcadores y fármacos, pueden unirse al ligando que contiene un dominio variable sencillo (monómero) o más de un dominio variable sencillo o resto (multímero, proteína de fusión, conjugado y ligando de especificidad dual como se define en este documento) que se une a la albúmina de suero, de manera directa o mediante engarces como se describe anteriormente.

Un aspecto de la invención proporciona un producto de fusión, por ejemplo, una proteína de fusión o fusión con un péptido o conjugado con un fármaco NCE (nueva entidad química) que comprende un fármaco polipeptídico fusionado o conjugado (para un NCE) a cualquier variante o resto como se describe anteriormente, en la que la variante o resto es DOM7h-14-10 (o una variante que tiene una identidad de secuencia de aminoácidos de al menos el 95, 96, 97, 98 ó 99% con la secuencia de aminoácidos de DOM7h-14-10. DOM7h-14-10 producen únicamente una modesta disminución de afinidad cuando se fusiona o se conjuga con el compañero haciéndole útil en los productos de fusión.

La invención proporciona una composición que comprende una variante,

proteína de fusión, conjugado o ligando de cualquier aspecto de la invención y un diluyente, transportador, excipiente o vehículo farmacéuticamente aceptable.

También se incluye en este documento un ácido nucleico aislado que codifica cualquiera de las variantes, restos, proteínas de fusión, conjugados o ligandos descritos en este documento, por tanto, un ligando que contiene una variante de dominio variable sencillo (monómero) de la invención o más de una variante de dominio variable sencillo (por ejemplo, multimérico, proteína de fusión, conjugado, y ligando de especificidad dual como se define en este documento) que se une específicamente a la albúmina de suero o que se une específicamente a la albúmina de suero humana y al menos a una albúmina de suero no humana o fragmentos funcionalmente activos de los mismos. También se incluye en este documento un vector y/o un vector de expresión, una célula huésped que comprende el vector, por ejemplo, una célula vegetal o animal y/o una línea celular transformada con un vector, un método de expresión y/o de producción de una o más variantes, restos, proteínas de fusión o ligandos que contienen una variante de dominio variable sencillo (monómero) o resto o más de una variante de dominio variable sencillo o resto (por ejemplo, multimérico, proteína de fusión, conjugado, y ligando específico dual como se define en este documento) que se une específicamente a la albúmina de suero, o fragmento (o fragmentos) de la misma codificada por dichos vectores, que incluye en algunos casos cultivar la célula huésped de manera que la una o más variantes, proteínas de fusión, ligandos o fragmentos de los mismos se expresen y opcionalmente recuperen el ligando que contiene un dominio variable sencillo (monómero) o más de un dominio de variable sencillo (por ejemplo, multimérico, proteína de fusión, conjugado, y ligando específico dual como se define en este documento) que se une específicamente a la albúmina de suero, del medio de cultivo de la célula huésped. También se incluyen métodos para poner en contacto un ligando

descrito en este documento con albúmina de suero, que incluye albúmina de suero y/o albúmina (o albúminas) de suero no humanas, y/o una o más dianas distintas de la albúmina de suero, en la que las dianas incluyen moléculas biológicamente activas e incluyen proteínas de animales, citocinas como las enumeradas anteriormente e incluyen métodos en los que el poner en contacto se realiza *in vitro* así como la administración de cualquiera de las variantes, restos, proteínas de fusión o ligandos descritos en este documento a un animal huésped individual o célula *in vitro* y/o *ex vivo*. Preferiblemente, la administración de ligandos descritos en este documento que comprenden un dominio de variable sencillo (inmunoglobulina o no inmunoglobulina) dirigidos a la albúmina de suero y/o albúmina (o albúminas) de suero no humanas, y uno o más dominios dirigidos a una o más dianas distintas a la albúmina de suero, aumentarán la semivida, incluyendo la semivida T beta y/o terminal del ligando anti-diana. Las moléculas de ácido nucleico que codifican las variantes, proteínas de fusión o dominios sencillos que contienen ligandos o fragmentos de los mismos, incluyendo fragmentos funcionales de los mismos, se contemplan en este documento. Los vectores que codifican las moléculas de ácido nucleico que incluyen pero preferiblemente no limitan vectores de expresión, se contemplan en este documento, como también células huésped de una línea celular u organismo que contiene uno o más de estos vectores de expresión. También se contemplan métodos para producir cualquier variante, proteína de fusión o ligando, incluyendo, pero preferiblemente sin limitación, cualquiera de los ácidos nucleicos, vectores y células huésped mencionadas anteriormente.

Un aspecto de la invención proporciona un ácido nucleico que comprende una secuencia de nucleótidos que codifica una variante de acuerdo con la invención o un ligando multiespecífico de la invención o una proteína de fusión de la invención.

Un aspecto de la invención proporciona un ácido nucleico que comprende la

secuencia de nucleótidos de una variante de DOM7h-14 seleccionada de DOM7h-14-10, DOM7h-14-18, DOM7h-14-28, DOM7h-14-36 y DOM7h-14-19 o una secuencia de nucleótidos que es al menos 70, 75, 80, 85, 90, 95, 96, 97, 98 ó 99% idéntica a dicha secuencia seleccionada.

Un aspecto de la invención proporciona un vector que comprende el ácido nucleico de la invención. Un aspecto de la invención proporciona una célula huésped aislada que comprende el vector.

Se hace referencia al documento WO2008/096158 para detalles de sistemas de vectores de bibliotecas, combinación de dominios variables sencillos, caracterización de ligandos específicos duales, estructura de ligandos específicos duales, armazones para usar en la construcción de ligandos específicos duales, usos de dAb anti-albúmina de suero y ligandos multiespecíficos y ligandos que mejoran la semivida y composiciones y formulaciones que comprenden dAb anti-albúmina de suero. Estas descripciones se incorporan en este documento como referencia para proporcionar una guía de uso con la presente invención, que incluyen variantes, restos, ligandos, proteínas de fusión, conjugados, ácidos nucleicos, vectores, huéspedes y composiciones de la presente invención.

Las secuencias de la variante DOM7h-11, que no son de acuerdo con la invención, se describen en una Solicitud de Patente provisional de Estados Unidos en trámite junto con la presente titulada VARIANTES DE UNIÓN ANTI-ALBÚMINA DE SUERO MEJORADAS, presentada el mismo día que la presente solicitud. Estas secuencias de las variantes de DOM7h-11 (SEC ID Nº: 1-10 en la solicitud en trámite junto con la presente) se incorporan en este documento como referencia como se ha descrito de forma explícita.

SECUENCIAS

Tabla 1: Secuencias de Aminoácidos de dAbs Variante DOM7h-14

DOM7h-14-10 (SEC ID Nº: 1)

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILFGSRLQSGVP

SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

DOM7h-14-18 (SEC ID Nº: 2)

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQSGVP

SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

DOM7h-14-19 (SEC ID Nº: 3)

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLIWFGSRLQSGV

P

SRFSGSGSGTDFTLTISSLQPEDFATYHCAQAGTHPTTFGQGTKVEIKR

DOM7h-14-28 (SEC ID Nº: 4)

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILFGSRLQSGVP

SRFSGSGSGTDFTLTISSLQPEDFATYYCAQTGTHPTTFGQGTKVEIKR

DOM7h-14-36 (SEC ID Nº: 5)

DIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPKLLILWNSRLQSGVP

SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Tabla 2: Secuencias de Nucleótidos de dAbs Variante DOM7h-14

DOM7h-14-10 (SEC ID Nº: 6)

GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA
CCGTGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA
GTTGGTACCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTTGTTT
GGTTCCCGGT TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC
TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG
CTACGTACTA CTGTGCGCAG GCTGGGACGC ATCCTACGAC GTTCGGCCAA
GGGACCAAGG TGGAAATCAA ACGG

DOM7h-14-18 (SEC ID Nº: 7)

GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA
CCGTGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA
GTTGGTACCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCCTTGCT
TTTTCCCGTT TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC
TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG
CTACGTACTA CTGCGGCGCAG GCTGGGACGC ATCCTACGAC GTTCGGCCAA
GGGACCAAGG TGGAAATCAA ACGG

DOM7h-14-19 (SEC ID Nº: 8)

GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA
CCGTGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA
GTTGGTACCA GCAGAAACCA GGGAAAGCCC CAAAGCTCCT GATCTGGTTT
GGTTCCCGGT TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC

TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG CTACGTACCA CTGTGCGCAG GCGGGGACGC ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-14-28 (SEC ID Nº: 9)

GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGTACCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTTGTTT GGTTCCCGGT TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACGGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCGCAG ACTGGGACGC ATCCCACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-14-36 (SEC ID Nº: 10)

GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGACGTTAA GTTGGTACCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCCTTTGG AATTCCCGTT TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCGCAG GCTGGGACGC ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

Tabla 3: Secuencias de Aminoácidos de dAbs anti-TNFR1

>DOM1h-509 (SEC ID Nº: 11)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSQYRMHWVRQAPGKSLEWVSSIDTRGS
STYYADPVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKAVTMFSPFFDYWGQGT
LVTVSS

>DOM1h-510 (SEC ID Nº: 12)

EVQLLESGGGLVQPGGSLRLSCAASGFTFADYGMRWVRQAPGKGLEWVSSITRTGR
VTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWRNRHGEYLADFDYW
GQGTLVTVSS

>DOM1h-543 (SEC ID Nº: 13)

EVQLLESGGGLVQPGGSLRLSCAASGFTFMRYRMHWVRQAPGKGLEWVSSIDSNGS
STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRTERSPVFDYWGQG
TLVTVSS

>DOM1h-549 (SEC ID Nº: 14)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVDYEMHWVRQAPGKGLEWVSSISESGTT
TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKRRFSASTFDYWGQGTLV
TVSS

>DOM1h-574 (SEC ID Nº: 15)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGHWEPFDYWGQGT
LVTVSS

>DOM1h-574-1 (SEC ID Nº: 16)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPYDYWGQGT
LVTVSS

>DOM1h-574-2 (SEC ID Nº: 17)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDYWGQGT
LVTVSS

>DOM1h-574-7 (SEC ID Nº: 18)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-8 (SEC ID Nº: 19)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-9 (SEC ID Nº: 20)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYMQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGT
LVTVSS

>DOM1h-574-10 (SEC ID Nº: 21)

EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKDLEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-11 (SEC ID N°: 22)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDHWGQGT
LVTVSS

>DOM1h-574-12 (SEC ID N°: 23)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDYWGQGT
LVTVSS

>DOM1h-574-13 (SEC ID N°: 24)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDYWGQGT
LVTVSS

>DOM1h-574-14 (SEC ID N°: 25)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-15 (SEC ID N°: 26)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-16 (SEC ID Nº: 27)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-17 (SEC ID Nº: 28)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTGD
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-18 (SEC ID Nº: 29)

EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKDLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-19 (SEC ID Nº: 30)

EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKDLEWVSQISNTGD
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-25 (SEC ID Nº: 31)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTL
VTVSS

>DOM1h-574-26 (SEC ID Nº: 32)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFEYWGQGTL
VTVSS

>DOM1h-574-27 (SEC ID Nº: 33)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTL
VTVSS

>DOM1h-574-28 (SEC ID Nº: 34)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-29 (SEC ID Nº: 35)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTL
VTVSS

>DOM1h-574-30 (SEC ID Nº: 36)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAAYYCAIYTGRWEPFDYWGQGT
LVTVSS

>DOM1h-574-31 (SEC ID Nº: 37)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFNYWGQGTL
VTVSS

>DOM1h-574-32 (SEC ID Nº: 38)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-33 (SEC ID Nº: 39)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNSLYLQMNSLRAEDTAVYYCAIYTGRWVPFDNWGQGT
LVTVSS

>DOM1h-574-35 (SEC ID Nº: 40)

EVQLLESGGGLVQPGGSLRLSCAASGFTFITYSMGWVRQAPGKGLEWVSQISNTGDR
TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFQYWGQGTLV
TVSS

>DOM1h-574-36 (SEC ID Nº: 41)

EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-37 (SEC ID Nº: 42)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-38 (SEC ID Nº: 43)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGT
LVTVSS

>DOM1h-574-39 (SEC ID Nº: 44)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGT
LVTVSS

>DOM1h-574-40 (SEC ID Nº: 45)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFKYWGQGTL
VTVSS

>DOM1h-574-53 (SEC ID Nº: 46)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSKYSMGWVRQAPGKGLEWVSQISNTGE
RRYYADSVKGRFTISRDNPKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFEYWGQGT
LVTVSS

>DOM1h-574-54 (SEC ID Nº: 47)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVNYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPYEYWGQGTL
VTVTS

>DOM1h-574-65 (SEC ID Nº: 48)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-66 (SEC ID Nº: 49)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGT
LVTVSS

>DOM1h-574-67 (SEC ID Nº: 50)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGT
LVTVSS

>DOM1h-574-68 (SEC ID Nº: 51)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGT
LVTVSS

>DOM1h-574-69 (SEC ID Nº: 52)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-70 (SEC ID Nº: 53)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAVYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-71 (SEC ID Nº: 54)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTL
VTVSS

>DOM1h-574-72 (SEC ID Nº: 55)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-73 (SEC ID Nº: 56)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTL
VTVSS

>DOM1h-574-74 (SEC ID Nº: 57)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-75 (SEC ID Nº: 58)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-76 (SEC ID Nº: 59)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGT
LVTVSS

>DOM1h-574-77 (SEC ID Nº: 60)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGT
LVTVSS

>DOM1h-574-78 (SEC ID Nº: 61)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGT
LVTVSS

>DOM1h-574-79 (SEC ID Nº: 62)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-84 (SEC ID Nº: 63)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-85 (SEC ID Nº: 64)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGT
LVTVSS

>DOM1h-574-86 (SEC ID Nº: 65)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGT
LVTVSS

>DOM1h-574-87 (SEC ID Nº: 66)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGT
LVTVSS

>DOM1h-574-88 (SEC ID Nº: 67)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-90 (SEC ID Nº: 68)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKFSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-91 (SEC ID Nº: 69)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-92 (SEC ID Nº: 70)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-93 (SEC ID Nº: 71)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-94 (SEC ID Nº: 72)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAAYYCAIYTGRWPDFDYWGQGT
LVTVSS

>DOM1h-574-95 (SEC ID Nº: 73)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAAYYCAIYTGRWPDFEYWGQGT
LVTVSS

>DOM1h-574-96 (SEC ID Nº: 74)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFDYWGQGT
LVTVSS

>DOM1h-574-97 (SEC ID Nº: 75)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFEYWGQGTL
VTVSS

>DOM1h-574-98 (SEC ID Nº: 76)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFDYWGQGT
LVTVSS

>DOM1h-574-99 (SEC ID Nº: 77)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFEYWGQGT
LVTVSS

>DOM1h-574-100 (SEC ID Nº: 78)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISAWGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-101 (SEC ID Nº: 79)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDGGQ
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-102 (SEC ID Nº: 80)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDSGY
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-103 (SEC ID Nº: 81)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDGGT
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-104 (SEC ID Nº: 82)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDKGT
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-105 (SEC ID Nº: 83)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISETGR
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-106 (SEC ID Nº: 84)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQINNTGS
TTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-107 (SEC ID Nº: 85)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-108 (SEC ID Nº: 86)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-109 (SEC ID Nº: 87)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-110 (SEC ID Nº: 88)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-111 (SEC ID Nº: 89)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGT
LVTVSS

>DOM1h-574-112 (SEC ID Nº: 90)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-113 (SEC ID Nº: 91)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RRYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-114 (SEC ID Nº: 92)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQILNTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-115 (SEC ID Nº: 93)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-116 (SEC ID Nº: 94)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RRYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-117 (SEC ID Nº: 95)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RRYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-118 (SEC ID Nº: 96)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAVYTGRWVSFEYWGQGT
LVTVSS

>DOM1h-574-119 (SEC ID Nº: 97)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCALYTGRWVSFEYWGQGT
LVTVSS

>DOM1h-574-120 (SEC ID Nº: 98)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAVYTGRWVPFEYWGQGT
LVTVSS

>DOM1h-574-121 (SEC ID Nº: 99)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCALYTGRWVPFEYWGQGT
LVTVSS

>DOM1h-574-122 (SEC ID Nº: 100)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTAD
RRYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-123 (SEC ID Nº: 101)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-124 (SEC ID Nº: 102)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RRYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-125 (SEC ID Nº: 103)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTAD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-126 (SEC ID Nº: 104)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-127 (SEC ID Nº: 105)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RRYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-128 (SEC ID Nº: 106)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTAD
RRYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-129 (SEC ID Nº: 107)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIVNTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-130 (SEC ID Nº: 108)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-131 (SEC ID Nº: 109)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-132 (SEC ID Nº: 110)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGT
LVTVSS

>DOM1h-574-133 (SEC ID Nº: 111)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTL
VTVSS

>DOM1h-574-134 (SEC ID N°: 112)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYSHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-135 (SEC ID N°: 113)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-137 (SEC ID N°: 114)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYTDAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTL
VTVSS

>DOM1h-574-138 (SEC ID N°: 115)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-139 (SEC ID N°: 116)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-140 (SEC ID Nº: 117)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-141 (SEC ID Nº: 118)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-142 (SEC ID Nº: 119)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-143 (SEC ID Nº: 120)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-144 (SEC ID Nº: 121)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTAD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-145 (SEC ID Nº: 122)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTGD
RRYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-146 (SEC ID Nº: 123)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTGD
RRYYDDAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-147 (SEC ID Nº: 124)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWGPFVYWGQGT
LVTVSS

>DOM1h-574-148 (SEC ID Nº: 125)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFAYWGQGTL
VTVSS

>DOM1h-574-149 (SEC ID Nº: 126)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWGPFQYWGQGT
LVTVSS

>DOM1h-574-150 (SEC ID Nº: 127)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFQYWGQGT
LVTVSS

>DOM1h-574-151 (SEC ID Nº: 128)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-152 (SEC ID Nº: 129)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFQYWGQGT
LVTVSS

>DOM1h-574-153 (SEC ID Nº: 130)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFQYWGQGT
LVTVSS

>DOM1h-574-154 (SEC ID Nº: 131)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-155 (SEC ID Nº: 132)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-156 (SEC ID Nº: 133)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-157 (SEC ID Nº: 134)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGT
LVTVSS

>DOM1h-574-158 (SEC ID Nº: 135)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGT
LVTVSS

>DOM1h-574-159 (SEC ID Nº: 136)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTL
VTVSS

>DOM1h-574-160 (SEC ID Nº: 137)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTL
VTVSS

>DOM1h-574-161 (SEC ID Nº: 138)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYSHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-162 (SEC ID Nº: 139)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYSHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-163 (SEC ID Nº: 140)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-164 (SEC ID Nº: 141)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-165 (SEC ID N°: 142)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-166 (SEC ID N°: 143)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-167 (SEC ID N°: 144)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-169 (SEC ID N°: 145)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-170 (SEC ID N°: 146)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-171 (SEC ID Nº: 147)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-172 (SEC ID Nº: 148)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTAD
RTYYDHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-173 (SEC ID Nº: 149)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTAD
RRYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-174 (SEC ID Nº: 150)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RRYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-175 (SEC ID Nº: 151)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTAD
RRYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-176 (SEC ID Nº: 152)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RRYYDHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-177 (SEC ID Nº: 153)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTAD
RRYYDHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-178 (SEC ID Nº: 154)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTAD
RRYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-179 (SEC ID Nº: 155)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RRYYDDAVKGRFTITRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-180 (SEC ID Nº: 156)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

Tabla 4: Secuencias de Nucleótidos de dAbs anti-TNFR1

>DOM1h-509 (SEC ID Nº: 157)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAGTCAGTATAGGATGCATTGGGT
CCGCCAGGCTCCAGGGAAGAGTCTAGAGTGGGTCTCAAGTATTGATACTAGGGGT
TCGTCTACATACTACGCAGACCCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAAGCTGTGACGATGTTTTCTCCTTTTTTTGACTACTGGGG
TCAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-510 (SEC ID Nº: 158)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGCTGATTATGGGATGCGTTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTACGCGGACTGGT
CGTGTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATGGCGGAATCGGCATGGTGAGTATCTTGCTGATTTTG
ACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-543 (SEC ID Nº: 159)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTATGAGGTATAGGATGCATTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCGATTGATTCTAATGGT
TCTAGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
GTATATTACTGTGCGAAAGATCGTACGGAGCGTTCGCCGGTTTTTGACTACTGGGG
TCAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-549 (SEC ID Nº: 160)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTGATTATGAGATGCATTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTAGTGAGAGTGGT
ACGACGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAACGTCGTTTTTCTGCTTCTACGTTTGACTACTGGGGTCA
GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574 (SEC ID Nº: 161)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATATACGGGTCATTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-1 (SEC ID Nº: 162)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATATACGGGTCGTTGGGAGCCTTATGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-2 (SEC ID Nº: 163)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-4 (SEC ID Nº: 164)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC

GGTATATTACTGTGCGAAATATACGGGTCGTTGGGAGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-180 (SEC ID N°: 165)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCT
GATCGTACATACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-7 (SEC ID N°: 166)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-8 (SEC ID N°: 167)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGATGGGT
CCGCCAGGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGAATACGGGT

GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACAGTCTCGAGC

>DOM1h-574-9 (SEC ID Nº: 168)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATATCCCGCGACA
ATTCCAAGAACACGCTGTATATGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-10 (SEC ID Nº: 169)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGGTAAGTATTCGATGGGGTGGG
TCCGCCAGGCTCCAGGGAAGGATCTAGAGTGGGTCTCACAGATTTCGAATACGGG
TGGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-11 (SEC ID Nº: 170)

GAGGTGCAGCTGTTGGAGTCAGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG

CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATATACGGGTCGTTGGGAGCCTTTTGACCACTGGGGTC
AGGGGACCCTGGTCACCGTCTCGAGC

>DOM1h-574-12 (SEC ID Nº: 171)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-13 (SEC ID Nº: 172)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-14 (SEC ID Nº: 173)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-15 (SEC ID Nº: 174)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-16 (SEC ID Nº: 175)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGATGGGT
CCGCCAGGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC

AGGGAACCCTGGTCACAGTCTCGAGC

>DOM1h-574-17 (SEC ID Nº: 176)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGATGGGT
CCGCCAGGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACAGTCTCGAGC

>DOM1h-574-18 (SEC ID Nº: 177)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGGTAAGTATTCGATGGGGTGGG
TCCGCCAGGCTCCAGGGAAGGATCTAGAGTGGGTCTCACAGATTTCGAATACGGG
TGATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-19 (SEC ID Nº: 178)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGGTAAGTATTCGATGGGGTGGG
TCCGCCAGGCTCCAGGGAAGGATCTAGAGTGGGTCTCACAGATTTCGAATACGGG
TGATCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA

ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-25 (SEC ID Nº: 179)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-26 (SEC ID Nº: 180)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-27 (SEC ID Nº: 181)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT

CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCGGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGAAGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-28 (SEC ID Nº: 182)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-29 (SEC ID Nº: 183)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-30 (SEC ID Nº: 184)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGCATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-31 (SEC ID Nº: 185)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTAACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-32 (SEC ID Nº: 186)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-33 (SEC ID N°: 187)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACTCGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGTGCCTTTTGACAACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-35 (SEC ID N°: 188)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTATTACGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTCAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-36 (SEC ID N°: 189)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGGTAAGTATTCGATGGGGTGGG
TCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGG
TGATCGTACATACTACGCGGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG

CGGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGT

CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-37 (SEC ID Nº: 190)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG

CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTTTTAAGTATTCGATGGGGTGGGT

CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT

GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA

ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAAGACACCGC

GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC

AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-38 (SEC ID Nº: 191)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG

CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT

CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGT

GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA

ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC

GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC

AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-39 (SEC ID Nº: 192)

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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT

GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-40 (SEC ID Nº: 193)

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CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTAAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-53 (SEC ID Nº: 194)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAGTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GAGCGTAGATACTACGCAGACTCAGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATCCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGAGCCTTTTGAATACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-54 (SEC ID Nº: 195)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG

CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAACTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCGGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTATGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCACGAGC

>DOM1h-574-65 (SEC ID Nº: 196)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGATA
ATTCCAAGAACACACTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-66 (SEC ID Nº: 197)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGTATATTACTGTGCGATATATACGGGTCGTTGGAAGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-67 (SEC ID Nº: 198)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-68 (SEC ID Nº: 199)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGTATATTACTGTGCGATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-69 (SEC ID Nº: 200)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGG

TCAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-70 (SEC ID Nº: 201)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGGTATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-71 (SEC ID Nº: 202)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-72 (SEC ID Nº: 203)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA

ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-73 (SEC ID Nº: 204)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-74 (SEC ID Nº: 205)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-75 (SEC ID Nº: 206)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT

CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGT
GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-76 (SEC ID Nº: 207)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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CCGCCAGGCCCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGG
TGATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGAAGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-77 (SEC ID Nº: 208)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGT
GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-78 (SEC ID Nº: 209)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGT
GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-79 (SEC ID Nº: 210)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGT
GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-84 (SEC ID Nº: 211)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-85 (SEC ID Nº: 212)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGAAGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-86 (SEC ID Nº: 213)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCCCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAAGACACCGC
GGTATATTACTGTGCGATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-87 (SEC ID Nº: 214)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC

GGTATATTACTGTGCGATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-88 (SEC ID Nº: 215)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-90 (SEC ID Nº: 216)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTTTTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGG
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>DOM1h-574-91 (SEC ID Nº: 217)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT

GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-92 (SEC ID Nº: 218)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
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>DOM1h-574-93 (SEC ID Nº: 219)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGT
GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
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>DOM1h-574-94 (SEC ID Nº: 220)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG

CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
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AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGCATATTACTGTGCGATATATACGGGTCGGTGGCCCGACTTTGACTACTGGGG
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>DOM1h-574-95 (SEC ID Nº: 221)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
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>DOM1h-574-96 (SEC ID Nº: 222)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGCCCGACTTTGACTACTGGGGT
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>DOM1h-574-97 (SEC ID Nº: 223)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-98 (SEC ID Nº: 224)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-99 (SEC ID Nº: 225)

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GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGCCCGACTTTGAGTACTGGGGT

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>DOM1h-574-100 (SEC ID Nº: 226)

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>DOM1h-574-101 (SEC ID Nº: 227)

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TCAGAGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
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CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-102 (SEC ID Nº: 228)

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TACCGCACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA

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>DOM1h-574-103 (SEC ID Nº: 229)

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TACGCGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
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>DOM1h-574-104 (SEC ID Nº: 230)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-105 (SEC ID Nº: 231)

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>DOM1h-574-106 (SEC ID Nº: 232)

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>DOM1h-574-107 (SEC ID Nº: 233)

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>DOM1h-574-108 (SEC ID Nº: 234)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-109 (SEC ID Nº: 235)

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>DOM1h-574-110 (SEC ID Nº: 236)

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>DOM1h-574-111 (SEC ID Nº: 237)

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>DOM1h-574-112 (SEC ID Nº: 238)

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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-113 (SEC ID Nº: 239)

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CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-114 (SEC ID Nº: 240)

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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-115 (SEC ID Nº: 241)

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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-116 (SEC ID Nº: 242)

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>DOM1h-574-117 (SEC ID Nº: 243)

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>DOM1h-574-118 (SEC ID Nº: 244)

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>DOM1h-574-119 (SEC ID Nº: 245)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-120 (SEC ID Nº: 246)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTTACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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>DOM1h-574-121 (SEC ID Nº: 247)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-122 (SEC ID Nº: 248)

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GATCGTAGATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-123 (SEC ID Nº: 249)

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GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-124 (SEC ID Nº: 250)

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GATCGTAGATACTACGCACACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-125 (SEC ID Nº: 251)

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GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-126 (SEC ID Nº: 252)

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TGATCGTAGATACTACGCACACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
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CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-127 (SEC ID Nº: 253)

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GATCGTAGATACTACGCACACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA

ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-128 (SEC ID Nº: 254)

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GATCGTAGATACTACGCACACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-129 (SEC ID Nº: 255)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-130 (SEC ID Nº: 256)

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AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
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>DOM1h-574-131 (SEC ID Nº: 257)

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GATCGTACATACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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>DOM1h-574-132 (SEC ID Nº: 258)

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>DOM1h-574-133 (SEC ID Nº: 259)

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TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-134 (SEC ID N°: 260)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
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GATCGTACATACTACTCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-135 (SEC ID N°: 261)

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>DOM1h-574-137 (SEC ID Nº: 262)

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>DOM1h-574-138 (SEC ID Nº: 263)

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>DOM1h-574-139 (SEC ID Nº: 264)

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>DOM1h-574-140 (SEC ID N°: 265)

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>DOM1h-574-141 (SEC ID N°: 266)

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>DOM1h-574-142 (SEC ID N°: 267)

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>DOM1h-574-143 (SEC ID Nº: 268)
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>DOM1h-574-144 (SEC ID Nº: 269)
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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-145 (SEC ID Nº: 270)
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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-146 (SEC ID Nº: 271)

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AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
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>DOM1h-574-147 (SEC ID Nº: 272)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-148 (SEC ID Nº: 273)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-149 (SEC ID Nº: 274)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-150 (SEC ID Nº: 275)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACTCTGGTCACCGTCTCGAGC

>DOM1h-574-151 (SEC ID Nº: 276)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-152 (SEC ID Nº: 277)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-153 (SEC ID Nº: 278)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-154 (SEC ID Nº: 279)
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GATCGTAGATACTACGATCACTCTGTGAAGGGCCGGTTCACTATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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>DOM1h-574-155 (SEC ID Nº: 280)
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>DOM1h-574-156 (SEC ID Nº: 281)
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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
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>DOM1h-574-157 (SEC ID N°: 282)

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TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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>DOM1h-574-158 (SEC ID N°: 283)

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TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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>DOM1h-574-159 (SEC ID N°: 284)

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TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-160 (SEC ID Nº: 285)

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GATCGTACATACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-161 (SEC ID Nº: 286)

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TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCG
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>DOM1h-574-162 (SEC ID Nº: 287)

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TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCG
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>DOM1h-574-163 (SEC ID Nº: 288)

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TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-164 (SEC ID Nº: 289)

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GATCGTACATACTACACACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-165 (SEC ID Nº: 290)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-166 (SEC ID Nº: 291)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-167 (SEC ID Nº: 292)

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TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-168 (SEC ID Nº: 293)
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>DOM1h-574-169 (SEC ID Nº: 294)
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>DOM1h-574-170 (SEC ID Nº: 295)
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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
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>DOM1h-574-171 (SEC ID Nº: 296)

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GATCGTACATACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCG
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>DOM1h-574-172 (SEC ID Nº: 297)

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GATCGTACATACTACGATCACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
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>DOM1h-574-173 (SEC ID Nº: 298)

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>DOM1h-574-174 (SEC ID Nº: 299)

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GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-175 (SEC ID Nº: 300)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCT
GATCGTAGATACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-176 (SEC ID Nº: 301)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCT
GATCGTAGATACTACGATCACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-177 (SEC ID Nº: 302)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCT
GATCGTAGATACTACGATCACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGGACCCTGGTCACCGTCTCGAGC

>DOM1h-574-178 (SEC ID Nº: 303)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCT
GATCGTAGATACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT

CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-179 (SEC ID Nº: 304)

GAGGTGCAGCTGCTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCT
GATCGTAGATACTACGATGACGCGGTGAAGGGCCGGTTCACCATCACCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

Tabla 5: Fusiones dAb anti-albúmina de suero (DOM7h)

(usados en estudios de Rata):

Fusión DOM7h-14/Exendina-4 **número DMS 7138**

Secuencia de aminoácidos (SEC ID Nº: 305)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGGGS
DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGAALPRTFGQGTKVEIKR

Secuencia de nucleótidos (SEC ID Nº: 306)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGT
GCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGCACCTCCG

CCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGCGGTGGCGGGTC

GGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGT

GTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTGGTACCA

GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTCCTCGTTGCAA

AGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA

CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCTCAGGGTGCG

GCGTTGCCTAGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Fusión DOM7h-14-10/Exendina-4 número DMS 7139

Secuencia de aminoácidos (SEC ID Nº: 307)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGGGS

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSG

VPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKR

Secuencia de nucleótidos (SEC ID Nº: 308)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGT

GCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGCACCTCCG

CCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGCGGTGGCGGGTC

GGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGT

GTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTGGTACCA

GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTCCTCGTTGCAA

AGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA

CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCTCAGGGTTTG

AGGCATCCTAAGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Fusión DOM7h-14-18/Exendina-4 número DMS 7140

Secuencia de aminoácidos (SEC ID Nº: 309)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGGGS

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSG

VPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLMKPMTFGQGTKVEIKR

Secuencia de nucleótidos (SEC ID Nº: 310)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGT

GCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGGCACCTCCG

CCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGCGGTGGCGGGTC

GGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGT

GTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTGGTACCA

GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTCCTCGTTGCAA

AGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA

CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCTCAGGGTCTT

ATGAAGCCTATGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Fusión DOM7h-14-19/Exendina-4 número DMS 7141

Secuencia de aminoácidos (SEC ID Nº: 311)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGGGS

DIQMTQSPSSLSASVGDRVTISCRASQWIGSQLSWYQQKPGEAPKLLIMWRSSLQSG

VPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGAALPRTFGQGTKVEIKR

Secuencia de nucleótidos (SEC ID Nº: 312)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGT

GCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGCACCTCCG

CCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGCGGTGGCGGGTC

GGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGT

GTCACCATCTCTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTGGTACCA

GCAGAAACCAGGGGAAGCCCCTAAGCTCCTGATCATGTGGCGTTCCTCGTTGCAA

AGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA

CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCTCAGGGTGCG

GCGTTGCCTAGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Fusión DOM7h-11/Exendina-4 número DMS 7142

Secuencia de aminoácidos (SEC ID Nº: 313)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGGGS

DIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPKLLIWFGSRLQSGV

PSRFSSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Secuencia de nucleótidos (SEC ID Nº: 314)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGT

GCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGCACCTCCG
CCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGCGGTGGCGGGTC
GGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGT
GTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGACGTTAAGTTGGTACC
AGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTGGTTTGGTTCCCGGTTGCA
AAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA
CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGG
GACGCATCCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Fusión DOM7h-11-12/Exendina-4 número DMS 7147

Secuencia de aminoácidos (SEC ID Nº: 315)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGGGS
DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILFGSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Secuencia de nucleótidos (SEC ID Nº: 316)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGT
GCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGCACCTCCG
CCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGCGGTGGCGGGTC
GGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGT
GTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACC
AGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTTGTTTGGTTCCCGGTTGCAA
AGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA

CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGG

GACGCATCCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Fusión DOM7h-11-15/Exendina-4 número DMS 7143

Secuencia de aminoácidos (SEC ID Nº: 317)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGGGS

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQSGVP

SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Secuencia de nucleótidos (SEC ID Nº: 318)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGT

GCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGCACCTCCG

CCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGCGGTGGCGGGTC

GGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGT

GTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACC

AGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCCCGTTTGCAA

AGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA

CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGCGCGCAGGCTGG

GACGCATCCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Fusión DOM7h-14-10/G4SC - NCE

Secuencia de aminoácidos (SEC ID Nº: 319) que codifica DOM7h14-10/G4SC

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKRGGGGSC

La cisteína C-terminal puede unirse a una nueva entidad química (compuesto químico farmacéutico NCE), por ejemplo usando enlace maleimida.

Secuencia de nucleótidos (SEC ID Nº: 320) que codifica DOM7h14-10/G4SC

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGT
CACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTGGTACCAGC
AGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTCCTCGTTGCAAAGT
GGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCAT
CAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCTCAGGGTTTGAGGC
ATCCTAAGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGGTGGCGGAG
GGGGTTCCTGT

Fusión DOM7h14-10/TVAAPSC

Secuencia de aminoácidos (SEC ID Nº: 321)

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKRTVAAPSC

La cisteína C-terminal puede unirse a una nueva entidad química (compuesto químico farmacéutico NCE), por ejemplo usando enlace maleimida.

Secuencia de nucleótidos (SEC ID Nº: 322)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGT
CACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTGGTACCAGC
AGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTCCTCGTTGCAAAGT
GGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCAT
CAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCTCAGGGTTTGAGGC
ATCCTAAGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGACCGTCGCTGC
TCCATCTTGT

(usada en estudios de ratón):-

Fusión DOM7h-11/DOM1m-21-23 número DMS 5515

Secuencia de aminoácidos (SEC ID Nº: 323)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDSYGR
GTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNAFDYWGQGT
QVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPK
LLIWFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTK
VEIKR

Secuencia de aminoácidos más secuencia de nucleótidos más etiqueta myc (SEC ID Nº: 324)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDSYGR
GTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNAFDYWGQGT

QVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPK

LLIWFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTK

VEIKRAAAEQKLISEEDLN

Secuencia de nucleótidos (SEC ID Nº: 325)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG

CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGGGGTGGCT

CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTGATTCTTATGGT

CGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCAGCATCTCCCGCGACA

ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC

CGTATATTACTGTGCGAAAATTTCTCAGTTTGGGTCAAATGCGTTTGACTACTGGG

GTCAGGGAACCCAGGTCACCGTCTCGAGCGCTAGCACCAGTGGTCCATCGGACAT

CCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCACCA

TCACTTGCCGGGCAAGTCGTCCGATTGGGACGACGTTAAGTTGGTACCAGCAGAA

ACCAGGGAAAGCCCCTAAGCTCCTGATCTGGTTTGGTTCCCGGTTGCAAAGTGGG

GTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAG

CAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCAT

CCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Secuencia de nucleótidos más etiqueta myc (SEC ID Nº: 326)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG

CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGGGGTGGCT

CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTGATTCTTATGGT

CGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCAGCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
CGTATATTACTGTGCGAAAATTTCTCAGTTTGGGTCAAATGCGTTTGACTACTGGG
GTCAGGGAACCCAGGTCACCGTCTCGAGCGCTAGCACCAGTGGTCCATCGGACAT
CCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCACCA
TCACTTGCCGGGCAAGTCGTCCGATTGGGACGACGTTAAGTTGGTACCAGCAGAA
ACCAGGGAAAGCCCCTAAGCTCCTGATCTGGTTTGGTTCCCGGTTGCAAAGTGGG
GTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAG
CAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCAT
CCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAA
CAAAAACTCATCTCAGAAGAGGATCTGAATTAA

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Secuencia de aminoácidos (SEC ID Nº: 327)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDSYGR
GTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNAFDYWGQGT
QVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPK
LLILFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKV
EIKR

Secuencia de aminoácidos más secuencia de nucleótidos más etiqueta myc (SEC ID Nº: 328)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDSYGR

GTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNAFDYWGQGT
QVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCPASRPIGTMLSWYQQKPGKAPK
LLILFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKV
EIKRAAAEQKLISEEDLN

Secuencia de nucleótidos (SEC ID Nº: 329)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGGGGTGGCT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTGATTCTTATGGT
CGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCAGCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
CGTATATTACTGTGCGAAAATTTCTCAGTTTGGGTCAAATGCGTTTGACTACTGGG
GTCAGGGAACCCAGGTCACCGTCTCGAGCGCTAGCACCAGTGGTCCATCGGACAT
CCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCACCA
TCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACCAGCAGAA
ACCAGGGAAAGCCCCTAAGCTCCTGATCTTGTTTGGTTCCCGGTTGCAAAGTGGG
GTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAG
CAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCAT
CCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Secuencia de nucleótidos más etiqueta myc (SEC ID Nº: 330)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGGGGTGGCT

CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTGATTCTTATGGT
CGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCAGCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
CGTATATTACTGTGCGAAAATTTCTCAGTTTGGGTCAAATGCGTTTGACTACTGGG
GTCAGGGAACCCAGGTCACCGTCTCGAGCGCTAGCACCAGTGGTCCATCGGACAT
CCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCACCA
TCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACCAGCAGAA
ACCAGGGAAAGCCCCTAAGCTCCTGATCTTGTTTGGTTCCCGGTTGCAAAGTGGG
GTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAG
CAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCAT
CCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAA
CAAAAACTCATCTCAGAAGAGGATCTGAATTAA

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Secuencia de aminoácidos (SEC ID Nº: 331)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDSYGR
GTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNAFDYWGQGT
QVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPK
LLILAFSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKV
EIKR

Secuencia de aminoácidos más secuencia de nucleótidos más etiqueta myc (SEC ID Nº: 332)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDSYGR

GTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNAFDYWGQGT

QVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPK

LLILAFSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKV

EIKRAAAEQKLISEEDLN

Secuencia de nucleótidos (SEC ID Nº: 333)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG

CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGGGGTGGCT

CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTGATTCTTATGGT

CGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCAGCATCTCCCGCGACA

ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC

CGTATATTACTGTGCGAAAATTTCTCAGTTTGGGTCAAATGCGTTTGACTACTGGG

GTCAGGGAACCCAGGTCACCGTCTCGAGCGCTAGCACCAGTGGTCCATCGGACAT

CCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCACCA

TCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACCAGCAGAA

ACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCCCGTTTGCAAAGTGGGG

TCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC

AGTCTGCAACCTGAAGATTTTGCTACGTACTACTGCGCGCAGGCTGGGACGCATC

CTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Secuencia de nucleótidos más etiqueta myc (SEC ID Nº: 334)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG

CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGGGGTGGCT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTGATTCTTATGGT
CGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCAGCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
CGTATATTACTGTGCGAAAATTTCTCAGTTTGGGTCAAATGCGTTTGACTACTGGG
GTCAGGGAACCCAGGTCACCGTCTCGAGCGCTAGCACCAGTGGTCCATCGGACAT
CCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCACCA
TCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACCAGCAGAA
ACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCCCGTTTGCAAAGTGGGG
TCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGTCTGCAACCTGAAGATTTTGCTACGTACTACTGCGCGCAGGCTGGGACGCATC
CTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAAC
AAAAACTCATCTCAGAAGAGGATCTGAATTAA

cuando en esta tabla se indica una molécula etiquetada con myc, ésta era la versión usada en estudios PK en los ejemplos. Cuando no se proporcionan secuencias etiquetadas con myc, los estudios PK en los ejemplos no se realizaron con material etiquetado con myc, es decir, los estudios se realizaron con las construcciones mostradas no etiquetados.

EJEMPLIFICACIÓN

En el apartado experimental toda la numeración se realiza de acuerdo con Kabat (Kabat, E.A. National Institutes of Health (US) & Columbia University. Sequences of proteins of immunological interst, 5 ed. (US Dept. Of Health and Human Services Public Health Service, National Institues of Health, Bethesda, MD, 1991)).

Se describen variantes derivadas de DOM7h-11 y DOM7h-14. Las variantes DOM7h-11 no son de acuerdo con la invención.

EJEMPLO 1: Maduración de Afinidad Vk

Selecciones:

Se obtuvieron antígenos de HSA (Albúmina de Suero Humana) y RSA (Albúmina de Suero de Rata) de Sigma (esencialmente sin ácidos grasos, ~99% (electroforesis en gel de agarosa), polvo liofilizado Cat. Nº A3782 y A6414 respectivamente).

Se prepararon productos biotinilados de los dos antígenos anteriores usando Sulfo-NHS-SS-Biotina unida a Ez (Pierce, Cat. Nº 21331). El reactivo sin biotina se eliminó pasando las muestras dos veces a través de una columna de desalinización PD10 seguido de diálisis durante una noche frente un volumen sobrante1000x de PBS a 4 ºC. El producto resultante se ensayó por espectrofotometría de masas y se observaron 1-2 biotinas por molécula.

Bibliotecas de maduración de afinidad:

Se crearon bibliotecas propensas a errores y CDR usando los dAb parentales DOM7h-11 y DOM7h-14 (véase el documento WO208/096158 para las secuencias de DOM7h-11 y DOM7h-14). Las bibliotecas de CDR se crearon en el vector pDOM4 y las bibliotecas propensas a errores se generaron en el vector pDOM33 (para permitir la selección con o sin tratamiento con proteasa). El vector pDOM4, es un derivado del vector del fago Fd en el que la secuencia peptídica de señal del *gen III* se reemplazó con el péptido de señal de la proteína de superficie glicolipídica anclada (GAS) de levadura. Éste también contiene una etiqueta *c-myc* entre la secuencia líder y el *gen III*, que restablece al *gen III* en fase de lectura. Esta secuencia líder actúa bien en vectores de

presentación de fagos pero también en otros vectores de expresión procariotas y puede usarse universalmente. pDOM33 es una versión modificada del vector pDOM4 en el que se ha eliminado la etiqueta c-myc lo que hace que la fusión fago-dAb sea resistente a la tripsina proteasa. Esto permite el uso de tripsina en la selección del fago para seleccionar los dAbs que son más estables a proteasa (véase el documento WO2008149143).

Para las bibliotecas de maduración propensas a errores, el ADN plasmídico que codifica el dAb a madurar se amplificó por PCR, usando el KIT DE MUTAGÉNESIS ALEATORIA GENEMORPH® II (kit de mutagénesis único, aleatorio Stratagene). Se realizó la digestión del producto con *Sal* I y *Not* I en una reacción de ligación con el vector del fago de corte pDOM33.

Para las bibliotecas CDR, se realizaron reacciones PCR usando oligonucleótidos degenerados que contenían codones NNK o NNS para diversificar las posiciones necesarias en el dAb a madurar afinidad. A continuación se usó PCR de ensamblaje para generar un inserto diversificado de longitud completa. La digestión del inserto se realizó con *Sal* I y *Not* I y se usó en una reacción de ligación con pDOM4 para mutagénesis de restos múltiples y pDOM5 para mutagénesis de restos sencillos. El vector pDOM5 es un vector de expresión basado en pUC119 en el que la expresión de la proteína se realiza mediante el promotor LacZ. Una secuencia líder GAS1 (véase el documento WO 2005/093074) garantiza la secreción del dAbs soluble, aislado en el periplasma y sobrenadante de cultivo de *E. coli.* Los dAbs se clonaron usando SalI/NotI en este vector, que añade una etiqueta myc en el extremo C del dAb. Este protocolo usando *SalI* y *Not I* da como resultado la inclusión de una secuencia de aminoácidos ST en el extremo N.

La ligación producida por cualquier método se usó después para transformar la

cepa *E. coli* TB1 por electroporación y las células transformadas se cultivaron en placas en agar TY 2x que contenía tetraciclina 15 µg/ml, produciendo tamaños de bibliotecas de $>5\times10^7$ clones.

Las bibliotecas propensas a errores tenían la siguiente tasa de mutación promedio y tamaño: DOM7h-11 (2,5 mutaciones por dAb), tamaño: $6,1 \times 10^8$, DOM7h-14 (2,9 mutaciones por dAb), tamaño: $5,4 \times 10^8$.

Cada biblioteca CDR tiene una diversidad de cuatro aminoácidos. Se generaron dos bibliotecas para cada una de las CDR 1 y 3 y una biblioteca para CDR2. Las posiciones diversificadas en cada biblioteca son las siguientes (aminoácidos en base a la secuencia DPK9 ficticia para VK):

	Tamaño de la biblioteca	
	DOM7h-11	DOM7h-11
1 – Q27, S28, S30, S31 (CDR1)	$8,8 \times 10^7$	$5,8 \times 10^7$
2 – S30, S31, Y32, N34 (CDR1)	$4,6 \times 10^8$	$4,2 \times 10^8$
3 – Y49, A50, A51, S53 (CDR2)	$3,9 \times 10^8$	$2,4 \times 10^8$
4 – Q89, S91, Y92, S93 (CDR3	$1,8 \times 10^8$	$2,5 \times 10^8$
5 – Y92, Y93, T94, N96 (CDR3)	$4,0 \times 10^8$	$3,3 \times 10^8$

Ejemplo 2: Estrategias de selección:

Se adoptaron tres estrategias de selección de fagos para maduración de afinidad Vκ AlbudAb™ (dAB anti-albúmina de suero):

1) Selecciones frente HSA únicamente:

Se realizaron tres rondas de selección frente a HSA. Las bibliotecas propensas a errores

y cada biblioteca de CDR se seleccionaron como un grupo individual en todas las rondas. La primera ronda de selección se realizó frente HSA revestida de modo pasivo sobre un inmunotubo a 1 mg/ml. La segunda ronda se realizó frente HSA 100 nM y la tercera ronda frente HSA 10 nM (selecciones para CDR) o 20 ó 100 nM (selecciones para propensas a Error), ambas como selecciones solubles seguido de una cuarta ronda de selección con las bibliotecas propensas a errores frente HSA 1,5 nM como una selección soluble. Las bibliotecas propensas a errores se eluyeron con glicina 0,1 M pH 2,0 antes de la neutralización con Tris 1 M pH 8,0 y las bibliotecas CDR se eluyeron con tripsina 1 mg/ml antes de la infección en células TG1 en fase logarítmica. La tercera ronda de cada selección se subclonó en pDOM5 para la exploración. Las selecciones solubles usaron HSA biotinilado.

2) Selecciones de tripsina frente HSA:

Para seleccionar los dAbs con resistencia a proteasa aumentada en comparación con el clon parental y con las propiedad biofísicas potencialmente mejoradas, se usó tripsina en selecciones de fagos (véase el documento WO2008149143). Se realizaron cuatro rondas de selección frente a HSA. La primera ronda de selección de bibliotecas propensas a errores se realizó frente a HSA revestida de modo pasivo a 1 mg/ml sin tripsina; la segunda ronda frente HSA revestida de modo pasivo a 1 mg/ml con tripsina 20 μg/ml durante 1 hora a 37°C; la tercera ronda de selección se realizó por selección soluble usando HSA biotinilado frente a HSA 100 nM con 20 μg/ml o 100 μg/ml de tripsina durante 1 hora a 37°C. La ronda de selección final se realizó por selección soluble usando HSA biotinilada frente a HSA 100 nM con tripsina 100 μg/ml durante una noche a 37°C.

3) Selecciones de entrecruzamiento frente HSA (ronda 1) y RSA (rondas 2-4):

La primera ronda de selección se realizó frente HSA revestida de modo pasivo 1mg/ml o HSA 1 µM (selección soluble), seguido de tres rondas adicionales de selecciones solubles frente RSA biotinilada a concentraciones de 1 µM para la ronda 1, 100 nm para la ronda 2 y 20 nM, 10 nM o 1 nM para la ronda 3.

Estrategia de exploración y determinación de afinidad:

Después de la selección en cada caso se preparó un conjunto de ADN de fagos de la ronda de selección apropiada usando un kit QIAfilter midiprep (Qiagen), la digestión del ADN se realizó usando las enzimas de restricción Sal1 y Not1 y los genes V enriquecidos se ligaron en los sitios correspondientes en pDOM5 el vector de expresión soluble que expresa el dAb con una etiqueta myc (véase el documento PCT/EP2008/067789). El ADN ligado se usó para electro transformar células HB 2151 de *E. coli* que después se cultivaron durante una noche en placas de agar que contenían el antibiótico carbenicilina. Las colonias resultantes se evaluaron individualmente para la unión al antígeno. En cada caso se ensayaron al menos 96 clones para la unión a HSA, CSA, (Albúmina de Suero de mono *Cynomolgus*), MSA (albúmina de suero de ratón) y RSA por BIAcore™ (resonancia de plasmón superficial). El antígeno MSA se obtuvo de Sigma (esencialmente sin ácidos grasos, ~99% (electroforesis en gel de agarosa), polvo liofilizado Cat. Nº A3559) y CSA se purificó de la albúmina de suero de *Cynomolgus* usando resina azul prometic (Amersham). Se produjeron fragmentos solubles de dAb en cultivos de bacterias en medios de cultivo ONEX (Novagen) durante una noche a 37ºC en placas de 96 pocillos. El sobrenadante de cultivo conteniendo dAb soluble se centrifugó y se analizó por BIAcore para la unión a microplacas CM5 con HSA, CSA, MSA y RS de elevada densidad. Se descubrió que los

clones se unían a todas estas especies de albúmina de suero mediante exploración de velocidad de disociación. Los clones se secuenciaron revelando secuencias dAb únicas.

La identidad mínima de los clones seleccionados con respecto al parental (a nivel de aminoácidos) eral del 97,2% (DOM7h-11-3: 97,2%, DOM7h-11-12: 98,2%, DOM7h11-15: 96,3%, DOM7h-11-18: 98,2%, DOM7h-11-19: 97,2%).

La identidad mínima de los clones seleccionados con respecto al parental (a nivel de aminoácidos) era del 96,3% (DOM7h-14-10: 96,3%, DOM7h-14-18: 96,3%, DOM7h-14-19: 98,2%, DOM7h-14-28: 99,1%, DOM7h-14-36: 97,2%).

Los dAb únicos se expresaron como sobrenadantes bacterianos en un matraz agitador de 2,5 l en medio Onex a 30ºC durante 48 h a 250 rpm. Los dAb se purificaron del medio de cultivo mediante absorción por proteína L agarosa seguido de elución con glicina 10 mM pH 2,0. La unión a HSA, CSA, MSA y RSA por BIAcore se confirmó usando proteína purificada a 3 concentraciones 1 μM, 500 nM y 50 nM. Para determinar la afinidad de unión (K_D) de los AlbudAbs para cada albúmina de suero; los dAb purificados se analizaron por BIAcore sobre un intervalo de concentración de albúmina de 5000 nM a 39 nM (5000 nM, 2500 nM, 1250 nM, 625 nM, 312 nM, 156 nM, 78 nM, 39 nM).

Tabla 6

AlbudAb	**Afinidad (K_D) para SA (nM)**	**Kd**	**Ka**
	Rata		
DOM7h-14	60	2,095E-01	4,00E+06
DOM7h-14-10	4	9,640E-03	4,57E+06
DOM7h-14-18	410	2,275E-01	5,60E+05
DOM7h-14-19	890	2,870E-01	3,20E+05

AlbudAb	Afinidad (K_D) para SA (nM)	Kd	Ka
DOM7h-14-28	45 (140)	7,0E-02 (1,141e-1)	2,10E+06 (8,3e5)
DOM7h-14-36	30 (6120)	2,9E-02 (5,54e-2)	1,55E+06 (9e3)
DOM 7h-11	2100	1,00E-01	4,80E+04
DOM 7h-11-3	10000 (88000)	(7,18e-1)	(8,11e3)
DOM7h-11-12	200	5,22E-01	2,76E+06
DOM7h-11-15	20	2,10E-02	1,10E+06
DOM7h-11-18	80 (29000)	6,0E-02 (3,7e-1)	1,64E+06 (1,3e4)
DOM7h-11-19	28 (17000)	9,1e-02 (1,4e-1)	9,80E+05 (8,1e3)
	Cyno		
DOM 7h-14	66	9,65E-02	1,50E+06
DOM7h-14-10	9	1,15E-02	1,60E+06
DOM7h-14-18	180	1,05E-01	6,30E+5
DOM7h-14-19	225	1,56E-01	7,00E+05
DOM7h-14-28	66 (136)	1,3E-01 (1,34e-1)	2,50E+06 (9,3e5)
DOM7h-14-36	35 (7830)	1,9E-02 (1,1e-1)	9,80E+06 (1,43e4)
DOM 7h-11	1000	6,82E-01	8,00E+05
DOM 7h-11-3	670 (200)	9,6E-02 (1,5e-1)	2,90E+05 (7,26e5)
DOM7h-11-12	≥6000		
DOM7h-11-15	3	5,57E-03	5,80E+06
DOM7h-11-18	10000 (65000)	1,36 (4,8e-1)	2,25E+05 (7,3e3)
DOM7h-11-19	≥10000 (375000)	(6,2e-1)	(1,7e3)
	Ratón		
DOM 7h-14	12	4,82E-02	4,10E+06
DOM7h-14-10	30	3,41E-02	1,29E+06

AlbudAb	Afinidad (K_D) para SA (nM)	Kd	Ka
DOM7h-14-18	65	9,24E-02	2,28E+06
DOM7h-14-19	60	5,76E-02	1,16E+06
DOM7h-14-28	26 (31)	3,4E-02 (7,15e-2)	1,60E+06 (2,28e6)
DOM7h-14-36	35 (33)	2,3E-02 (7,06e-2)	8,70E+05 (2,11e6)
DOM 7h-11	5000	9,00E-01	
DOM 7h-11-3	≥10000 (36000)	(6,12e-1)	(1,67e4)
DOM7h-11-12	130	1,89E-01	1,53E+06
DOM7h-11-15	10	9,40E-03	1,10E+06
DOM7h-11-18	150 (1600)	2,4E-02 (6,23e-2)	4,40E+05 (4e4)
DOM7h-11-19	100 (18000)	3,7E-02 (8,8e-2)	1,40E+06 (4,9e3)
	Humana		
DOM 7h-14	33	4,17E-02	1,43E+06
DOM 7h-14-10	12	1,39E-02	1,50E+06
DOM 7h-14-18	280	3,39E-02	1,89E+05
DOM 7h-14-19	70	5,25E-02	8,26E+05
DOM 7h-14-28	30 (8260)	3,3E-02 (5,6e-2)	1,24E+06 (6,78e3)
DOM 7h-14-36	28 (1260)	2,4E-02 (6,7e-2)	1,23E+06 (5,4e4)
DOM 7h-11	2800	6,41E-01	7,00E+05
DOM 7h-11-3	32 (130)	1,6E-02 (2,35e-2)	6,50E+05 (1,86e5)

AlbudAb	Afinidad (K_D) para SA (nM)	Kd	Ka
DOM7h-11-12	350	4,13E-01	1,26E+06
DOM7h-11-15	1	1,84E-03	2,00E+06
DOM7h-11-18	36 (32000)	5,1E-02 (2,7e-1)	3,40E+06 (8,39e3)
DOM7h-11-19	65 (38000)	1,1E-01 (2,09e-1)	1,80E+06 (5,4e3)

*: los valores entre paréntesis proceden de un segundo experimento SPR independiente.

Todas las variantes derivadas de DOM7h-14 tienen reactividad cruzada para la albúmina de suero, rata, ser humano y cyno. DOM7h-14-10 tenía afinidad mejorada para la albúmina de suero de rata, cyno y ser humano en comparación con la parental. DOM7h-14-28 tenía afinidad mejorada para RSA. DOM7h-14-36 tenía afinidad mejorada para RSA, CSA y MSA.

DOM7h-11-3 tenía afinidad mejorada para CSA y HSA. DOM7h-14-12 tenía afinidad mejorada para RSA, MSA y HSA. DOM7h-11-15 tenía afinidad mejorada para RSA, MSA, CSA y HSA. DOM7h-11-18 y DOM7h-11-19 tenía la afinidad mejorada para RSA, MSA y HSA.

Ejemplo 3: Orígenes de clones clave del linaje DOM7h-11:

DOM7h-11-3: A partir de la maduración de afinidad realizada frente a HSA usando la biblioteca CDR2 (Y49, A50, A51, S53), producción de la ronda 3 HSA 10 nM.

DOM7h-11-12: A partir de la maduración de afinidad realizada frente HSA usando la biblioteca propensa a error, producción de la ronda 3 (HSA, 100 nM) con tripsina 100

μg/ml.

DOM7h-11-15: A partir de selecciones de entrecruzamiento realizadas frente HSA como 1 ronda seguido 3 rondas adicionales de selección frente RSA usando la biblioteca CDR2 (Y49, A50, A51, S53) a selección de 3 rondas con 1 nM de RSA.

DOM7h-11-18: A partir de selecciones de entrecruzamiento realizadas frente HSA como 1 ronda seguido 3 rondas adicionales de selección frente RSA usando la biblioteca propensa a error, producción de la ronda 3 con 20 nM de RSA.

DOM7h-11-19: A partir de selecciones de entrecruzamiento realizadas frente HSA como 1 ronda seguido 3 rondas de selección adicionales frente RSA usando la biblioteca propensa a error, producción de la ronda 3 con 5 nM de RSA.

Tabla 7: Secuencias CDR (de acuerdo con Kabat; ref. como se ha indicado anteriormente)

AlbudAb	CDR		
	CDR1	CDR2	CDR3
DPK9 Vk ficticia	SQSISSYLN (SEC ID Nº: 335)	YAASSLQS (SEC ID Nº: 336)	QQSYSTPNT (SEC ID Nº: 337)
DOM7h-11	SRPIGTTLS (SEC ID Nº: 338)	WFGSRLQS (SEC ID Nº: 339)	AQAGTHPTT (SEC ID Nº: 340)
DOM7h-11-12	SRPIGTMLS (SEC ID Nº: 341)	LFGSRLQS (SEC ID Nº: 342)	AQAGTHPTT (SEC ID Nº: 343)
DOM 7h-11-15	SRPIGTMLS (SEC ID Nº: 344)	LAFSRLQS (SEC ID Nº: 345)	AQAGTHPTT (SEC ID Nº: 346)
DOM 7h-11-18	SRPIGTMLS (SEC ID Nº: 347)	WFGSRLQS (SEC ID Nº: 348)	AQAGTHPTT (SEC ID Nº: 349)

AlbudAb	CDR		
	CDR1	CDR2	CDR3
DOM 7h-11-19	SRPIGTMLS (SEC ID Nº: 350)	LFGSRLQS (SEC ID Nº: 351)	AQTGTHPTT (SEC ID Nº: 352)
DOM 7h-11-3	SRPIGTTLS (SEC ID Nº: 353)	LWFSRLQS (SEC ID Nº: 354)	AQAGTHPTT (SEC ID Nº: 355)

Ejemplo 4: Orígenes de clones clave del linaje DOM7h-14:

DOM7h-14-19: A partir de la maduración de afinidad realizada frente a HSA usando la biblioteca propensa a error, producción ronda 3 (HSA, 100 nM) con tripsina 100 µg/ml.

DOM7h-14-10, DOM7h-14-18, DOM7h-14-28, DOM7h-14-36: A partir de la maduración de afinidad realizada frente a HSA usando la biblioteca de CDR3 (Y92, Y93, T94, N96), producción ronda 3.

Tabla 8: Secuencias CDR (de acuerdo con Kabat); ref. como se ha indicado anteriormente)

AlbudAb	CDR		
	CDR1	CDR2	CDR3
DPK9 Vk ficticia	SQSISSYLN (SEC ID Nº: 335)	YAASSLQS (SEC ID Nº: 336)	QQSYSTPNT (SEC ID Nº: 337)
DOM 7h-14	SQWIGSQLS (SEC ID Nº: 356)	MWRSSLQS (SEC ID Nº: 357)	AQGAALPRT (SEC ID Nº: 358)
DOM 7h-14-10	SQWIGSQLS (SEC ID Nº: 359)	MWRSSLQS (SEC ID Nº: 360)	AQGLRHPKT (SEC ID Nº: 361)
DOM 7h-14-18	SQWIGSQLS (SEC ID Nº: 362)	MWRSSLQS (SEC ID Nº: 363)	AQGLMKPMT (SEC ID Nº: 364)

AlbudAb	CDR		
	CDR1	CDR2	CDR3
DOM 7h-14-19	SQWIGSQLS (SEC ID Nº: 365)	MWRSSLQS (SEC ID Nº: 366)	AQGAALPRT (SEC ID Nº: 367)
DOM 7h-14-28	SQWIGSQLS (SEC ID Nº: 368)	MWRSSLQS (SEC ID Nº: 369)	AQGAALPKT (SEC ID Nº: 370)
DOM 7h-14-36	SQWIGSQLS (SEC ID Nº: 371)	MWRSSLQS (SEC ID Nº: 372)	AQGFKKPRT (SEC ID Nº: 373)

Ejemplo 5: Expresión y Caracterización Biofísica:

El nivel de expresión bacteriano se determinó de la manera habitual en matraces de agitación de 2,5 l seguido del cultivo en medio Onex a 30ºC durante 48 horas a 250 rpm. Las características biofísicas se determinaron por SEC MALLS y DSC.

SEC MALLS (cromatografía de exclusión por tamaño con dispersión de luz LÁSER multiángulo) es una técnica no invasiva para la caracterización de macromoléculas en solución. En resumen, las proteínas (a una concentración de 1 mg/ml en tampón PBS de Dubelcco a 0,5 ml/min) se separaron de acuerdo con sus propiedades hidrodinámicas por cromatografía de exclusión por tamaño (columna: TSK3000 de TOSOH Biosciences; S200 de Phamarcia). Después de la separación, se midió la propensión de la proteína a la dispersión lumínica usando un detector de dispersión de luz LÁSER multiángulo (MALLS). La intensidad de la luz dispersa cuando la proteína pasa a través del detector se mide como una función de ángulo. Esta medida tomada junto con la concentración de la proteína determinada usando el detector de índice refractivo (RI) permite calcular la masa molar usando ecuaciones apropiadas (parte integral del análisis informático Astra v.5.3.4.12).

DSC (Calorimetría de Escáner Diferencial): en resumen, la proteína se calentó a

una velocidad constante de 180 ºC/h (PBS 1 mg/ml) y se midió un cambio térmico detectable asociado a la desnaturalización térmica. Se determinó el punto medio de transición ($_{app}T_m$), que se describe como la temperatura en la cual el 50% de la proteína se encuentra en su conformación nativa y el otro 50% desnaturalizada. En este caso, el valor DSC determinó el punto medio de transición aparente ($_{app}T_m$) ya que la mayoría de las proteínas examinadas no estaban completamente replegadas. A mayor Tm, más estable la molécula. Las curvas desdobladas se analizaron mediante ecuaciones que no eran de 2 estados. El paquete informático usado era Origin^R v7.0383.

Tabla 9

AlbudAb	Parámetros Biofísicos	
	SEC MALLS	DSC Tm (ºC)
DOM7h-14	M	60
DOM 7h-14-10	M	59
DOM 7h-14-18	M	58
DOM 7h-14-19	M	59
DOM 7h-14-28	M	58,3/60,2
DOM 7h-14-36	M	59,2
DOM 7h-11	M	66,9-72,2
DOM 7h-11-3	M (95%)*	66,6/70,5
DOM 7h-11-12	M (<2% D)	71,7
DOM 7h-11-15	M (<5% D)	58,5-60,5
DOM 7h-11-18	M (98%)	58,9/65,8
DOM 7h-11-19	M	71,8/76,6

*en otro ensayo, se observó principalmente monomérico mediante SEC MALLS, aunque inferior al 95%.

En la Tabla 9 se observan los niveles de expresión para todos los clones en el

intervalo de 15 a 119 mg/l en *E. coli.*

En las variantes DOM7h-14 y DOM7h-11, durante la maduración de afinidad se mantuvieron los parámetros biofísicos favorables (monoméricos en solución según se determina por SEC MALL y appTm >55 ºC según se determina por DSC) y los niveles de expresión. El estado monomérico es ventajoso porque evita la dimerización y el riesgo de productos que puedan entrecruzarse con las dianas tales como receptores de la superficie celular.

Ejemplo 6: Determinación de semivida en suero en rata, ratón y mono *Cynomolgus* Se clonaron AlbudAbs DOM7h-14-10, DOM7h-14-18, DOM7h-14-19, DOM7h-11, DOM7h11-12 y DOM7h-11-15 en el vector pDOM5. Para cada AlbudAb™, se expresaron cantidades de 20-50 mg en *E. coli* y se purificaron del sobrenadante de cultivo bacteriano usando la resina de afinidad para proteína L y se eluyó con glicina 100 mM pH 2. Las proteínas se llevaron a una concentración superior a 1 mg/ml, el tampón se intercambió a PBS y la endotoxina se agotó usando columnas de giro Q (Vivascience). Para realizar el análisis farmacocinético (PK) de Rata, se dosificaron AlbudAbs como inyecciones i.v. únicas de 2,5 mg/kg usando 3 ratas por compuesto. Las muestras de suero se tomaron a 0,16, 1, 4, 12, 24, 48, 72, 120, 168 h. El análisis de los niveles en suero se realizó mediante ELISA anti-myc según el método descrito a continuación.

Para el PK de Ratón, se dosificaron DOM7h-11, DOM7h11-12 y DOM7h-11-15 como inyecciones i.v. únicas de 2,5 mg/kg por dosis a un grupo de 3 sujetos y las muestras de suero se tomaron a 10 min; 1 h; 8 h; 24 h; 48 h; 72 h; 96 h. El análisis de los niveles en suero se realizó mediante ELISA anti-myc según el método descrito a continuación.

Para el PK del mono *Cynomolgus* se dosificaron DOM7h-14-10 y DOM7h11-15 como inyecciones i.v. únicas de 2,5 mg/kg por dosis a un grupo de tres hembras de mono *Cynomolgus* y las muestras de suero se tomaron a 0,083, 0,25, 0,5, 1, 2, 4, 8, 24, 48, 96, 144, 192, 288, 336, 504 h. El análisis de los niveles en suero se realizó mediante ELISA anti-myc según el método descrito a continuación.

Método de ELISA anti-myc

La concentración de AlbudAb en suero se midió por ELISA anti-myc. En resumen, en placas NuncMaxisorp de 96 pocillos, se revistió durante una noche anticuerpo policlonal de cabra anti-myc (1:500; Abcam, catálogo número ab9132) y se bloqueó con BSA/PBS al 5% + tween al 1%. Se añadieron muestras de suero a un intervalo de diluciones junto a concentraciones conocidas convencionales. La unión de AlbudAb marcado con myc se detectó a continuación usando un anti-Vk policlonal de conejo (1:1000; reactivo casero, las extracciones se agruparon y la proteína A se purificó antes del uso) seguido de un anticuerpo HRP anti-IgG de conejo (1:10.000; Sigma, catálogo número A2074). Las placas se lavaron entre cada etapa del ensayo con PBS 3 x + Tween 20 al 0,1% seguido de PBS 3 x. Después del último lavado se añadió TMB (Sustrato de Peroxidasa para Micropocillo de Componente SureBlue TMB1, KPL, catálogo número 52-00-00) y se dejó desarrollar. El proceso se detuvo con HCl 1 M y después se midió la señal usando una absorbancia a 450 nm.

A partir de datos ELISA sin procesar, la concentración de muestras desconocidas se estabilizó por interpolación frente a la curva convencional teniendo en cuenta los factores de dilución. La concentración media que resulta de cada momento se determinó a partir de valores de repetición y se introdujeron en un paquete de análisis WinNonLin (por ejemplo, versión 5.1 (disponible de Pharsight Corp., Mountain View,

CA94040, USA). Los datos se ajustaron usando un modelo no-compartimental, en el que los parámetros PK se estimaron mediante el programa informático para proporcionar las semividas terminales. La información de la dosificación y los momentos se seleccionaron para reflejar la fase terminal de cada perfil PK.

Tabla 10: PK de AlbudAb™ Sencillo

Especie	AlbudAb	Albúmina K_D (nM)	Parámetros PK			
			AUC h x μg/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
Rata	**DOM7h-14***	60				
	DOM7h-14-10	4	2134,6	1,2	42,1	71,2
	DOM7h-14-18	410	617,3	4,1	38,4	228,1
	DOM7h-14-19	890	632,6	4,1	36,3	213,3
	DOM7h-11	2100	320,1	7,8	23,3	263,9
	DOM7h-11-12	200	398,7	6,4	35,5	321,2
	DOM7h-11-15	20	843,4	3,0	30,3	130,7
Ratón	**DOM7h-11**	5000	304,7	8,2	18,3	216,8
	DOM7h-11-12	130	646,6	3,9	43,9	244,8
	DOM7h-11-15	10	499,2	5,0	33,7	243,4
Cyno	**DOM7h-14***	66			217,5	
	DOM7h-14-10	9	6174,6	0,4	200,8	117,8
	DOM7h-11*	3300			135,1	
	DOM7h-11-15	3	4195	0,6	198,1	170,3

* Datos históricos

Los parámetros farmacocinéticos obtenidos de estudios de rata, ratón y mono *Cynimolgus* se ajustaron usando un modelo no - compartimental. Clave: AUC: Área bajo la curva del tiempo de dosificación extrapolado al infinito; CL: eliminación; t1/2: es el tiempo durante el cual la concentración en sangre se divide en dos; Vz: volumen de distribución en base a la fase terminal.

DOM7h-11-12 y DOM7h-11-15 tienen una AUC y un t1/2 mejorados en rata y ratón en comparación con el parental. DOM7h-11-15 también tiene una AUC y un t1/2 mejorados en Cyno en comparación con el parental. Esta mejora del AUC/t1/2 equivale a una KD mejorada *in vitro* para la albúmina de suero.

Ejemplo 7: Fusiones AlbudAb™ IFN

Clonación y expresión

Al igual que en los AlbudAbs sencillos, los Albudabs Vk madurados por afinidad se unieron al Interferón alfa 2b (IFNα2b) para determinar si se mantenía un PK útil del AlbudAb como una proteína de fusión.

Secuencia de aminoácidos del Interferón alfa 2b:

CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE
MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILA
VRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE (SEC ID Nº: 374)

Secuencia de nucleótidos del Interferón alfa 2b:

TGTGATCTGCCTCAAACCCACAGCCTGGGTAGCAGGAGGACCTTGATGCTCCTGG
CACAGATGAGGAGAATCTCTCTTTTCTCCTGCTTGAAGGACAGACATGACTTTGGA
TTTCCCCAGGAGGAGTTTGGCAACCAGTTCCAAAAGGCTGAAACCATCCCTGTCCT
CCATGAGATGATCCAGCAGATCTTCAATCTCTTCAGCACAAAGGACTCATCTGCTG

CTTGGGATGAGACCCTCCTAGACAAATTCTACACTGAACTCTACCAGCAGCTGAAT
GACCTGGAAGCCTGTGTGATACAGGGGGTGGGGGTGACAGAGACTCCCCTGATG
AAGGAGGACTCCATTCTGGCTGTGAGGAAATACTTCCAAAGAATCACTCTCTATCT
GAAAGAGAAGAAATACAGCCCTTGTGCCTGGGAGGTTGTCAGAGCAGAAATCATG
AGATCTTTTTCTTTGTCAACAAACTTGCAAGAAAGTTTAAGAAGTAAGGAA (SEC ID Nº: 375)

Mediante una región engarzadora TVAAPS (véase el documento WO2007085814) se realizó la unión del IFNa2b con AlbudAb. Las construcciones se clonaron por SOE-PCR (extensión de solapamiento simple de acuerdo con el método de Horton *y col.* Gene, 77, p 61 (1989)). Se realizó por separado la amplificación PCR del AlbudAb y de las secuencias IFN usando cebadores con un solapamiento ~15 pares de bases en la región engarzadora TVAAPS. Los cebadores usados son los siguientes:

IFNα2b SOE fragmento 5'	GCCCGGATCCACCGGCTGTGATCTG (SEC ID Nº: 376)
IFNα2b SOE fragmento 3'	GGAGGATGGAGACTGGGTCATCTGGATGTC (SEC ID Nº: 377)
Vk SOE fragmento 5'	GACATCCAGATGACCCAGTCTCCATCCTCC (SEC ID Nº: 378)
Vk SOE fragmento 5' para introducir también una etiqueta myc	GCGCAAGCTTTTATTAATTCAGATCCTCTTC TGAGATGAGTTTTTGTTCTGCGGCCGCCCGT TTGATTTCCACCTTGGTCCC (SEC ID Nº: 379)

Los fragmentos se purificaron por separado y posteriormente se ensamblaron en una reacción SOE (extensión PCR por extensión de solapamiento simple) usando

únicamente los cebadores flanqueantes.

IFNα2b SOE fragmento 5'	GCCCGGATCCACCGGCTGTGATCTG (SEC ID Nº: 380)
Vk SOE fragmento 3' para introducir también una etiqueta myc	GCGCAAGCTTTTATTAATTCAGATCCTCTTC TGAGATGAGTTTTTGTTCTGCGGCCGCCCGT TTGATTTCCACCTTGGTCCC (SEC ID Nº: 381)

La digestión del producto PCR ensamblado se realizó con las enzimas de restricción BamHI y HindIII y el gen se ligó en los sitios correspondientes en el pDOM50, un vector de expresión de mamíferos que es un derivado de pTT5 con una secuencia líder secretora IgG de ratón V-J2-C N-terminal para facilitar la expresión en el medio celular.

Secuencia líder (aminoácidos):

METDTLLLWVLLLWVPGSTG (SEC ID Nº: 382)

Secuencia líder (nucleótidos):

ATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTGCTGTGGGTGCCCGGATCC ACCGGGC (SEC ID Nº: 383)

Se preparó un ADN plasmídico usando QIAfilter megaprep (Qiagen). Se transfectó ADN 1 µg /ml con Fectin-293 en células HEK293E y se cultivaron en medio sin suero. La proteína se expresó en el cultivo durante 5 días y se purificó del sobrenadante del cultivo usando la resina de afinidad a proteína L y se eluyó con glicina

100 mM pH 2. Las proteínas se llevaron a una concentración superior a 1 mg/ml, se intercambió tampón a PBS y las endotoxinas se agotaron usando columnas de giro Q (Vivascience).

Tabla 11: Secuencias Interferón alfa 2b-AlbudAb con y sin etiqueta-myc (como secuencias de aminoácidos y nucleótidos)

El Interferón alfa 2b es N-terminal con respecto a AlbudAb en las siguientes fusiones.

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
DMS7321 (IFNα2b-DOM7h-14)	CDLPQTHSLGS	TGCGACTTGCC	CDLPQTHSLGS	TGCGACTTGCC
	RRTLMLLAQMR	ACAGACACATA	RRTLMLLAQMR	ACAGACACATA
	RISLFSCLKDRH	GTTTGGGATCA	RISLFSCLKDRH	GTTTGGGATCA
	DFGFPQEEFGN	AGAAGAACATT	DFGFPQEEFGN	AGAAGAACATT
	QFQKAETIPVLH	GATGTTATTAG	QFQKAETIPVLH	GATGTTATTAG
	EMIQQIFNLFST	CACAAATGCGT	EMIQQIFNLFST	CACAAATGCGT
	KDSSAAWDETL	AGAATTTCTTT	KDSSAAWDETL	AGAATTTCTTT
	LDKFYTELYQQ	GTTCTCTTGTC	LDKFYTELYQQ	GTTCTCTTGTC
	LNDLEACVIQG	TAAAGGACCGT	LNDLEACVIQG	TAAAGGACCGT
	VGVTETPLMKE	CACGACTTCG	VGVTETPLMKE	CACGACTTCG
	DSILAVRKYFQR	GATTCCCTCAG	DSILAVRKYFQR	GATTCCCTCAG
	ITLYLKEKKYSP	GAAGAGTTTG	ITLYLKEKKYSP	GAAGAGTTTG
	CAWEVVRAEIM	GAAACCAATTC	CAWEVVRAEIM	GAAACCAATTC
	RSFSLSTNLQE	CAAAAAGCAGA	RSFSLSTNLQE	CAAAAAGCAGA

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
	SLRSKETVAAP	AACTATTCCTG	SLRSKETVAAP	AACTATTCCTG
	SDIQMTQSPSS	TCTTGCACGAA	SDIQMTQSPSS	TCTTGCACGAA
	LSASVGDRVTIT	ATGATCCAGCA	LSASVGDRVTIT	ATGATCCAGCA
	CRASQWIGSQL	AATATTCAATTT	CRASQWIGSQL	AATATTCAATTT
	SWYQQKPGKA	GTTTTCTACAA	SWYQQKPGKA	GTTTTCTACAA
	PKLLIMWRSSL	AGGACTCATCA	PKLLIMWRSSL	AGGACTCATCA
	QSGVPSRFSGS	GCCGCTTGGG	QSGVPSRFSGS	GCCGCTTGGG
	GSGTDFTLTISS	ATGAAACTCTG	GSGTDFTLTISS	ATGAAACTCTG
	LQPEDFATYYC	TTAGATAAATT	LQPEDFATYYC	TTAGATAAATT
	AQGAALPRTFG	CTACACTGAAC	AQGAALPRTFG	CTACACTGAAC
	QGTKVEIKR	TATATCAACAA	QGTKVEIKR	TATATCAACAA
	AAAEQKLISEE	CTGAACGATCT	(SEC ID N°: 386)	CTGAACGATCT
	DLN* (SEC ID	AGAGGCTTGC		AGAGGCTTGC
	N°: 334)	GTTATTCAGGG		GTTATTCAGGG
		TGTAGGAGTTA		TGTAGGAGTTA
		CTGAAACTCCC		CTGAAACTCCC
		CTAATGAAAGA		CTAATGAAAGA
		AGATTCAATTC		AGATTCAATTC
		TAGCCGTTAGA		TAGCCGTTAGA
		AAATACTTTCA		AAATACTTTCA
		GCGTATCACAT		GCGTATCACAT
		TGTATTTAAAG		TGTATTTAAAG

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		GAAAAGAAATA		GAAAAGAAATA
		CTCCCCATGTG		CTCCCCATGTG
		CATGGGAGGT		CATGGGAGGT
		GGTTAGAGCA		GGTTAGAGCA
		GAAATTATGAG		GAAATTATGAG
		GTCCTTCTCTC		GTCCTTCTCTC
		TTTCTACGAAT		TTTCTACGAAT
		TTGCAAGAATC		TTGCAAGAATC
		TTTGAGATCTA		TTTGAGATCTA
		AGGAAACCGT		AGGAAACCGT
		CGCTGCTCCAT		CGCTGCTCCAT
		CTGACATCCAG		CTGACATCCAG
		ATGACCCAGTC		ATGACCCAGTC
		TCCATCCTCCC		TCCATCCTCCC
		TGTCTGCATCT		TGTCTGCATCT
		GTAGGAGACC		GTAGGAGACC
		GTGTCACCATC		GTGTCACCATC
		ACTTGCCGGG		ACTTGCCGGG
		CAAGTCAGTG		CAAGTCAGTG
		GATTGGGTCTC		GATTGGGTCTC
		AGTTATCTTGG		AGTTATCTTGG
		TACCAGCAGAA		TACCAGCAGAA

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		ACCAGGGAAA GCCCCTAAGCT CCTGATCATGT GGCGTTCCTC GTTGCAAAGTG GGGTCCCATC ACGTTTCAGTG GCAGTGGATC TGGGACAGATT TCACTCTCACC ATCAGCAGTCT GCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTGC GGCGTTGCCT AGGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGGG **CGGCCGCAGA** **ACAAAAACTCA**		ACCAGGGAAA GCCCCTAAGCT CCTGATCATGT GGCGTTCCTC GTTGCAAAGTG GGGTCCCATC ACGTTTCAGTG GCAGTGGATC TGGGACAGATT TCACTCTCACC ATCAGCAGTCT GCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTGC GGCGTTGCCT AGGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG (SEC ID Nº: 387)

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
		TCTCAGAAGAG GATCTGAATTA A (SEC ID Nº: 385)		
DMS732 (IFNα2b-DOM7h-14-10)	CDLPQTHSLGS	TGCGACTTGCC	CDLPQTHSLGS	TGCGACTTGCC
	RRTLMLLAQMR	ACAGACACATA	RRTLMLLAQMR	ACAGACACATA
	RISLFSCLKDRH	GTTTGGGATCA	RISLFSCLKDRH	GTTTGGGATCA
	DFGFPQEEFGN	AGAAGAACATT	DFGFPQEEFGN	AGAAGAACATT
	QFQKAETIPVLH	GATGTTATTAG	QFQKAETIPVLH	GATGTTATTAG
	EMIQQIFNLFST	CACAAATGCGT	EMIQQIFNLFST	CACAAATGCGT
	KDSSAAWDETL	AGAATTTCTTT	KDSSAAWDETL	AGAATTTCTTT
	LDKFYTELYQQ	GTTCTCTTGTC	LDKFYTELYQQ	GTTCTCTTGTC
	LNDLEACVIQG	TAAAGGACCGT	LNDLEACVIQG	TAAAGGACCGT
	VGVTETPLMKE	CACGACTTCG	VGVTETPLMKE	CACGACTTCG
	DSILAVRKYFQR	GATTCCCTCAG	DSILAVRKYFQR	GATTCCCTCAG
	ITLYLKEKKYSP	GAAGAGTTTG	ITLYLKEKKYSP	GAAGAGTTTG
	CAWEVVRAEIM	GAAACCAATTC	CAWEVVRAEIM	GAAACCAATTC
	RSFSLSTNLQE	CAAAAAGCAGA	RSFSLSTNLQE	CAAAAAGCAGA
	SLRSKETVAAP	AACTATTCCTG	SLRSKETVAAP	AACTATTCCTG
	SDIQMTQSPSS	TCTTGCACGAA	SDIQMTQSPSS	TCTTGCACGAA
	LSASVGDRVTIT	ATGATCCAGCA	LSASVGDRVTIT	ATGATCCAGCA
	CRASQWIGSQL	AATATTCAATTT	CRASQWIGSQL	AATATTCAATTT

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
	SWYQQKPGKA PKLLIMWRSSL QSGVPSRFSGS GSGTDFTLTISS LQPEDFATYYC AQGLRHPKTFG QGTKVEIKR **AAAEQKLISEE DLN*** (SEC ID Nº: 388)	GTTTTCTACAA AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA	SWYQQKPGKA PKLLIMWRSSL QSGVPSRFSGS GSGTDFTLTISS LQPEDFATYYC AQGLRHPKTFG QGTKVEIKR (SEC ID Nº: 390)	GTTTTCTACAA AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		GAAATTATGAG		GAAATTATGAG
		GTCCTTCTCTC		GTCCTTCTCTC
		TTTCTACGAAT		TTTCTACGAAT
		TTGCAAGAATC		TTGCAAGAATC
		TTTGAGATCTA		TTTGAGATCTA
		AGGAAACCGT		AGGAAACCGT
		CGCTGCTCCAT		CGCTGCTCCAT
		CTGACATCCAG		CTGACATCCAG
		ATGACCCAGTC		ATGACCCAGTC
		TCCATCCTCCC		TCCATCCTCCC
		TGTCTGCATCT		TGTCTGCATCT
		GTAGGAGACC		GTAGGAGACC
		GTGTCACCATC		GTGTCACCATC
		ACTTGCCGGG		ACTTGCCGGG
		CAAGTCAGTG		CAAGTCAGTG
		GATTGGGTCTC		GATTGGGTCTC
		AGTTATCTTGG		AGTTATCTTGG
		TACCAGCAGAA		TACCAGCAGAA
		ACCAGGGAAA		ACCAGGGAAA
		GCCCCTAAGCT		GCCCCTAAGCT
		CCTGATCATGT		CCTGATCATGT
		GGCGTTCCTC		GGCGTTCCTC

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		GTTGCAAAGTG GGGTCCCATC ACGTTTCAGTG GCAGTGGATC TGGGACAGATT TCACTCTCACC ATCAGCAGTCT GCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTTTG AGGCATCCTAA GACGTTCGGC CAAGGGACCA AGGTGGAAATC AAACGG**GCGG CCGCAGAACA AAAACTCATCT CAGAAGAGGA TCTGAATTAA** (SEC ID Nº: 389)		GTTGCAAAGTG GGGTCCCATC ACGTTTCAGTG GCAGTGGATC TGGGACAGATT TCACTCTCACC ATCAGCAGTCT GCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTTTG AGGCATCCTAA GACGTTCGGC CAAGGGACCA AGGTGGAAATC AAACGG (SEC ID Nº: 391)
DMS7323	CDLPQTHSLGS	TGCGACTTGCC	CDLPQTHSLGS	TGCGACTTGCC

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
(IFNα2b-DOM7h-14-18)	RRTLMLLAQMR	ACAGACACATA	RRTLMLLAQMR	ACAGACACATA
	RISLFSCLKDRH	GTTTGGGATCA	RISLFSCLKDRH	GTTTGGGATCA
	DFGFPQEEFGN	AGAAGAACATT	DFGFPQEEFGN	AGAAGAACATT
	QFQKAETIPVLH	GATGTTATTAG	QFQKAETIPVLH	GATGTTATTAG
	EMIQQIFNLFST	CACAAATGCGT	EMIQQIFNLFST	CACAAATGCGT
	KDSSAAWDETL	AGAATTTCTTT	KDSSAAWDETL	AGAATTTCTTT
	LDKFYTELYQQ	GTTCTCTTGTC	LDKFYTELYQQ	GTTCTCTTGTC
	LNDLEACVIQG	TAAAGGACCGT	LNDLEACVIQG	TAAAGGACCGT
	VGVTETPLMKE	CACGACTTCG	VGVTETPLMKE	CACGACTTCG
	DSILAVRKYFQR	GATTCCCTCAG	DSILAVRKYFQR	GATTCCCTCAG
	ITLYLKEKKYSP	GAAGAGTTTG	ITLYLKEKKYSP	GAAGAGTTTG
	CAWEVVRAEIM	GAAACCAATTC	CAWEVVRAEIM	GAAACCAATTC
	RSFSLSTNLQE	CAAAAAGCAGA	RSFSLSTNLQE	CAAAAAGCAGA
	SLRSKETVAAP	AACTATTCCTG	SLRSKETVAAP	AACTATTCCTG
	SDIQMTQSPSS	TCTTGCACGAA	SDIQMTQSPSS	TCTTGCACGAA
	LSASVGDRVTIT	ATGATCCAGCA	LSASVGDRVTIT	ATGATCCAGCA
	CRASQWIGSQL	AATATTCAATTT	CRASQWIGSQL	AATATTCAATTT
	SWYQQKPGKA	GTTTTCTACAA	SWYQQKPGKA	GTTTTCTACAA
	PKLLIMWRSSL	AGGACTCATCA	PKLLIMWRSSL	AGGACTCATCA
	QSGVPSRFSGS	GCCGCTTGGG	QSGVPSRFSGS	GCCGCTTGGG
	GSGTDFTLTISS	ATGAAACTCTG	GSGTDFTLTISS	ATGAAACTCTG
	LQPEDFATYYC	TTAGATAAATT	LQPEDFATYYC	TTAGATAAATT

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
	AQGLMKPMTF GQGTKVEIKR**A AAEQKLISEEDL N*** (SEC ID Nº: 392)	CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA GAAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA	AQGLMKPMTF GQGTKVEIKR (SEC ID Nº: 394)	CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA GAAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		AGGAAACCGT		AGGAAACCGT
		CGCTGCTCCAT		CGCTGCTCCAT
		CTGACATCCAG		CTGACATCCAG
		ATGACCCAGTC		ATGACCCAGTC
		TCCATCCTCCC		TCCATCCTCCC
		TGTCTGCATCT		TGTCTGCATCT
		GTAGGAGACC		GTAGGAGACC
		GTGTCACCATC		GTGTCACCATC
		ACTTGCCGGG		ACTTGCCGGG
		CAAGTCAGTG		CAAGTCAGTG
		GATTGGGTCTC		GATTGGGTCTC
		AGTTATCTTGG		AGTTATCTTGG
		TACCAGCAGAA		TACCAGCAGAA
		ACCAGGGAAA		ACCAGGGAAA
		GCCCCTAAGCT		GCCCCTAAGCT
		CCTGATCATGT		CCTGATCATGT
		GGCGTTCCTC		GGCGTTCCTC
		GTTGCAAAGTG		GTTGCAAAGTG
		GGGTCCCATC		GGGTCCCATC
		ACGTTTCAGTG		ACGTTTCAGTG
		GCAGTGGATC		GCAGTGGATC
		TGGGACAGATT		TGGGACAGATT

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		TCACTCTCACC ATCAGCAGTCT GCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTCTT ATGAAGCCTAT GACGTTCGGC CAAGGGACCA AGGTGGAAATC AAACGG**GCGG CCGCAGAACA AAAACTCATCT CAGAAGAGGA TCTGAATTAA** (SEC ID Nº: 393)		TCACTCTCACC ATCAGCAGTCT GCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTCTT ATGAAGCCTAT GACGTTCGGC CAAGGGACCA AGGTGGAAATC AAACGG (SEC ID Nº: 395)
DMS7324 (IFNα2b-DOM7h-14-19)	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN QFQKAETIPVLH EMIQQIFNLFST	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT GATGTTATTAG CACAAATGCGT	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN QFQKAETIPVLH EMIQQIFNLFST	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT GATGTTATTAG CACAAATGCGT

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
	KDSSAAWDETL	AGAATTTCTTT	KDSSAAWDETL	AGAATTTCTTT
	LDKFYTELYQQ	GTTCTCTTGTC	LDKFYTELYQQ	GTTCTCTTGTC
	LNDLEACVIQG	TAAAGGACCGT	LNDLEACVIQG	TAAAGGACCGT
	VGVTETPLMKE	CACGACTTCG	VGVTETPLMKE	CACGACTTCG
	DSILAVRKYFQR	GATTCCCTCAG	DSILAVRKYFQR	GATTCCCTCAG
	ITLYLKEKKYSP	GAAGAGTTTG	ITLYLKEKKYSP	GAAGAGTTTG
	CAWEVVRAEIM	GAAACCAATTC	CAWEVVRAEIM	GAAACCAATTC
	RSFSLSTNLQE	CAAAAAGCAGA	RSFSLSTNLQE	CAAAAAGCAGA
	SLRSKETVAAP	AACTATTCCTG	SLRSKETVAAP	AACTATTCCTG
	SDIQMTQSPSS	TCTTGCACGAA	SDIQMTQSPSS	TCTTGCACGAA
	LSASVGDRVTIS	ATGATCCAGCA	LSASVGDRVTIS	ATGATCCAGCA
	CRASQWIGSQL	AATATTCAATTT	CRASQWIGSQL	AATATTCAATTT
	SWYQQKPGEA	GTTTTCTACAA	SWYQQKPGEA	GTTTTCTACAA
	PKLLIMWRSSL	AGGACTCATCA	PKLLIMWRSSL	AGGACTCATCA
	QSGVPSRFSGS	GCCGCTTGGG	QSGVPSRFSGS	GCCGCTTGGG
	GSGTDFTLTISS	ATGAAACTCTG	GSGTDFTLTISS	ATGAAACTCTG
	LQPEDFATYYC	TTAGATAAATT	LQPEDFATYYC	TTAGATAAATT
	AQGAALPRTFG	CTACACTGAAC	AQGAALPRTFG	CTACACTGAAC
	QGTKVEIKR	TATATCAACAA	QGTKVEIKR	TATATCAACAA
	AAAEQKLISEE	CTGAACGATCT	(SEC ID Nº: 398)	CTGAACGATCT
	DLN* (SEC ID	AGAGGCTTGC		AGAGGCTTGC
	Nº: 396)	GTTATTCAGGG		GTTATTCAGGG

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		TGTAGGAGTTA		TGTAGGAGTTA
		CTGAAACTCCC		CTGAAACTCCC
		CTAATGAAAGA		CTAATGAAAGA
		AGATTCAATTC		AGATTCAATTC
		TAGCCGTTAGA		TAGCCGTTAGA
		AAATACTTTCA		AAATACTTTCA
		GCGTATCACAT		GCGTATCACAT
		TGTATTTAAAG		TGTATTTAAAG
		GAAAAGAAATA		GAAAAGAAATA
		CTCCCCATGTG		CTCCCCATGTG
		CATGGGAGGT		CATGGGAGGT
		GGTTAGAGCA		GGTTAGAGCA
		GAAATTATGAG		GAAATTATGAG
		GTCCTTCTCTC		GTCCTTCTCTC
		TTTCTACGAAT		TTTCTACGAAT
		TTGCAAGAATC		TTGCAAGAATC
		TTTGAGATCTA		TTTGAGATCTA
		AGGAAACCGT		AGGAAACCGT
		CGCTGCTCCAT		CGCTGCTCCAT
		CTGACATCCAG		CTGACATCCAG
		ATGACCCAGTc		ATGACCCAGTc
		TCCATCCTCCC		TCCATCCTCCC

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		TGTCTGCATCT		TGTCTGCATCT
		GTAGGAGACC		GTAGGAGACC
		GTGTCACCATC		GTGTCACCATC
		TCTTGCCGGG		TCTTGCCGGG
		CAAGTCAGTG		CAAGTCAGTG
		GATTGGGTCTC		GATTGGGTCTC
		AGTTATCTTGG		AGTTATCTTGG
		TACCAGCAGAA		TACCAGCAGAA
		ACCAGGGGAA		ACCAGGGGAA
		GCCCCTAAGCT		GCCCCTAAGCT
		CCTGATCATGT		CCTGATCATGT
		GGCGTTCCTC		GGCGTTCCTC
		GTTGCAAAGTG		GTTGCAAAGTG
		GGGTCCCATC		GGGTCCCATC
		ACGTTTCAGTG		ACGTTTCAGTG
		GCAGTGGATC		GCAGTGGATC
		TGGGACAGATT		TGGGACAGATT
		TCACTCTCACC		TCACTCTCACC
		ATCAGCAGTCT		ATCAGCAGTCT
		GCAACCTGAA		GCAACCTGAA
		GATTTTGCTAC		GATTTTGCTAC
		GTACTACTGTG		GTACTACTGTG

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		CTCAGGGTGC GGCGTTGCCT AGGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG**G CGGCCGCAGA ACAAAAACTCA TCTCAGAAGAG GATCTGAATTA A** (SEC ID Nº: 397)		CTCAGGGTGC GGCGTTGCCT AGGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG (SEC ID Nº: 399)
DMS7325 (IFNα2b-DOM7h-11)	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN QFQKAETIPVLH EMIQQIFNLFST KDSSAAWDETL LDKFYTELYQQ LNDLEACVIQG VGVTETPLMKE	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT GATGTTATTAG CACAAATGCGT AGAATTTCTTT GTTCTCTTGTC TAAAGGACCGT CACGACTTCG	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN QFQKAETIPVLH EMIQQIFNLFST KDSSAAWDETL LDKFYTELYQQ LNDLEACVIQG VGVTETPLMKE	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT GATGTTATTAG CACAAATGCGT AGAATTTCTTT GTTCTCTTGTC TAAAGGACCGT CACGACTTCG

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
	DSILAVRKYFQR	GATTCCCTCAG	DSILAVRKYFQR	GATTCCCTCAG
	ITLYLKEKKYSP	GAAGAGTTTG	ITLYLKEKKYSP	GAAGAGTTTG
	CAWEVVRAEIM	GAAACCAATTC	CAWEVVRAEIM	GAAACCAATTC
	RSFSLSTNLQE	CAAAAAGCAGA	RSFSLSTNLQE	CAAAAAGCAGA
	SLRSKETVAAP	AACTATTCCTG	SLRSKETVAAP	AACTATTCCTG
	SDIQMTQSPSS	TCTTGCACGAA	SDIQMTQSPSS	TCTTGCACGAA
	LSASVGDRVTIT	ATGATCCAGCA	LSASVGDRVTIT	ATGATCCAGCA
	CRASRPIGTTLS	AATATTCAATTT	CRASRPIGTTLS	AATATTCAATTT
	WYQQKPGKAP	GTTTTCTACAA	WYQQKPGKAP	GTTTTCTACAA
	KLLIWFGSRLQ	AGGACTCATCA	KLLIWFGSRLQ	AGGACTCATCA
	SGVPSRFSGSG	GCCGCTTGGG	SGVPSRFSGSG	GCCGCTTGGG
	SGTDFTLTISSL	ATGAAACTCTG	SGTDFTLTISSL	ATGAAACTCTG
	QPEDFATYYCA	TTAGATAAATT	QPEDFATYYCA	TTAGATAAATT
	QAGTHPTTFGQ	CTACACTGAAC	QAGTHPTTFGQ	CTACACTGAAC
	GTKVEIKR	TATATCAACAA	GTKVEIKR	TATATCAACAA
	AAAEQKLISEE	CTGAACGATCT	(SEC ID Nº: 402)	CTGAACGATCT
	DLN* (SEC ID	AGAGGCTTGC		AGAGGCTTGC
	Nº: 400)	GTTATTCAGGG		GTTATTCAGGG
		TGTAGGAGTTA		TGTAGGAGTTA
		CTGAAACTCCC		CTGAAACTCCC
		CTAATGAAAGA		CTAATGAAAGA
		AGATTCAATTC		AGATTCAATTC

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		TAGCCGTTAGA		TAGCCGTTAGA
		AAATACTTTCA		AAATACTTTCA
		GCGTATCACAT		GCGTATCACAT
		TGTATTTAAAG		TGTATTTAAAG
		GAAAAGAAATA		GAAAAGAAATA
		CTCCCCATGTG		CTCCCCATGTG
		CATGGGAGGT		CATGGGAGGT
		GGTTAGAGCA		GGTTAGAGCA
		GAAATTATGAG		GAAATTATGAG
		GTCCTTCTCTC		GTCCTTCTCTC
		TTTCTACGAAT		TTTCTACGAAT
		TTGCAAGAATC		TTGCAAGAATC
		TTTGAGATCTA		TTTGAGATCTA
		AGGAAACCGT		AGGAAACCGT
		CGCTGCTCCAT		CGCTGCTCCAT
		CTGACATCCAG		CTGACATCCAG
		ATGACCCAGTC		ATGACCCAGTC
		TCCATCCTCCC		TCCATCCTCCC
		TGTCTGCATCT		TGTCTGCATCT
		GTAGGAGACC		GTAGGAGACC
		GTGTCACCATC		GTGTCACCATC
		ACTTGCCGGG		ACTTGCCGGG

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		CAAGTCGTCC		CAAGTCGTCC
		GATTGGGACG		GATTGGGACG
		ACGTTAAGTTG		ACGTTAAGTTG
		GTACCAGCAG		GTACCAGCAG
		AAACCAGGGA		AAACCAGGGA
		AAGCCCCTAAG		AAGCCCCTAAG
		CTCCTGATCTG		CTCCTGATCTG
		GTTTGGTTCCC		GTTTGGTTCCC
		GGTTGCAAAGT		GGTTGCAAAGT
		GGGGTCCCAT		GGGGTCCCAT
		CACGTTTCAGT		CACGTTTCAGT
		GGCAGTGGAT		GGCAGTGGAT
		CTGGGACAGA		CTGGGACAGA
		TTTCACTCTCA		TTTCACTCTCA
		CCATCAGCAGT		CCATCAGCAGT
		CTGCAACCTGA		CTGCAACCTGA
		AGATTTTGCTA		AGATTTTGCTA
		CGTACTACTGT		CGTACTACTGT
		GCGCAGGCTG		GCGCAGGCTG
		GGACGCATCC		GGACGCATCC
		TACGACGTTCG		TACGACGTTCG
		GCCAAGGGAC		GCCAAGGGAC

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		CAAGGTGGAA ATCAAACGGG **CGGCCGCAGA ACAAAAACTCA TCTCAGAAGAG GATCTGAATTA A** (SEC ID Nº: 401)		CAAGGTGGAA ATCAAACGG (SEC ID Nº: 403)
DMS7326 (IFNα2b-DOM7h-11-12)	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN QFQKAETIPVLH EMIQQIFNLFST KDSSAAWDETL LDKFYTELYQQ LNDLEACVIQG VGVTETPLMKE DSILAVRKYFQR ITLYLKEKKYSP CAWEVVRAEIM RSFSLSTNLQE	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT GATGTTATTAG CACAAATGCGT AGAATTTCTTT GTTCTCTTGTC TAAAGGACCGT CACGACTTCG GATTCCCTCAG GAAGAGTTTG GAAACCAATTC CAAAAAGCAGA	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN QFQKAETIPVLH EMIQQIFNLFST KDSSAAWDETL LDKFYTELYQQ LNDLEACVIQG VGVTETPLMKE DSILAVRKYFQR ITLYLKEKKYSP CAWEVVRAEIM RSFSLSTNLQE	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT GATGTTATTAG CACAAATGCGT AGAATTTCTTT GTTCTCTTGTC TAAAGGACCGT CACGACTTCG GATTCCCTCAG GAAGAGTTTG GAAACCAATTC CAAAAAGCAGA

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
	SLRSKETVAAP SDIQMTQSPSS LSASVGDRVTIT CRASRPIGTML SWYQQKPGKA PKLLILFGSRLQ SGVPSRFSGSG SGTDFTLTISSL QPEDFATYYCA QAGTHPTTFGQ GTKVEIKR **AAAEQKLISEE DLN*** (SEC ID Nº: 404)	AACTATTCCTG TCTTGCACGAA ATGATCCAGCA AATATTCAATTT GTTTTCTACAA AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG	SLRSKETVAAP SDIQMTQSPSS LSASVGDRVTIT CRASRPIGTML SWYQQKPGKA PKLLILFGSRLQ SGVPSRFSGSG SGTDFTLTISSL QPEDFATYYCA QAGTHPTTFGQ GTKVEIKR (SEC ID Nº: 406)	AACTATTCCTG TCTTGCACGAA ATGATCCAGCA AATATTCAATTT GTTTTCTACAA AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		GAAAAGAAATA		GAAAAGAAATA
		CTCCCCATGTG		CTCCCCATGTG
		CATGGGAGGT		CATGGGAGGT
		GGTTAGAGCA		GGTTAGAGCA
		GAAATTATGAG		GAAATTATGAG
		GTCCTTCTCTC		GTCCTTCTCTC
		TTTCTACGAAT		TTTCTACGAAT
		TTGCAAGAATC		TTGCAAGAATC
		TTTGAGATCTA		TTTGAGATCTA
		AGGAAACCGT		AGGAAACCGT
		CGCTGCTCCAT		CGCTGCTCCAT
		CTGACATCCAG		CTGACATCCAG
		ATGACCCAGTC		ATGACCCAGTC
		TCCATCCTCCC		TCCATCCTCCC
		TGTCTGCATCT		TGTCTGCATCT
		GTAGGAGACC		GTAGGAGACC
		GTGTCACCATC		GTGTCACCATC
		ACTTGCCGGG		ACTTGCCGGG
		CAAGTCGTCC		CAAGTCGTCC
		GATTGGGACG		GATTGGGACG
		ATGTTAAGTTG		ATGTTAAGTTG
		GTACCAGCAG		GTACCAGCAG

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		AAACCAGGGA AAGCCCCTAAG CTCCTGATCTT GTTTGGTTCCC GGTTGCAAAGT GGGGTCCCAT CACGTTTCAGT GGCAGTGGAT CTGGGACAGA TTTCACTCTCA CCATCAGCAGT CTGCAACCTGA AGATTTTGCTA CGTACTACTGT GCGCAGGCTG GGACGCATCC TACGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG**G** **CGGCCGCAGA** **ACAAAAACTCA**		AAACCAGGGA AAGCCCCTAAG CTCCTGATCTT GTTTGGTTCCC GGTTGCAAAGT GGGGTCCCAT CACGTTTCAGT GGCAGTGGAT CTGGGACAGA TTTCACTCTCA CCATCAGCAGT CTGCAACCTGA AGATTTTGCTA CGTACTACTGT GCGCAGGCTG GGACGCATCC TACGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG (SEC ID Nº: 407)

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		TCTCAGAAGAG GATCTGAATTA A (SEC ID Nº: 405		
DMS7327 (IFNα2b-DOM7h-11-15)	CDLPQTHSLGS	TGCGACTTGCC	CDLPQTHSLGS	TGCGACTTGCC
	PRTLMLLAQMR	ACAGACACATA	RRTLMLLAQMR	ACAGACACATA
	RISLFSCLKDRH	GTTTGGGATCA	RISLFSCLKDRH	GTTTGGGATCA
	DFGFPQEEFGN	AGAAGAACATT	DFGFPQEEFGN	AGAAGAACATT
	QFQKAETIPVLH	GATGTTATTAG	QFQKAETIPVLH	GATGTTATTAG
	EMIQQIFNLFST	CACAAATGCGT	EMIQQIFNLFST	CACAAATGCGT
	KDSSAAWDETL	AGAATTTCTTT	KDSSAAWDETL	AGAATTTCTTT
	LDKFYTELYQQ	GTTCTCTTGTC	LDKFYTELYQQ	GTTCTCTTGTC
	LNDLEACVIQG	TAAAGGACCGT	LNDLEACVIQG	TAAAGGACCGT
	VGVTETPLMKE	CACGACTTCG	VGVTETPLMKE	CACGACTTCG
	DSILAVRKYFQR	GATTCCCTCAG	DSILAVRKYFQR	GATTCCCTCAG
	ITLYLKEKKYSP	GAAGAGTTTG	ITLYLKEKKYSP	GAAGAGTTTG
	CAWEVVRAEIM	GAAACCAATTC	CAWEVVRAEIM	GAAACCAATTC
	RSFSLSTNLQE	CAAAAAGCAGA	RSFSLSTNLQE	CAAAAAGCAGA
	SLRSKETVAAP	AACTATTCCTG	SLRSKETVAAP	AACTATTCCTG
	SDIQMTQSPSS	TCTTGCACGAA	SDIQMTQSPSS	TCTTGCACGAA
	LSASVGDRVTIT	ATGATCCAGCA	LSASVGDRVTIT	ATGATCCAGCA
	CRASRPIGTML	AATATTCAATTT	CRASRPIGTML	AATATTCAATTT

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
	SWYQQKPGKA PKLLILAFSRLQ SGVPSRFSGSG SGTDFTLTISSL QPEDFATYYCA QAGTHPTTFGQ GTKVEIKR **AAAEQKLISEE DLN*** (SEC ID Nº: 408)	GTTTTCTACAA AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA	SWYQQKPGKA PKLLILAFSRLQ SGVPSRFSGSG SGTDFTLTISSL QPEDFATYYCA QAGTHPTTFGQ GTKVEIKR (SEC ID Nº: 410)	GTTTTCTACAA AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		GAAATTATGAG		GAAATTATGAG
		GTCCTTCTCTC		GTCCTTCTCTC
		TTTCTACGAAT		TTTCTACGAAT
		TTGCAAGAATC		TTGCAAGAATC
		TTTGAGATCTA		TTTGAGATCTA
		AGGAAACCGT		AGGAAACCGT
		CGCTGCTCCAT		CGCTGCTCCAT
		CTGACATCCAG		CTGACATCCAG
		ATGACCCAGTC		ATGACCCAGTC
		TCCATCCTCCC		TCCATCCTCCC
		TGTCTGCATCT		TGTCTGCATCT
		GTAGGAGACC		GTAGGAGACC
		GTGTCACCATC		GTGTCACCATC
		ACTTGCCGGG		ACTTGCCGGG
		CAAGTCGTCC		CAAGTCGTCC
		GATTGGGACG		GATTGGGACG
		ATGTTAAGTTG		ATGTTAAGTTG
		GTACCAGCAG		GTACCAGCAG
		AAACCAGGGA		AAACCAGGGA
		AAGCCCCTAAG		AAGCCCCTAAG
		CTCCTGATCCT		CTCCTGATCCT
		TGCTTTTTCCC		TGCTTTTTCCC

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		GTTTGCAAAGT GGGGTCCCAT CACGTTTCAGT GGCAGTGGAT CTGGGACAGA TTTCACTCTCA CCATCAGCAGT CTGCAACCTGA AGATTTTGCTA CGTACTACTGC GCGCAGGCTG GGACGCATCC TACGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG**G CGGCCGCAGA ACAAAAACTCA TCTCAGAAGAG GATCTGAATTA A** (SEC ID Nº: 409)		GTTTGCAAAGT GGGGTCCCAT CACGTTTCAGT GGCAGTGGAT CTGGGACAGA TTTCACTCTCA CCATCAGCAGT CTGCAACCTGA AGATTTTGCTA CGTACTACTGC GCGCAGGCTG GGACGCATCC TACGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG (SEC ID Nº: 411)

Las secuencias de aminoácidos y nucleótidos resaltadas en negrita representan

el sitio de clonación y la etiqueta MYC. * representa el codon de terminación en el extremo del gen.

Determinación de Afinidad y Caracterización Biofísica:

Para determinar la afinidad de unión (K_D) de las proteínas de fusión AlbudAb-IFNα2b a cada albúmina de suero; las proteínas de fusión purificadas se analizaron por BIAcore sobre albúmina (inmovilizada mediante acoplamiento de amina primaria sobre matrices CM5; BIAcore) usando concentraciones de las proteínas de fusión de 5000 nM a 39 nM (5000 nM, 2500 nM, 1250 nM, 625 nM, 312 nM, 156 nM, 78 nM, 39 nM) en tampón HBS-EP BIAcore.

Tabla 12: Afinidad para SA

AlbudAb	**Fusión**	**Afinidad para SA (nM)**	**Kd**	**Ka**
		Rata		
DOM7h-14	IFNα2b	350	4,500E-02	1,28E+05
DOM7h-14-10	IFNα2b	16	4,970E-03	5,90E+05
DOM 7h-14-18	IFNα2b	780	2,127E-01	5,80E+05
DOM 7h-14-19	IFNα2b	1900	1,206E-01	7,96E+04
DOM 7h-11	IFNα2b	6000	7,500E-01	nd
DOM 7h-11-12	IFNα2b	1700	3,100E-01	1,30E+05
DOM 7h-11-15	IFNα2b	200	1,660E-02	1,50E+05
		Cyno		
DOM 7h-14	IFNα2b	60	1,32E-02	5,0E+05
DOM 7h-14-10	IFNα2b	19	7,05E-03	4,50E+05
DOM 7h-14-18	IFNα2b	sin unión	sin unión	sin unión
DOM 7h-14-19	IFNα2b	520	8,47E-02	2,73E+05

AlbudAb	Fusión	Afinidad para SA (nM)	Kd	Ka
DOM 7h-11	IFNα2b	3300	3,59E-01	1,20E+05
DOM 7h-11-12	IFNα2b	630	3,45E-01	7,00E+05
DOM 7h-11-15	IFNα2b	15	4,86E-03	3,60E+05
		Ratón		
DOM 7h-14	IFNα2b	240	3,21E-02	1,50E+06
DOM 7h-14-10	IFNα2b	60	3,45E-02	6,86E+05
DOM 7h-14-18	IFNα2b	180	1,50E-01	9,84E+05
DOM 7h-14-19	IFNα2b	490	4,03E-02	1,19E+05
DOM 7h-11	IFNα2b	6000	1,55E-01	nd
DOM 7h-11-12	IFNα2b	150	9,49E-02	6,30E+05
DOM 7h-11-15	IFNα2b	28	6,69E-03	2,80E+05
		Humano		
DOM 7h-14	IFNα2b	244	2,21E-02	9,89E+04
DOM 7h-14-10	IFNα2b	32	6,58E-03	3,48E+05
DOM 7h-14-18	IFNα2b	470	2,75E-01	6,15E+05
DOM 7h-14-19	IFNα2b	350	4,19E-02	1,55E+05
DOM 7h-11	IFNα2b	670	2,02E-01	7,00E+05
DOM 7h-11-12	IFNα2b	500	1,66E-01	3,90E+05
DOM 7h-11-15	IFNα2b	10	1,87E-03	3,50E+05

Cuando IFNα2b está unido a las variantes AlbudAb, en todos los casos la afinidad de unión de AlbudAb para la albúmina de suero se reduce. DOM7h-14-10 y DOM7-11-15 conservan afinidad de unión mejorada para la albúmina de suero en todas las especies en comparación con el parental. DOM7h-11-12 también muestra afinidad

de unión mejorada para la albúmina de suero en todas las especies en comparación con el parental.

Tabla 13: Caracterización Biofísica

La Caracterización Biofísica se realizó por SEC MALLS y DSC como se ha descrito anteriormente para los AlbudAbs sencillos.

AlbudAb	Fusión	Número DMS	Parámetros biofísicos	
			SEC MALLS	DSC Tm (°C)
DOM 7h-14	IFNα2b	DMS7321	M/D	58-65
DOM 7h-14-10	IFNα2b	DMS7322	M/D	55-65
DOM 7h-14-18	IFNα2b	DMS7323	M/D	55-65
DOM 7h-14-19	IFNα2b	DMS7324	M/D	59-66
DOM 7h-11	IFNα2b	DMS7325	M/D	65,8-66,2
DOM 7h-11-12	IFNα2b	DMS7326	M/D	67-67,3
DOM 7h-11-15	IFNα2b	DMS7327	M/D	56,3-66,2

M/D indica un equilibrio de monómero/dímero según se detecta por SEC MALLS

En la Tabla 13 se observa la expresión para todos los clones en el intervalo de 17,5 a 54 mg/l en HEK293.

Para las variantes IFNα2b-DOM7h-14 e IFNα2b-DOM7h-11, durante la maduración de afinidad se mantuvieron parámetros biofísicos y niveles de expresión favorables.

Determinación del PK para fusiones AlbudAb-IFNα2b

Las fusiones AlbudAbs IFNα2b DMS7321 (IFNα2b-DOM7h-14) DMS7322 (IFNα2b-DOM7h-14-10) DMS7323 (IFNα2b-DOM7h-14-18), DMS7324 (IFNα2b-

DOM7h-14-19), DMS7325 (IFNα2b-DOM7h-11), DMS7326 (IFNα2b-DOM7h-11-12), DMS7327 (IFNα2b-DOM7h-11-15) se expresaron con la etiqueta myc en cantidades de 20-50 mg en células HEK293 y se purificaron del sobrenadante de cultivo usando resina de afinidad a proteína L y se eluyó con glicina 100 mM pH2. Las proteínas se llevaron a una concentración superior a 1 mg/ml, se intercambio de tampón en PBS de Dulbecco y la endotoxina se agotó usando columnas de giro Q (Vivascience).

Para el PK de Rata, se dosificó IFN-AlbudAb como inyecciones i.v. únicas de 2,0 mg/kg usando 3 ratas por compuesto. Se tomaron muestras de suero a 0,16, 1, 4, 8, 24, 48, 72, 120, 168 h. El análisis de los niveles en suero se realizó por EASY ELISA de acuerdo con las instrucciones del fabricante (GE Healthcare, número de catálogo RPN5960).

Para el PK de Ratón, se dosificó DMS7322 (IFN2b-DOM7h-14-10) DMS7325 (IFN2b-DOM7h-11), DMS7326 (IFN2b-DOM7h-11-12), DMS7327 (IFN2b-DOM7h-11-15) todos etiquetados con myc como inyecciones i.v. únicas de 2,0 mg/kg por grupos de dosis de 3 sujetos y las muestras de suero se tomaron a 10 min; 1 h, 8 h; 24 h; 48 h; 72 h; 96 h. El análisis de los niveles en suero se realizó por EASY ELISA de acuerdo con las instrucciones del fabricante (GE Healthcare, número de catálogo RPN5960).

Tabla 14:

Especie	AlbudAb	Fusión	Albúmina K_D (nM)	Parámetros PK			
				AUC h x μg/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
Rata	**7h-14**	IFNα2b	350	832,1	2,4	27	94,5
	7h-14-10	IFNα2b	16	1380,7	1,5	35,8	75,2
	7h-14-18	IFNα2b	780	691,2	2,9	22,4	93,7

Especie	AlbudAb	Fusión	Albúmina K_D (nM)	Parámetros PK			
				AUC h x µg/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
	7h-14-19	IFNα2b	1900	969,4	2,2	25	78,7
	7h-11	IFNα2b	6000	327,9	6,5	11	101,9
	7h-11-12	IFNα2b	1700	747,1	2,8	25,8	104,7
	7h-11-15	IFNα2b	200	1118,7	1,8	39,5	103,6
Ratón	**7h-14**	IFNα2b	240	761,2	2,6	30,4	115,3
	7h-14-10	IFNα2b	60	750,5	2,7	30,9	118,6
	7h-11	IFNα2b	6000	493,9	4,0	8,8	51,2
	7h-11-12	IFNα2b	150	439,6	4,5	21,5	140,9
	7h-11-15	IFNα2b	28	971,8	2,1	33,6	99,6

Los parámetros farmacocinéticos obtenidos de estudios de rata y ratón se ajustaron usando un modelo no-compartimental. Clave: AUC: Área bajo la curva del tiempo de dosificación extrapolado al infinito; CL: eliminación; t1/2: es el tiempo durante el cual la concentración en sangre se divide en dos; Vz: volumen de distribución en base a la fase terminal.

Se ensayaron IFNα2b-AlbudAbs en rata y ratón. Para todas las proteínas de fusión de la variante IFNα2b-DOM7h-11 tanto en rata como en ratón, el valor t1/2 mejoró en comparación con el parental. La mejora del t1/2 equivale a una KD mejorada *in vitro* para la albúmina de suero.

Para las variantes IFNα2b-DOM7h-14-10 la mejora de K_D *in vitro* para la albúmina de suero también equivale a una mejora del t1/2 en rata.

Todas las proteínas de fusión IFNα2b-AlbudAbs mostraron una disminución en la unión a RSA de 5 a 10 veces en comparación con AlbudAb sencillo. Este efecto es más pronunciado (es decir, 10 veces) en la serie DOM7h-14 que en la serie DOM7h-11 (únicamente una disminución de 5 veces).

Ejemplo 8: Fusiones AlbudAb adicionales con proteínas, péptidos y NCE.

Se ensayaron diversas AlbudAbs fusionadas a otras entidades químicas concretamente anticuerpos de dominio (dAbs), péptidos y compuestos NCE. Los resultados se muestran en la tabla 15.

Tabla 15:

Especie	AlbudAb	Fusión	Albúmina K_D (nM)	Paráme-tros PK			
				AUC h x µg/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
Rata	DOM7h-14	Exendina-4	2400	18	57,1	11	901,9
	DOM7h-14-10	Exendina-4	19	43,6	23,1	22,1	740,3
	DOM7h-14-18	Exendina-4	16000	16,9	75,7	9,4	1002,5
	DOM7h-14-19	Exendina-4	17000	31,4	32,5	11,9	556,7
	DOM7h-11	Exendina-4	24000	6,1	168	7,1	1684,1
	DOM7h-11-12	Exendina-4	1400	24,2	59,9	13	1068,7

Especie	AlbudAb	Fusión	Albúmina K_D (nM)	Paráme-tros PK			
				AUC h x µg/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
	DOM7h-11-15	Exendina-4	130	36,3	27,6	19,3	765,7
	DOM7h14-10	NCE-GGGGSC	62				
	DOM7h14-10	NCE-TVAAPSC	35				
Humano	DOM7h-14	NCE	204				
Ratón	DOM7h-11	DOM1m-21-23		234	10,7	4,7	72,5
	DOM7h-11-12	DOM1m-21-23		755	3,3	18	86,2
	DOM7h-11-15	DOM1m-21-23		1008	2,5	17,4	62,4

Clave: DOM1m-21-23 es un dAb anti-TNFR1, Exendina-4 es un péptido (un agonista de GLP-1) de 39 aminoácidos de longitud. NCE, NCE-GGGGSC y NCE-TVAAPSC se describen a continuación.

Anteriormente se ha descrito el uso de fusiones genéticas con un dAb de unión a albúmina (AlbudAb) para ampliar la semivida PK del dAbs anti-TNFR1 *in vivo* (véase, por ejemplo los documentos WO04003019, WO2006038027, WO2008149148). En estas solicitudes estas solicitudes PCT se hace referencia a los protocolos. En la tabla

anterior, DOM1m-21-23 es un dAb anti-TNFR1 de ratón.

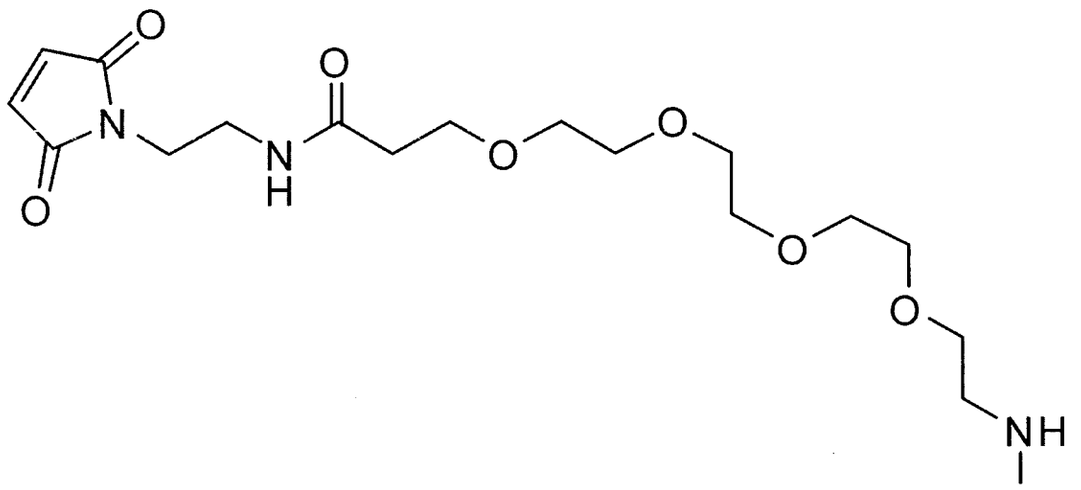
Para producir las fusiones genéticas de exendina-4 o con DOM7h-14 (u otro AlbudAb) que se unen a la albúmina de suero, la secuencia AlbudAb-engarce-exendina-4 se clonó en el vector pTT 5 (obtenible de CNRC, Canadá). En cada caso la exendina-4 estaba en el extremo 5' de la construcción y el dAb en el extremo 3'. El engarce era un engarce $(G_4S)_3$. Se preparó ADN sin endotoxina en *E. coli* usando lisis alcalina (usando el kit Giga para plásmido sin endotoxina, obtenible de Qiagen CA) y se usó para transfectar células HEK293E (obtenibles de CNRC, Canadá). La transfección se realizó en matraces de células HEK293E / 250 ml a $1,75x10^6$ céls/ml usando 333 µl de fectin 293 (Invitrogen) y 250 µg de ADN por matraz y la expresión se realizó a 30ºC durante 5 días. El sobrenadante se recogió por centrifugación y la purificación se realizó por purificación de afinidad en proteína L. La proteína se unió en lotes a la resina, se rellenó en una columna y se lavó con volúmenes de 10 columnas de PBS. La proteína se eluyó con 50 ml de glicina 0,1 M pH 2 y se neutralizó con Tris pH 8. La proteína del tamaño esperado se identificó sobre un gel SDS-PAGE.

Fusiones NCE Albudab:

Se ensayó una fusión de AlbudAb con una nueva entidad química (NEC). La NCE, un inhibidor de ADAMTS-4 de molécula pequeña se sintetizó con un engarce PEG (engarce PEG 4 (es decir, moléculas PEG 4 antes de la maleimida) y un grupo maleimida para la conjugación al AlbudAb. La conjugación del NCE al AlbudAb se realiza mediante un resto de cistina modificado por ingeniería genética en la posición de aminoácido R108C o después de un espaciador de 5 aminoácidos (GGGGSC) o 6 aminoácidos (TVAAPSC) en el extremo del AlbudAb. En resumen, el AlbudAb se redujo con TCEP (Pierce, Catálogo Número 77720), se desalinizó usando una columna PD10

(GE healthcare) en Bis-Tris 25 mM, EDTA 5 mM, glicerol al 10% (v/v) pH 6,5. Se añadió un exceso molar de 5 veces del NCE activado en DMSO no sobrepasando el 10% de concentración final (V/V). La reacción se incubó durante una noche a temperatura ambiente y se dializó exhaustivamente en Tris 20 mM pH 7,4.

Engarce PEG:



Secuencias:

DOM7h-14 R108C:

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLPHPKTFGQGTKVEIKC (SEC ID Nº: 412)

Nucleótidos:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGT CACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTGGTACCAGC AGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTCCTCGTTGCAAAGT GGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCAT CAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCTCAGGGTTTGAGGC

ATCCTAAGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAATGC (SEC ID Nº: 413)

Véase la Tabla 5 para las secuencias de DOM7h-14-10/TVAAPSC y DOM7h-14-10/GGGGSC (es decir, DOM7h-14-10/G4SC).

NCE-AlbudAbs DOM7h-14-10 GGGGSC y DOM7h14-10 TVAAPSC, muestran una disminución de afinidad *in vitro* de 5 a 10 veces (K_D) para RSA según se determina por BIAcore cuando se fusionan a la entidad química. Aún no se dispone de los datos PK para estas moléculas.

Fusión dAb-Albudab: los 2 AlbudAbs DOM7h-11 con la mayor afinidad para RSA experimentaron una disminución de afinidad para RSA de 2 veces en un BIAcore cuando se fusionaron a un anticuerpo de dominio terapéutico (DOM1m-21-23) en comparación con AlbudAb no fusionado. El clon DOM7h-11 muestra una K_D micromolar cuando se fusiona (2,8 μM) así como cuando no se fusiona (~5 μM).

Fusión Exendina-4 AlbudAb: el efecto de la fusión de AlbudAbs a un péptido en la capacidad de unión a RSA es aproximadamente de 10 veces, excepto DOM7h-14-10, que únicamente muestra una disminución de unión de 4 veces. El efecto, sin embargo, es más pronunciado para la serie DOM7h-14 (excepto DOM7h-14-10) que lo que parece ser para la serie DOM7h-11.

Para todos los datos anteriores, el T1/2 de la fusión aumentó con afinidad mejorada para las SA de las especies.

Generalmente se clasifican los efectos terapéuticos de Albudab como que son terapéuticamente susceptibles (para el tratamiento y/o profilaxis de enfermedades, afecciones o indicaciones) cuando las fusiones AlbudAb-fármaco muestran un intervalo de afinidad (K_D) de 0,1 nM a 10 nM para la unión a la albúmina de suero.

Los intervalos terapéuticos de las fusiones AlbudAbs y AlbudAb (Proteína-

AlbudAb por ejemplo IFNa2b-DOM7h-14-10; Péptido-AlbudAbs por ejemplo Exendina-4-DOM7h-14-10; dAb-AlbudAbs por ejemplo DOM1m21-23-DOM7h11-15; NCE-AlbudAb por ejemplo ADAMTS-4-DOM7h-14-10) se definen a continuación: se muestran intervalos de afinidad (K_D) que son útiles para la terapia de afecciones, enfermedades o indicaciones crónicas o agudas que se muestran. También se muestran intervalos de afinidad marcados como "intermedios". AlbudAb y las fusiones en este intervalo son útiles en enfermedades, afecciones o indicaciones agudas o crónicas. De este modo, la afinidad de la AlbudAb o fusión para la albúmina de suero puede adaptarse o seleccionarse de acuerdo con la enfermedad, afección o indicación a tratar. Como se describe anteriormente, la invención proporciona AlbudAbs con afinidades que permiten que cada AlbudAb se clasifique como "afinidad elevada", "afinidad media" o "afinidad baja", permitiendo de esta manera al experto en la materia seleccionar la AlbudAb apropiada de la invención de acuerdo con la terapia en cuestión. Véase la Figura 2.

Ejemplo 9: Secuencias DOM7h-11-15^{S12P}

Secuencia de Aminoácidos de DOM7h-11-15^{S12P}

DIQMTQSPSSLPASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQSGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR (SEC ID Nº: 414)

Un aspecto de la invención proporciona un ácido nucleico que comprende la secuencia de nucleótidos de DOM7h-11-15^{S12P} o una secuencia de nucleótidos tiene una identidad de secuencia de al menos el 80% con respecto a dicha secuencia seleccionada. DOM7h-11-15^{S12P} se produjo usando la siguiente secuencia de ácidos nucleicos (la C subrayada indica el cambio (frente a los ácidos nucleicos que codifican

DOM7h-11-15) que conduce una prolina en la posición 12):

GACATCCAGATGACCCAGTCTCCATCCTCCCTGCCTGCATCTGTAGGAGACCGTGT
CACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACCAG
CAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCCCGTTTGCAAAG
TGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCA
TCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGCGCGCAGGCTGGGAC
GCATCCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG (SEC ID Nº: 415)

DOM7h-11-15^{S12P} se construyó usando DOM7h-11-15 como un molde en una PCR en la que se usó un cebador para introducir la mutación S12P. La secuencia del cebador es:

GCAACAGCGTCGACGGACATCCAGATGACCCAGTCTCCATCCTCCCTGCCTGCAT CTGTAGG (SEC ID Nº: 416).

Un aspecto alternativo de la invención proporciona un ácido nucleico que comprende la secuencia de nucleótidos de la SEC ID Nº: 415 o una secuencia de nucleótidos tiene una identidad de secuencia de al menos el 80% con respecto a dicha secuencia seleccionada. En una realización, DOM7h-11-15^{S12P} se codifica por y se expresa a partir de un vector que contiene una región de engarce y una secuencia C-terminal que codifica una proteína o un fármaco peptídico de un dominio variable simple u otro fragmento de anticuerpo para preparar el producto de fusión de proteína *in-line*. El engarce, en una realización, comprende la secuencia de aminoácidos TVA, por ejemplo, TVAAPS. Otros aspectos de la invención son un vector que comprende el ácido nucleico; y una célula huésped aislada que comprende el vector. La invención también

proporciona un método de tratamiento o prevención de una enfermedad o trastorno en un paciente, que comprende administrar al menos una dosis de DOM7h-11-15^{S12P} a dicho paciente.

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Una variante de dominio variable sencillo de inmunoglobulina anti-albúmina de suero (SA) de DOM7h-14 (DOM7h-14 como se muestra en la Figura 1), en la que la variante comprende al menos una mutación en la región CDR3 de 92 a 96 (numeración de las posiciones de acuerdo con Kabat) en comparación con DOM7h-14 y en la que la variante tiene de 1 a 8 cambios en comparación con la secuencia de aminoácidos de DOM7h-14.

2. La variante de la reivindicación 1, en la que la variante comprende un motivo AQG(X1)(X2)(X3)P(X4)T, en el que A está en la posición 89 (de acuerdo con Kabat) y al menos una de (X1) a (X4) representa un cambio de aminoácidos en comparación con la secuencia de DOM7h14.

3. La variante de la reivindicación 1 ó 2, en la que la variante comprende una mutación en cada una de las posiciones 92, 93 y 94 y opcionalmente en la posición 96 (numeración de acuerdo con Kabat) comparada con DOM7h-14.

4. La variante de la reivindicación 3, en la que la variante comprende uno o más restos aminoacídicos seleccionados de

Posición 92 = L o F,

Posición 93 = R, M o K,

Posición 94 = H o K, y

Posición 96 = K o M (numeración de acuerdo con Kabat)

5. La variante de la reivindicación 1 o 2, en la que la variante comprende Lys o Met en la posición 96 (numeración de acuerdo con Kabat) en comparación con DOM7h-14.

6. La variante de la reivindicación 5, en la que la variante comprende uno o más restos aminoacídicos seleccionados de

Posición 92 = L o F,

Posición 93 = R, M o K,

Posición 94 = H o K (numeración de acuerdo con Kabat)

7. La variante de la reivindicación 1, en la que la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de un dominio variable sencillo seleccionado de DOM7h-14-10 (SEC ID Nº:1), DOM7h-14-18 (SEC ID Nº:2), DOM7h-14-28 (SEC ID Nº: 4) y DOM7h-14-36 (SEC ID Nº:5) o tiene hasta 4 cambios en comparación con la secuencia de aminoácidos seleccionada, en la que a variante comprende al menos una mutación en la región CDR3 de 92 a 96 (numeración de las posiciones de acuerdo con Kabat) comparada con DOM7h-14.

8. Un resto de unión a anti albúmina de suero (SA) que comprende la CDR3 de una variante seleccionada de cualquier reivindicación anterior.

9. El resto de unión de la reivindicación 8, que comprende la CDR1 de la variante seleccionada o una secuencia de aminoácidos que es al menos el 50% idéntica a la CDR1 de la variante seleccionada.

10. El resto de unión de la reivindicación 8 ó 9, que comprende la CDR2 de la variante seleccionada, o una secuencia de aminoácidos que es al menos el 50% idéntica a la CDR2 de la variante seleccionada.

11. Una variante de DOM7h14 de dominio variable sencillo de inmunoglobulina de anti albúmina de suero (SA), en el que la variante comprende una Ser en la posición 22 y una Glu en la posición 42 (numeración de acuerdo con Kabat) en comparación con DOM7h-14 y en la que la variante tiene de 0 a 4 cambios adicionales en comparación con la secuencia de aminoácidos de DOM7h-14.

12. La variante de la reivindicación 11, en la que la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de DOM7h-14-19 (SEC ID Nº:3) o tiene hasta 4 cambios en comparación con la secuencia de aminoácidos de DOM7h-14-19, en la que la variante comprende Ser en la posición 22 y Glu en la posición 42 (numeración de acuerdo con Kabat) en comparación con DOM7h-14.

13. La variante o resto de unión de cualquier reivindicación anterior, en la que la variante o resto de unión comprende un sitio de unión que se une específicamente a SA humana con una constate de disociación (KD) de aproximadamente 0.1 a aproximadamente 10.000nM, opcionalmente de aproximadamente 3 x 10^{-4} a aproximadamente 0,1 s^{-1} como se determina por resonancia de plasmón superficial.

14. La variante o resto de unión de cualquier reivindicación anterior, en la que la

variante o resto de unión comprende un sitio de unión que se une específicamente a SA humana con una constante de velocidad de disociación (K_d) de aproximadamente 1,5 x 10^{-4} a aproximadamente 0,1 s^{-1}, opcionalmente de aproximadamente 3 x 10^{-4} a aproximadamente 0,1 s^{-1}, como se determina por resonancia de plasmón superficial.

15. La variante o resto de unión de cualquier reivindicación anterior, en la que la variante comprende un sitio de unión que se une específicamente a SA humana con una constante de velocidad de asociación (K_a) de aproximadamente 2 x 10^6 a aproximadamente 1 x 10^4 $M^{-1}s^{-1}$, opcionalmente de aproximadamente 1 x 10^6 a aproximadamente 2 x 10^4 $M^{-1}s^{-1}$, como se determina por resonancia de plasmón superficial.

16. La variante o resto de unión de cualquier reivindicación anterior, en el que la variante comprende un sitio de unión que se une específicamente a SA de mono *Cynomolgus* con una constante de disociación (KD) de aproximadamente 0,1 a aproximadamente 10000 nM, opcionalmente de aproximadamente 1 a aproximadamente 6000 nM, como se determina por resonancia de plasmón superficial.

17. La variante o resto de unión de cualquier reivindicación anterior, en la que la variante comprende un sitio de unión que se une específicamente a SA de mono *Cynomolgus* con una constante de velocidad de disociación (K_d) de aproximadamente 1,5 x 10^{-4} a aproximadamente 0,1 s^{-1}, opcionalmente de aproximadamente 3 x 10^{-4} a aproximadamente 0,1 s^{-1}, como se determina por resonancia de plasmón superficial.

18. La variante o resto de unión de cualquier reivindicación anterior, en la que la

variante comprende un sitio de unión que se une específicamente a SA de mono *Cynomolgus* con una constante de velocidad de asociación (K_a) de aproximadamente 2 x 10^6 a aproximadamente 1 x 10^4 $M^{-1}s^{-1}$, opcionalmente de aproximadamente 1 x 10^6 a aproximadamente 5 x 10^3 $M^{-1}s^{-1}$, como se determina por resonancia de plasmón superficial.

19. Un ligando multiespecífico que comprende una variante anti-SA o resto de unión de cualquier reivindicación anterior que se une específicamente a un antígeno diana distinto de SA.

20. Un resto o dominio variable sencillo de variante anti-SA de una cualquiera de las reivindicaciones 1 a 18, en el que el dominio o resto variable se conjuga con un fármaco (opcionalmente un fármaco NCE), opcionalmente en el que el dominio o resto variable es DOM7h-14-10 (SEC ID Nº: 1).

21. Una proteína de fusión que comprende un fármaco polipeptídico o peptídico fusionado a una variante o resto de acuerdo con una cualquiera de las reivindicaciones 1 a 18, opcionalmente en el que la variante o resto es DOM7h-14-10 (SEC ID Nº: 1).

22. Una composición que comprende una variante, resto, proteína de fusión o ligando de cualquier reivindicación anterior y un diluyente, transportador, excipiente o vehiculo farmacéuticamente aceptable.

23. Un ácido nucleico que comprende una secuencia de nucleótidos que codifica una variante o resto de acuerdo con una cualquiera de las reivindicaciones 1 a 18 o un

ligando multiespecífico de la reivindicación 20 o proteína de fusión de la reivindicación.

24. Un ácido nucleico que comprende la secuencia de nucleótidos de una variante de DOM7h-14 seleccionada de la secuencia de nucleótidos de DOM7h-14-10 (SEC ID Nº: 1), DOM7h-14-18 (SEC ID Nº: 2), DOM7h-14-28 (SEC ID Nº: 4), DOM7h-14-36 (SEC ID Nº: 5) o DOM7h-14-19 (SEC ID Nº: 3) o una secuencia de nucleótidos que tiene una identidad de secuencia de al menos el 80% con dicha secuencia seleccionada.

25. Un vector que comprende el ácido nucleico de la reivindicación 23 ó 24.

26. Una célula huésped aislada que comprende el vector de la reivindicación 25.

27. Un método de tratamiento o prevención de enfermedad o trastorno en un paciente, que comprende administrar a dicho paciente al menos una dosis de una variante o resto de acuerdo con una cualquiera de las reivindicaciones 1 a 18.

Restos Kabat	'	'	'	'	5	'	'	'	'	10	'	'	'	'	15	'	'	'	'	20
DOM7h-14	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T
DOM7h-14-10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-18	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-36	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Restos Kabat	'	'	'	'	25	'	'	'	'	30	'	'	'	'	35	'	'	'	'	40
DOM7h-14	I	T	C	**R**	**A**	**S**	**Q**	**W**	**I**	**G**	**S**	**Q**	**L**	**S**	W	Y	Q	Q	K	P
DOM7h-14-10	.	.	.	-	-	-	-	-	-	-	-	-	-	-	.	.	.	.	.	.
DOM7h-14-18	.	.	.	-	-	-	-	-	-	-	-	-	-	-	.	.	.	.	.	.
DOM7h-14-19	.	S	.	-	-	-	-	-	-	-	-	-	-	-	.	.	.	.	.	.
DOM7h-14-28	.	.	.	-	-	-	-	-	-	-	-	-	-	-	.	.	.	.	.	.
DOM7h-14-36	.	.	.	-	-	-	-	-	-	-	-	-	-	-	.	.	.	.	.	.

Restos Kabat	'	'	'	'	45	'	'	'	'	50	'	'	'	'	55	'	'	'	'	60
DOM7h-14	G	K	A	P	K	L	L	I	M	**W**	**R**	**S**	**S**	**L**	**Q**	**S**	G	V	P	S
DOM7h-14-10	.	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	.	.	.	.
DOM7h-14-18	.	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	.	.	.	.
DOM7h-14-19	.	E	.	.	.	.	.	.	.	-	-	-	-	-	-	-	.	.	.	.
DOM7h-14-28	.	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	.	.	.	.
DOM7h-14-36	.	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	.	.	.	.

Restos Kabat	'	'	'	'	65	'	'	'	'	70	'	'	'	'	75	'	'	'	'	80
DOM7h-14	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P
DOM7h-14-10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Figura 1A

humano	Parámetros cinéticos basados en linajes DOM7h-14 y DOM7h-11 (intervalos confirmados por datos)		
	Intervalos globales		
	KD: 1 to 10000		
	Kd:1.5e-4 to 0.1 ; Ka:2e6 to 1e4		
Agentes terapéuticos	Crónico	Intermedio	Agudo
	Afinidad elevada	Afinidad media	Afinidad baja
	KD: 0,1-400	KD: 400-2000	KD: 2000-10000
	Kd:1,5e-4 to 8e-3 ; Ka:1e6 to 5e4	Kd: 8e-3 to 0,08 ; Ka: 2e4 to 5e4	Kd:0.08 to 0,1 ; Ka: 5e4 to 1e4
Intervalos opcionales	KD: 1-200	KD: 400-1500	KD: 2000-6000
	Kd:3e-4 to 2e-3; Ka: 1e6 to 5e4	Kd:8e-3 to 0,08; Ka: 2e4 to 6e4	Kd:0.08 to 0,1 ; Ka: 5e4 to 2e4
Ejemplos	DOM7h-11-15, DOM7h-14, DOM7h-14-10, DOM7h-14-18, DOM7h-14-19, DOM7h-11-18, DOM7h-11-19 DMS7321, DMS7322; DMS7324, DMS7327	DMS7325, DMS7326; DMS7323	DOM7h-11

Figura 2A

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Cyno			
	Intervalos globales		
	KD: 1 to 10000		
	Kd:1.5e-4 to 0.1 ; Ka:2e6 to 1e4		
Agentes terapéuticos	crónico	intermedio	agudo
	Afinidad alta	Afinidad media	Afinidad baja
	KD: 0,1-400	KD: 400-2000	KD: 2000-10000
	Kd:1,5e-4 to 8e-3 ; Ka:2e6 to 2e4	Kd: 8e-3 to 0,08 ; Ka: 2e4 to 5e4	Kd:0.08 to 0,1 ; Ka: 5e4 to 1e4
Intervalos opcionales	KD: 1-200	KD: 400-1500	KD: 2000-6000
	Kd:3e-4 to 2e-3; Ka: 1e6 to 1e4	Kd:2e-3 to 0,05; Ka: 2e4 to 1e4	Kd:0.08 to 0,1 ; Ka: 5e4 to 2e4
Ejemplos	DMS7327; DOM7h-11-15; DOM7h-14; DOM7h-14-10; DOM7h-14-18; DOM7h-14-19, DOM7h-14-28, DOM7h-14-36 DMS7321; DMS7322	DOM7h-11; DMS7326; DMS7324;	DOM7h11-12, DOM7h-11-18 DMS7325

Figura 2A

Rata			
	Intervalos globlales		
	KD: 1 to 10000		
	Kd: 2e-3 to 0,15 ; Ka: 2e6 to 1e4		
Agentes terapéuticos	crónico	Intermedio	Agudo
	Afinidad elevada	Afinidad media	Afinidad baja
	KD: 1-300	KD: 300-2000	KD: 2000-10000
	Kd:2e-3 to 5e-2 ; Ka:2e6 to 2e5	Kd:5e-2 to 0,09 ; Ka:2e5 to 4,5e4	Kd:0,09 to 0,15 ; Ka: 4,5e4 to 1,5e4
Intervalos opcionales	KD: 20-200	KD: 400-1800	KD: 2000-6000
	Kd:9e-3 to 2e-2 ; Ka: 1e6 to 1e5	Kd: 4e-2 to 0,09; Ka:1e5 to 5e4	Kd: 0,1 to 0,14 ; Ka: 5e4 to 3e4
Ejemplos	DOM7h-11-15; DOM7h-11-12; DOM7h-11-18, DOM7h-11-19, DOM7h-14-28, DOM7h-14-36, DOM7h-14 DMS7327; DMS7322	DOM7h-14-18; DOM7h-14-19; DMS7321; DMS7323, DMS7324, DMS7326;,	DMS7325; DOM7h-11;

Figura 2C

Ratón			
	Intervalos globales		
	KD: 1 to 10000		
	Kd: 2e-3 to 0.15 ; Ka: 2e6 to 1e4		
Agentes terapéuticos	crónico	intermedio	Agudo
	Afinidad elevada	Afinidad media	Afinidad baja
	KD: 1-100	KD: 100-2000	KD: 2000-10000
	Kd:2e-3 to 1e-2 ; Ka:2e6 to 1e5	Kd:1e-2 to 0,07 ; Ka: 1e5 to 3e4	Kd: 0,08 to 0,15; Ka: 4e4 to 1,5e4
Intervalos opcionales	KD: 1 to 80	KD: 120-2000	KD: 4000-10000
	Kd:2e-3 to 1e-2 ; Ka: 2e6 to 1,5e5	Kd: 9e-3 to 0,07 ; Ka: 1,3e5 to 3e4	Kd:0,1 to 0,15 ; Ka: 2.5e4 to 1,5e4
Ejemplos	DOM7h-11-15;; DOM7h-14; DOM7h-14-10, DOM7h-14-18, DOM7h-14-19, DOM7h-11-18, DOM7h-11-19, DOM7h-14-28, DOM7h-14-36 DMS7322, DMS7327	DMS7321; DMS7323; DMS7324; DOM7h-11-12; DMS7326	DMS7325; DOM7h-11

Figura 2D

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
Clube, Jasper Rupert
GLAXOSMITHKLINE
Global Patents (CN925.1)
980 Great West Road
Brentford, Middlesex TW8 9GS
GRANDE BRETAGNE

Date of mailing *(day/month/year)*	16 November 2010 (16-11-2010)
Applicant's or agent's file reference JRC/DB63557	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/EP2010/052007	International filing date *(day/month/year)* 17 February 2010 (17-02-2010)
Applicant GLAXO GROUP LIMITED	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	BÜCHLER, Stefanie Tel: +49 (0)89 2399-8090

Form PCT/ISA/220 (July 2009) *(See notes on accompanying sheet)*

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.
JRC/DB63557		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2010/052007	17/02/2010	19/02/2009
Applicant		
GLAXO GROUP LIMITED		

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

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

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

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of:

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

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

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

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

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

4. With regard to the **title,**

☒ the text is approved as submitted by the applicant

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant

☐ as selected by this Authority, because the applicant failed to suggest a figure

☐ as selected by this Authority, because this figure better characterizes the invention

b. ☒ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2010/052007

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

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

   a. (means)

   [X] on paper

   [X] in electronic form

   b. (time)

   [ ] in the international application as filed

   [ ] together with the international application in electronic form

   [X] subsequently to this Authority for the purpose of search

2. [X] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in 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/EP2010/052007

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/18 C07K16/28 C07K14/56 C07K14/575

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

B. FIELDS SEARCHED

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

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 practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/096158 A2 (DOMANTIS LTD [GB]; TOMLINSON IAN [GB]; JESPERS LAURENT [GB]; CLUBE JAS) 14 August 2008 (2008-08-14) cited in the application page 32, line 15 - line 24 page 33, line 7 - line 18 page 36, line 2 - line 11 page 44, line 25 - page 45, line 2; figure 24 page 84, line 11 - line 20 page 112, line 17 - page 123, line 17 claims 1-79; examples 13-17,24,26 ----- -/--	1-27

[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 document 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
8 July 2010	16/11/2010

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	Bayer, Annette

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/052007

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BARBAS C F ET AL: "Selection of human anti-hapten antibodies from semisynthetic libraries" GENE, ELSEVIER, AMSTERDAM, NL LNKD- DOI:10.1016/0378-1119(93)90251-W, vol. 137, no. 1, 27 December 1993 (1993-12-27), pages 57-62, XP023539595 ISSN: 0378-1119 [retrieved on 1993-12-27] page 58, left-hand column, paragraph 2 - right-hand column, paragraph 1 page 60, right-hand column, paragraph 1	1-27
A	RUDIKOFF S ET AL: "Single amino acid substitution altering antigen-binding specificity" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES (PNAS), NATIONAL ACADEMY OF SCIENCE, US LNKD- DOI:10.1073/PNAS.79.6.1979, vol. 79, 1 March 1982 (1982-03-01), pages 1979-1983, XP007901436 ISSN: 0027-8424 the whole document	1-21
A	MACCALLUM R M ET AL: "Antibody-antigen interactions: Contact analysis and binding site topography" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB LNKD- DOI:10.1006/JMBI.1996.0548, vol. 262, no. 5, 1 January 1996 (1996-01-01), pages 732-745, XP002242391 ISSN: 0022-2836 the whole document	1-21
A	VAJDOS F F ET AL: "Comprehensive Functional Maps of the Antigen-binding Site of an Anti-ErbB2 Antibody Obtained with Shotgun Scanning Mutagenesis" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB LNKD- DOI:10.1016/S0022-2836(02)00264-4, vol. 320, no. 2, 5 July 2002 (2002-07-05), pages 415-428, XP004449739 ISSN: 0022-2836 the whole document	1-21

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/052007

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WU HERREN ET AL: "Humanization of a murine monoclonal antibody by simultaneous optimization of framework and CDR residues" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 294, no. 1, 19 November 1999 (1999-11-19), pages 151-162, XP002582261 ISSN: 0022-2836 the whole document	1-21

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2010/052007

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

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

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

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

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

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

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

see additional sheet

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

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

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

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

1-27(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-27(partially)

   An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-10 (SEQ ID NO: 1) and related subject-matter.

   ---

2. claims: 1-27(partially)

   An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-18 (SEQ ID NO: 2) and related subject-matter.

   ---

3. claims: 1-27(partially)

   An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-19 (SEQ ID NO: 3) and related subject-matter.

   ---

4. claims: 1-27(partially)

   An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-28 (SEQ ID NO: 4) and related subject-matter.

   ---

5. claims: 1-27(partially)

   An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-36 (SEQ ID NO: 5) and related subject-matter.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/052007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008096153 A2	14-08-2008	AR 065260 A1	27-05-2009
		AU 2008212682 A1	14-08-2008
		CA 2677069 A1	14-08-2008
		CL 4232008 A1	24-10-2008
		EA 200900955 A1	30-04-2010
		EP 2139918 A2	06-01-2010
		JP 2010518062 T	27-05-2010
		KR 20090114445 A	03-11-2009
		US 2009259026 A1	15-10-2009

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/EP2010/052007	17.02.2010	19.02.2009

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/18 C07K16/28 C07K14/56 C07K14/575

Applicant
GLAXO GROUP LIMITED

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.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Bayer, Annette Telephone No. +49 89 2399-7103

Form PCT/ISA/237 (Cover Sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2010/052007

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 43bis.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 filed or furnished:

   a. (means)

      ☒ on paper

      ☒ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☒ subsequently to this Authority for the purposes of search

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 in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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

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

☐ the entire international application

☒ claims Nos. 1-27(partially)

because:

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

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

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

☒ no international search report has been established for the whole application or for said claims Nos. 1-27(partially)

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

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

☐ See Supplemental Box for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2010/052007

Box No. IV Lack of unity of invention

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

   ☐ paid additional fees

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

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

   ☒ not paid additional fees

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

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

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

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

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-27(partially)

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	1-27(partially)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-27(partially)
Industrial applicability (IA)	Yes:	Claims	1-27(partially)
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2010/052007

Re Item IV

This Authority considers that the application does not meet the requirements of unity of invention and that there are 5 inventions covered by the claims indicated as follows:

Invention 1: claims 1-27(partially)

An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-10 (SEQ ID NO: 1) and related subject-matter.

Invention 2: claims 1-27(partially)

An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-18 (SEQ ID NO: 2) and related subject-matter.

Invention 3: claims 1-27(partially)

An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-19 (SEQ ID NO: 3) and related subject-matter.

Invention 4: claims 1-27(partially)

An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-28 (SEQ ID NO: 4) and related subject-matter.

Invention 5: claims 1-27(partially)

An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-36 (SEQ ID NO: 5) and related subject-matter.

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:

The present application relates to anti-serum albumin single domain antibodies. Accordingly, the problem underlying the present application can be seen as the provision of anti-serum albumin single domain antibodies, the solution being binding members characterized by functional features or sequences.

The technical relationship and thus common concept within the meaning of Rule 13.2 PCT linking the different, alternative binding members is considered to be based on that they a) are anti-serum albumin single domain antibodies and b) that they are derived from the anti-serum albumin single domain antibody designated DOM7h-14.

However, the anti-serum albumin single domain antibody DOM7h-14 is known in the art from WO2008096158 (D1).

Such knowledge destroys the linking units and since no other technical feature can be distinguished which in the light of the prior art (including common general knowledge in the field) could be regarded as special common technical feature that defines a contribution over the prior art, the ISA is of the opinion that there is no single inventive concept (Rule 13.1 PCT) underlying the different inventions in the sense of Rule 13.2 PCT.

Consequently, there is lack of unity and the different inventions not belonging to a common inventive concept are formulated as different inventions pursuant to Article 17(3)(e) PCT. It should be noted that, for economical reasons, the inventions have been grouped with regard to the DOM7h-14 variants disclosed in the present application.

Since the Applicant did not pay additional search fees for the other inventions, an opinion will only be formulated for the subject-matter of the invention searched, i.e. invention 1 as formulated above.

Re Item V

Cited documents

Reference is made to the following documents:

D1 WO 2008/096158 A2 (DOMANTIS LTD [GB]; TOMLINSON IAN [GB]; JESPERS LAURENT [GB]; CLUBE JAS) 14 August 2008 (2008-08-14) cited in the application

D2 BARBAS C F ET AL: "Selection of human anti-hapten antibodies from semisynthetic libraries" GENE, ELSEVIER, AMSTERDAM, NL LNKD-DOI:10.1016/0378-1119(93)90251-W, vol. 137, no. 1, 27 December 1993 (1993-12-27) , pages 57-62, XP023539595 ISSN: 0378-1119 [retrieved on 1993-12-27]

D3 RUDIKOFF S ET AL: "Single amino acid substitution altering antigen-binding specificity" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES (PNAS), NATIONAL ACADEMY OF SCIENCE, US LNKD- DOI:10.1073/PNAS.79.6.1979, vol. 79, 1 March 1982 (1982-03-01) , pages 1979-1983, XP007901436 ISSN: 0027-8424

D4 MACCALLUM R M ET AL: "Antibody-antigen interactions: Contact analysis and binding site topography" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB LNKD- DOI:10.1006/JMBI.1996.0548, vol. 262, no. 5, 1 January 1996 (1996-01-01) , pages 732-745, XP002242391 ISSN: 0022-2836

D5 VAJDOS F F ET AL: "Comprehensive Functional Maps of the Antigen-binding Site of an Anti-ErbB2 Antibody Obtained with Shotgun Scanning Mutagenesis" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB LNKD- DOI:10.1016/S0022-2836(02)00264-4, vol. 320, no. 2, 5 July 2002 (2002-07-05) , pages 415-428, XP004449739 ISSN: 0022-2836

D6 WU HERREN ET AL: "Humanization of a murine monoclonal antibody by simultaneous optimization of framework and CDR residues" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 294, no. 1, 19 November 1999 (1999-11-19) , pages 151-162, XP002582261 ISSN: 0022-2836

As far as not otherwise indicated, reference is made to the passages cited in the International search report.

Inventive Step

1. It is well established in the art that the formation of an intact antigen-binding site depends on the complete variable regions of a given antibody, especially on its CDRs. It is expected that all of CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having functional antigen-binding sites. Even minor changes in the amino acid sequences of the variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by D3. D3 teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. D4 analyzes many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). D5 additionally states that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework

residues also contact antigen (page 416, left col.). D6 states that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.
Thus, the prior art teaches that the functional characteristics of an antibody, i.e. its antigen binding specificity, affinity and properties, are critically dependent on its complete variable regions. Accordingly, it is unlikely that all the antibodies encompassed by the present claims have the required function and thus solve the problem of the present invention (Article 33(3) PCT). For that reason, present claims 1-26 cannot be considered inventive.

2. Taking D1 as closest prior art which disclose anti-serum albumin immunoglobulin single variable domains (including the dAb designated DOM7h-14 from which DOM7h-14-10 derives) having affinities (KD) in the range of 300 nM up to 5 pM, nucleic acids encoding said dAbs, variants thereof, dual specific ligands comprising said dAbs and use thereof for treatment purposes, the problem underlying the present application could be considered in the provision of an alternative anti-serum albumin dAb, the solution being dAb designated DOM7h-14-10 characterized by its sequence (SEQ ID NO: 1). However, DOM7h-14-10 does not have any unexpected or improved properties compared to the prior art dAbs on which an inventive step could possibly be acknowledged. Thus, even if the claims would be restricted to the specific sequences of DOM7h-14-10 (DOM7h-14-10), no inventive step seems to be present for claims 1-27. In this regard it should be noted that the "surprising" finding of "beneficial mutations that can be targeted to the CDR3 region 92-96" as outlined in the present application on page 2, lines 16-18, is not at all surprising to the skilled person in view of the prior art. D2, for examples, teaches a) that diversity of the CDR3 of the light chain is limited to positions 92-96 as the remaining four positions are highly conserved in nature and b) that naturally occurring murine and human LCDR3 regions show strong conservation of Pro at Kabat position 95.

Further remark

Claim 27 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can depend upon the formulation of the claim. 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.

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

(19) World Intellectual Property Organization
International Bureau

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26 August 2010 (26.08.2010)

PCT

(10) International Publication Number
WO 2010/094722 A3

(51) International Patent Classification:
C07K 16/18 (2006.01) *C07K 14/56* (2006.01)
C07K 16/28 (2006.01) *C07K 14/575* (2006.01)

(21) International Application Number:
PCT/EP2010/052007

(22) International Filing Date:
17 February 2010 (17.02.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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61/163,990 27 March 2009 (27.03.2009) US

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DE ANGELIS, Elena** [GB/GB]; Domantis Limited, 315 Cambridge Science Park, Cambridge, Cambridgeshire CB4 0WG (GB). **ENEVER, Carolyn** [GB/GB]; Domantis Limited, 315 Cambridge Science Park, Cambridge, Cambridgeshire CB4 0WG (GB). **LIU, Haiqun** [CN/GB]; Domantis Limited, 315 Cambridge Science Park, Cambridge, Cambridgeshire CB4 0WG (GB). **SCHON, Oliver** [DE/GB]; Domantis Limited, 315 Cambridge Science Park, Cambridge, Cambridgeshire CB4 0WG (GB).

(74) Agents: **CLUBE, Jasper Rupert** et al.; GlaxoSmithKline, Global Patents CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(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, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

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

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

(88) Date of publication of the international search report:
13 January 2011

WO 2010/094722 A3

(54) Title: IMPROVED ANTI-SERUM ALBUMIN BINDING VARIANTS

(57) Abstract: The invention relates to improved variants of the anti-serum albumin immunoglobulin single variable domain DOM7h-14, as well as ligands and drug conjugates comprising such variants, compositions, nucleic acids, vectors and hosts.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/052007

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/18 C07K16/28 C07K14/56 C07K14/575

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

B. FIELDS SEARCHED

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

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 practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/096158 A2 (DOMANTIS LTD [GB]; TOMLINSON IAN [GB]; JESPERS LAURENT [GB]; CLUBE JAS) 14 August 2008 (2008-08-14) cited in the application page 32, line 15 - line 24 page 33, line 7 - line 18 page 36, line 2 - line 11 page 44, line 25 - page 45, line 2; figure 24 page 84, line 11 - line 20 page 112, line 17 - page 123, line 17 claims 1-79; examples 13-17,24,26 ----- -/--	1-27

[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 document 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
8 July 2010	16/11/2010

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	Bayer, Annette

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/052007

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BARBAS C F ET AL: "Selection of human anti-hapten antibodies from semisynthetic libraries" GENE, ELSEVIER, AMSTERDAM, NL LNKD- DOI:10.1016/0378-1119(93)90251-W, vol. 137, no. 1, 27 December 1993 (1993-12-27), pages 57-62, XP023539595 ISSN: 0378-1119 [retrieved on 1993-12-27] page 58, left-hand column, paragraph 2 - right-hand column, paragraph 1 page 60, right-hand column, paragraph 1	1-27
A	RUDIKOFF S ET AL: "Single amino acid substitution altering antigen-binding specificity" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES (PNAS), NATIONAL ACADEMY OF SCIENCE, US LNKD- DOI:10.1073/PNAS.79.6.1979, vol. 79, 1 March 1982 (1982-03-01), pages 1979-1983, XP007901436 ISSN: 0027-8424 the whole document	1-21
A	MACCALLUM R M ET AL: "Antibody-antigen interactions: Contact analysis and binding site topography" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB LNKD- DOI:10.1006/JMBI.1996.0548, vol. 262, no. 5, 1 January 1996 (1996-01-01), pages 732-745, XP002242391 ISSN: 0022-2836 the whole document	1-21
A	VAJDOS F F ET AL: "Comprehensive Functional Maps of the Antigen-binding Site of an Anti-ErbB2 Antibody Obtained with Shotgun Scanning Mutagenesis" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB LNKD- DOI:10.1016/S0022-2836(02)00264-4, vol. 320, no. 2, 5 July 2002 (2002-07-05), pages 415-428, XP004449739 ISSN: 0022-2836 the whole document	1-21

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/052007

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WU HERREN ET AL: "Humanization of a murine monoclonal antibody by simultaneous optimization of framework and CDR residues" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 294, no. 1, 19 November 1999 (1999-11-19), pages 151-162, XP002582261 ISSN: 0022-2836 the whole document	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2010/052007

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

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

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

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

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

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

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

see additional sheet

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

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

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

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

1-27(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-27(partially)

An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-10 (SEQ ID NO: 1) and related subject-matter.

---

2. claims: 1-27(partially)

An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-18 (SEQ ID NO: 2) and related subject-matter.

---

3. claims: 1-27(partially)

An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-19 (SEQ ID NO: 3) and related subject-matter.

---

4. claims: 1-27(partially)

An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-28 (SEQ ID NO: 4) and related subject-matter.

---

5. claims: 1-27(partially)

An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-14, wherein the variant comprises the amino acid sequence of DOM7h-14-36 (SEQ ID NO: 5) and related subject-matter.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/052007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008096158 A2	14-08-2008	AR 065260 A1	27-05-2009
		AU 2008212682 A1	14-08-2008
		CA 2677069 A1	14-08-2008
		CL 4232008 A1	24-10-2008
		EA 200900955 A1	30-04-2010
		EP 2139918 A2	06-01-2010
		JP 2010518062 T	27-05-2010
		KR 20090114445 A	03-11-2009
		US 2009259026 A1	15-10-2009

Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO

SUPEPINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-111117- -00000-0000

Fecha: 2011-08-30 17:03:37 Dep: 2020 DIP NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 254

PATENTE DE INVENCIÓN ☐ MODELO DE UTIL

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☒ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☒ Indicación que se solicita una PCT
- ☒ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☒ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Prosperidad para todos

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
GLAXO GROUP LIMITED

REFERENCIA	Radicación No.	11 111117
	Solicitud internacional	PCT/EP2010/052007
	Fecha inicio fase nacional	19/09/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	

15125

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (C)

23 SET. 2011

El anterior requerimiento fue notificado por fijación en lista de fecha_____.
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