SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-011416- -00000-0000
Fecha: 2011-02-01 18:10:39 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEVII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1085

BT

PCT

Industria y Comercio

SUPERINTENDENCIA

11-11416

INVENTARIO

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPOSICIONES Y MÉTODOS PARA ANTICUERPOS QUE SE DIRIGEN A LA PROTEÍNA DE COMPLEMENTO C5

SOLICITANTE: NOVARTIS AG

DIRECCIÓN: Lichtstrasse 35, CH- 4056 Basel, Suiza

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 02 de Febrero de 2011

P2011/0000020 05-03-2011

OLARTEMOURE

OLARTE MOURE & AS

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-011416- -00000-0000
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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2011/000020**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**	**Nombre:** NOVARTIS AG **Dirección:** Lichtstrasse 35, CH-4056 Basel **Nacionalidad o Domicilio:** Suiza **Lugar de Constitución:** Suiza **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** **C.C.** [ ] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** _____
REPRESENTANTE O APODERADO	**Nombre:** CARLOS P. OLARTE **Dirección:** Diagonal 34 No 5-28 Bogotá D.C. **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olarteraisbeck.com	**IDENTIFICACIÓN** **C.C.** [X] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **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/EP2009/060052 Fecha Agosto 03, 2009

Publicación Internacional No. WO 2010/015606 Fecha Febrero 11, 2010

(6) **Título (54)** COMPOSICIONES Y MÉTODOS PARA ANTICUERPOS QUE SE DIRIGEN A LA PROTEÍNA DE COMPLEMENTO C5

Clasificación Internacional (51) A61K 39/395, C07K 16/18

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Agosto 05, 2008	61/086.355

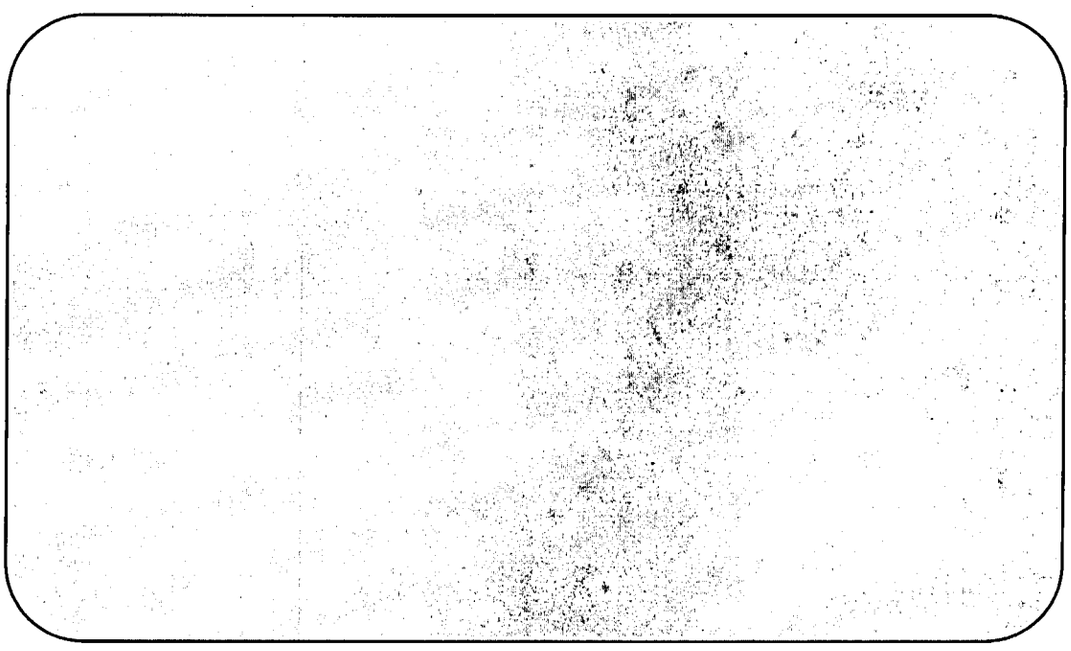
(9) **Comprobante de pago No.** 11- **Fecha** Febrero de 2011

2

(10) **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. Adjunto copia simple. Ver Exp. Nº 08.102.832
	Documento de cesión del inventor al solicitante o a su causante.
	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 E. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

3

LISTA DE INVENTORES

PCT/EP2009/060052

Beate DIEFENBACH-STREIBER,
Reiherweg 6,
86949 Windach
Alemania
Nacionalidad: Alemana

Adina EBERTH,
Friedrich-List Strasse 114,
81377 Múnich
Alemania
Nacionalidad: Alemana

Braydon Charles GUILD,
109 Riverdale Road,
Concord, Massachusetts 01742
Estados Unidos
Nacionalidad: Estadounidense

Yong-In KIM,
Novartis Institutes for BioMedical Research,
Inc., 500 Technology Square,
Cambridge, Massachusetts 02139
Estados Unidos
Nacionalidad: Korea

Michael ROGUSKA,
Novartis Institutes for BioMedical Research,
Inc., 500 Technology Square,
Cambridge, Massachusetts 02139
Estados Unidos
Nacionalidad: Estadounidense

Igor SPLAWSKI,
Novartis Institutes for BioMedical Research,
Inc., 500 Technology Square,
Cambridge, Massachusetts 02139
Estados Unidos
Nacionalidad: Polaca

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 009211

Bogotá D.C., Febrero 01 de 2011 - 16:51:59

RECIBIDO DE : OLARTERAISBECK NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION I	BANCO DE BOGOTA	062754387	353914470	01/02/2011	4.568.000.00

*** Conceptos Pagados ***

CANT.	PENTISTICO	CONCEPTO	Vr.UNITARIO	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. 11-011416- -00000-0000

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Act. 411 PRESENTACION Folios: 1085

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TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

Nota del traductor:

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambos personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Miniusticia

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

Teléfono: (57-1) 2182309, (57-1) 6232925.

E-mail: treseser1@yahoo.com. No. 8346

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahin
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoza
Simón Salinas

Of Counsel
Guillermo Chahin
Graciela Melo

Power of Attorney

Poder

The undersigned,

El suscrito,

NOVARTIS AG

domiciled in

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** 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, recourses, 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.

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** 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, recursos, 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:

Arthur Canonica

Pascal Traub

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

Attestation

1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.

2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.

3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)

M. Staehelin

Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven), 2009 (two thousand and nine).

Leg.Prot.Nr. 975 /2006

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)
   This official document
2. is signed by Erin M. Stuebbeler
3. in his/her function as Lic. iur.
4. and certified by the seal of the Obergericht

Certified 22. Aug. 2006

5. in Basel (Bâle) 6. on
7. by the State Chancery of the Canton of Basel-Stadt
8. no. C 0491 15'384
9. Seal/stamp: 10. Signature:

Heidi Fischer

STATE CHANCERY * BASLE-CITY *

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 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to the international application PCT/EP2009/060052,

Novartis AG, is entitled to apply for and be granted a patent by virtue of the following:

an assignment from:

DIEFENBACH-STREIBER, Beate, Reiherweg 6, 86949 Windach, DE, dated 19.08.2009

EBERTH, Adina, Friedrich-List Strasse 114, 81377 München, DE, dated 03.09.2009

GUILD, Braydon Charles, 109 Riverdale Road, Concord, MA 01742, US, dated 09.09.2009

KIM, Yong-In, Novartis Institutes for BioMedical Research, Inc., 500 Technology Square, Cambridge, MA 02139, US, dated 09.09.2009

ROGUSKA, Michael, Novartis Institutes for BioMedical Research, Inc., 500 Technology Square, Cambridge, MA 02139, US, dated 26.08.2009

SPLAWSKI, Igor, Novartis Institutes for BioMedical Research, Inc., 500 Technology Square, Cambridge, MA 02139, US, dated 26.08.2009

to Novartis AG.

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 February 2010 (11.02.2010)

PCT

(10) International Publication Number
WO 2010/015608 A1

(51) International Patent Classification:
A61K 39/395 (2006.01) *C07K 16/18* (2006.01)

(21) International Application Number:
PCT/EP2009/060052

(22) International Filing Date:
3 August 2009 (03.08.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/086,355 5 August 2008 (05.08.2008) US

(71) Applicant *(for all designated States except US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DIEFENBACH-STREIBER, Beate** [DE/DE]; Reiherweg 6, 86949 Windach (DE). **EBERTH, Adina** [DE/DE]; Friedrich-List Strasse 114, 81377 München (DE). **GUILD, Braydon Charles** [US/US]; 109 Riverdale Road, Concord, Massachusetts 01742 (US). **KIM, Yong-In** [KR/US]; Novartis Institutes for BioMedical Research, Inc., 500 Technology Square, Cambridge, Massachusetts 02139 (US). **ROGUSKA, Michael** [US/US]; Novartis Institutes for BioMedical Research, Inc., 500 Technology Square, Cambridge, Massachusetts 02139 (US). **SPLAWSKI, Igor** [PL/US]; Novartis Institutes for BioMedical Research, Inc., 500 Technology Square, Cambridge, Massachusetts 02139 (US).

(74) Agent: **VOEGELI-LANGE, Regina**; Novartis Pharma Ag, Patent Department, CH-4002 Basel (CH).

(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, 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))*

Published:

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

— *with sequence listing part of description (Rule 5.2(a))*

(54) Title: COMPOSITIONS AND METHODS FOR ANTIBODIES TARGETING COMPLEMENT PROTEIN C5

(57) Abstract: The present invention relates to antibodies targeting complement protein C5 and compositions and methods of use thereof.

WO 2010/015608 A1

COMPOSITIONS AND METHODS FOR ANTIBODIES TARGETING COMPLEMENT PROTEIN C5

1. INTRODUCTION

The present invention relates to antibodies targeting complement protein C5 and compositions and methods of use thereof.

2. BACKGROUND OF THE INVENTION

The normal role of complement, which is part of the innate immune system, is in host defense. Complement defends against bacterial infection, links adaptive and innate immunity, and disposes immune complexes and the products of inflammatory injury.

The defensive functions are accomplished by biologically active products generated in the course of complement activation, which opsonise infectious agents, promote inflammation or lyse susceptible targets (Marzari *et al.*, Eur J Immunol 32:2775-2782 (2002)). The complement system consists of about 25-30 plasma proteins which play a role in the immune system. The complement cascade is activated by at least three major pathways. The classical pathway is typically activated by immune-complexes, the alternative pathway can be activated by unprotected cell surfaces, and the mannose binding lectin (MBL) pathway is initiated by binding of MBL to cell surface carbohydrates (Trendelenburg, Swiss Med Wkly 137:413-417 (2007)).

All three pathways lead to the cleavage of C5 by the C5 convertase. The result of this cleavage is release of C5a fragment, a potent inflammatory molecule, and C5b which initiates the membrane attack complex (MAC). The complement products, once released, do not differentiate between foreign and self targets and, if not tightly regulated, often cause extensive damage of bystander cells and tissues in clinical conditions associated with unrestricted complement activation (Marzari *et al.*, 2002).

C5 is expressed intracellularly as a single pro-C5 peptide of 1676 amino acids that consist of an 18 residue signal sequence and an Arg-rich linker sequence (RPRR) situated between the mature N-terminal β chain and the C-terminal α chain. The mature C5 has a molecular weight of about 190 kDa, and consists of two polypeptide chains (α, 115 kDa and β, 75 kDa) which are connected by disulfide bonds. The C5 convertase cleaves C5 between residues 74 and 75 of the alpha chain to release the 74 amino acid C5a peptide and the C5b fragment which is subsequently incorporated into the membrane-attack complex (MAC).

Macular degeneration is a medical condition predominantly found in the elderly in which the center of the inner lining of the eye, known as the macula area of the retina, suffers thinning, atrophy, and in some cases, bleeding. This can result in loss of central vision, which entails inability to see fine details, to read, or to recognize faces. Pathogenesis of new

choroidal vessel formation is poorly understood, but factors such as inflammation, ischemia, and local production of angiogenic factors are thought to be important.

Despite current treatment options for treating diseases and disorders associated with the classical or alternative component pathways, particularly AMD, there remains a need for finding specific targets that lead to treatments which are effective and well-tolerated.

3. SUMMARY OF THE INVENTION

The present invention provides isolated complement C5-binding molecules (*e.g.*, C5-binding antibodies or antigen binding fragments thereof), pharmaceutical compositions comprising such molecules, methods of making such molecules and compositions, and methods of use thereof.

In some embodiments, the present invention provides isolated antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibody has an affinity constant (K_A) of at least 1×10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, or 10^{11} M^{-1}.

In some embodiments, the present invention provides isolated antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, and inhibit the alternative complete pathway as measured by in vitro hemolytic assay with an IC_{50} range from about 20pM to about 200 pM.

In some embodiments, the present invention provides isolated antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, and cross compete with an antibody described in Table 1 below. In some embodiments, the present invention provides isolated antibodies or antigen binding fragments thereof that bind to the same epitope of C5 protein as an antibody described in Table 1 below.

In some embodiments, the antibodies of the invention are isolated monoclonal antibodies that specifically bind to a C5 protein. In some embodiments, the antibodies of the invention are isolated human or humanized monoclonal antibodies that specifically bind to a C5 protein. In some embodiments, the antibodies of the invention are isolated chimeric antibodies that specifically bind to a C5 protein. In some embodiments, the antibodies of the invention comprise a human heavy chain constant region and a human light chain constant region.

In some embodiments, the present invention provides isolated antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies are single chain antibodies. In some embodiments, the antibodies of the invention are Fab fragments. In some embodiments, the antibodies of the invention are scFv.

In some embodiments, the present invention provides isolated antibodies or antigen-binding fragments thereof that specifically bind to both human C5 and cynomolgus C5. In some embodiments, the antibodies of the invention are an IgG isotype.

In some embodiments, the present invention provides isolated antibodies or antigen binding fragments thereof comprising a framework in which amino acids have been substituted into the antibody framework from the respective human VH or VL germline sequences.

In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise at least one complementarity determining (CDR) sequence having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 1, 2, 3, 4, 5, 6, 17, 18, 19, 20, 21, 22, 33, 34, 35, 36, 37, 38, 49, 50, 61, 62, 63, 64, 65, 66, 77, 78, 89, 95, 101, 107, 113, 119, 120, 131, 132, 133, 134, 135, 136, 145, 146, 147, 148, 149, 150, 159, 160, 161, 162, 163, 164, 173, 174, 175, 176, 177, 178, 195, 196, 197, 198, 199, 200, 209, 226, 235, 236, 237, 238, 239, or 240.

In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise at least one heavy chain CDR sequence that is identical to SEQ ID NO: 1, 2, 3, 17, 18, 19, 33, 34, 35, 49, 61, 62, 63, 77, 77, 95, 107, 113, 119, 132, 131, 133, 145, 146, 147, 159, 160, 161, 173, 174, 175, 195, 196, 197, 226, 235, 236, or 237.

In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise at least one light chain CDR sequence that is identical to SEQ ID NO: 4, 5, 6, 20, 21, 22, 36, 37, 38, 50, 64, 65, 66, 78, 89, 101, 120, 134, 135, 136, 148, 149, 150, 162, 163, 164, 176, 177, 178, 198, 199, 200, 209, 236, 239, or 240.

In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise a heavy chain CDR 1 selected from the group consisting SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235; a heavy chain CDR2 selected from the group consisting SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236; and a heavy chain CDR3 selected from the group consisting SEQ ID NOs: 3, 19, 35, 65, 133, 147, 161, 175, 197, and 237. In some embodiments, such antibodies or antigen binding fragments thereof further comprise a light chain CDR1 selected from the group consisting SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238; a light chain CDR2 selected from the group consisting SEQ ID NOs: 5, 21, 37, 65, 135, 149,

163, 177, 199, and 239; and a light chain CDR3 selected from the group consisting SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240.

In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise a light chain CDR 1 selected from the group consisting SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238; a light chain CDR2 selected from the group consisting SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239; and a light chain CDR3 selected from the group consisting SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240.

In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise a heavy chain variable region having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281. In some embodiments, such antibodies or antigen binding fragments thereof further comprise a light chain variable region having at leat 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, and 289.

In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise a light chain variable region having at leat 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, and 289.

In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise a heavy chain having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, or 282. In some embodiments, such antibodies further comprise a light chain having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, or 290.

In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise a light chain having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, or 290.

The present invention also comprises pharmaceutical compositions comprising one or more C5-binding molecules of the invention (*e.g.*, C5 binding antibodies or antigen binding fragments thereof) and a pharmaceutically acceptable carrier.

In some embodiments, the present invention provides nucleic acids comprising a nucleotide sequence encoding a polypeptide comprising a heavy chain variable region having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 215, 227, 241, 253, 257, 273, 277, or 281.

In some embodiments, the present invention provides nucleic acids comprising a nucleotide sequence encoding a polypeptide comprising a light chain variable region having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, and 289.

The present invention also provides vectors and host cells comprising such nucleic acids. In one embodiment, the present invention provides isolated host cells comprising (1) a recombinant DNA segment encoding a heavy chain of the antibodies of the invention, and (2) a second recombinant DNA segment encoding a light chain of the antibodies of the invention; wherein said DNA segments are respectively operably linked to a first and a second promoter, and are capable of being expressed in said host cell. In another embodiment, the present invention provides isolated host cells comprising a recombinant DNA segment encoding a heavy chain, and a light chain of the antibodies of the invention, respectively, wherein said DNA segment is operably linked to a promoter, and is capable of being expressed in said host cells. In some embodiments, the host cells are non-human mammalian cell line. In some embodiments, the antibodies or antigen binding fragments thereof are a human monoclonal antibody, or an antigen binding fragment thereof.

The present invention further provides treatment of diagnostic methods using the C5 binding molecules (*e.g.*, C5 binding antibodies or antigen binding fragments thereof) of the invention. In one embodiment, the present invention provides methods of treating age related macular degeneration comprising administering to a subject in need thereof an effective amount of a composition comprising an antibody or an antigen binding fragment thereof of the invention.

In another embodiment, the present invention provides methods of treating a disease comprising administering to a subject in need thereof an effective amount of a composition comprising an antibody or an antigen binding fragment thereof of the invention, wherein said disease is asthma, arthritis, autoimmune heart disease, multiple sclerosis, inflammatory bowel disease, ischemia-reperfusion injuries, Barraquer-Simons Syndrome, hemodialysis,

systemic lupus, lupus erythematosus, psoriasis, multiple sclerosis, transplantation, Alzheimer's disease, glomerulonephritis, or MPGN II.

The present invention also provides methods of treating paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to a subject in need thereof an effective amount of a composition comprising an antibody or antigen binding fragment thereof of the invention.

The present invention further provides methods of ameliorating a symptom associated with extracorporeal circulation comprising administering to a subject in need thereof an effective amount of a composition comprising an antibody or antigen binding fragment thereof of the invention.

3.1. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which this invention pertains.

The term "antibody" as used herein includes whole antibodies and any antigen binding fragment (*i. e.*, "antigen-binding portion") or single chains thereof. A naturally occurring "antibody" is a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (Clq) of the classical complement system.

The term "antigen binding portion" of an antibody, as used herein, refers to one or more fragments of an intact antibody that retain the ability to specifically bind to a given antigen (*e.g.*, C5). Antigen binding functions of an antibody can be performed by fragments of an intact antibody. Examples of binding fragments encompassed within the term "antigen binding portion" of an antibody include a Fab fragment, a monovalent fragment consisting of

the VL, VH, CL and CH1 domains; a $F(ab)_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; an Fd fragment consisting of the VH and CH1 domains; an Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a single domain antibody (dAb) fragment (Ward *et al.*, 1989 Nature 341:544-546), which consists of a VH domain; and an isolated complementarity determining region (CDR).

Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by an artificial peptide linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see, *e.g.*, Bird *et al.*, 1988 Science 242:423-426; and Huston *et al.*, 1988 Proc. Natl. Acad. Sci. 85:5879-5883). Such single chain antibodies include one or more "antigen binding portions" of an antibody. These antibody fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

Antigen binding portions can also be incorporated into single domain antibodies, maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, *e.g.*, Hollinger and Hudson, 2005, Nature Biotechnology, 23, 9, 1126-1136). Antigen binding portions of antibodies can be grafted into scaffolds based on polypeptides such as Fibronectin type III (Fn3) (see U.S. Pat. No. 6,703,199, which describes fibronectin polypeptide monobodies).

Antigen binding portions can be incorporated into single chain molecules comprising a pair of tandem Fv segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen binding regions (Zapata *et al.*, 1995 Protein Eng. 8(10):1057-1062; and U.S. Pat. No. 5,641,870).

As used herein, the term "Affinity" refers to the strength of interaction between antibody and antigen at single antigenic sites. Within each antigenic site, the variable region of the antibody "arm" interacts through weak non-covalent forces with antigen at numerous sites; the more interactions, the stronger the affinity.

As used herein, the term "Avidity" refers to an informative measure of the overall stability or strength of the antibody-antigen complex. It is controlled by three major factors: antibody epitope affinity; the valency of both the antigen and antibody; and the structural arrangement of the interacting parts. Ultimately these factors define the specificity of the antibody, that is, the likelihood that the particular antibody is binding to a precise antigen epitope.

The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, *e.g.*, hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. Amino acid analogs refer to compounds that have the same basic chemical structure as a naturally occurring amino acid, *i.e.*, an alpha carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

The term "binding specificity" as used herein refers to the ability of an individual antibody combining site to react with only one antigenic determinant. The combining site of the antibody is located in the Fab portion of the molecule and is constructed from the hypervariable regions of the heavy and light chains. Binding affinity of an antibody is the strength of the reaction between a single antigenic determinant and a single combining site on the antibody. It is the sum of the attractive and repulsive forces operating between the antigenic determinant and the combining site of the antibody.

Specific binding between two entities means a binding with an equilibrium constant (K_A) of at least 1×10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, or 10^{11} M^{-1}. The phrase "specifically (or selectively) binds" to an antibody (*e.g.*, a C5-binding antibody) refers to a binding reaction that is determinative of the presence of a cognate antigen (*e.g.*, a human C5 or cynomolgus C5) in a heterogeneous population of proteins and other biologics. In addition to the equilibrium constant (KA) noted above, an C5-binding antibody of the invention typically also has a dissociation rate constant (Kd) of about 1×10^{-2} s^{-1}, 1×10^{-3} s^{-1}, 1×10^{-4} s^{-1}, 1×10^{-4} s^{-1}, or lower, and binds to C5 with an affinity that is at least two-fold greater than its affinity for binding to a non-specific antigen (*e.g.*, C3, C4, BSA). The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen".

The term "chimeric antibody" is an antibody molecule in which (a) the constant region, or a portion thereof, is altered, replaced or exchanged so that the antigen binding site (variable region) is linked to a constant region of a different or altered class, effector function and/or species, or an entirely different molecule which confers new properties to the chimeric antibody, *e.g.*, an enzyme, toxin, hormone, growth factor, drug, etc.; or (b) the variable region, or a portion thereof, is altered, replaced or exchanged with a variable region having a

different or altered antigen specificity. For example, a mouse antibody can be modified by replacing its constant region with the constant region from a human immunoglobulin. Due to the replacement with a human constant region, the chimric antibody can retain its specificity in recognizing the antigen while having reduced antigenicity in human as compared to the original mouse antibody.

The term "complement C5 protein" or "C5" are used interchangeably, and refers to the C5 protein in different species. For example, human C5 has the sequence as set in SEQ ID NO: 296, cynomolgus C5 has the sequence as set in SEQ ID NO: 297 (*Macaca fascicularis*) (see Table 1). Human C5 can be obtained from Quidel (Cat. Number A403). Cynomolgus C5 can be produced as illustrated in the Example section below.

The term "conservatively modified variant" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid that encodes a polypeptide is implicit in each described sequence.

For polypeptide sequences, "conservatively modified variants" include individual substitutions, deletions or additions to a polypeptide sequence which result in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention. The following eight groups contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and 8) Cysteine (C), Methionine (M) (see, *e.g.*, Creighton, Proteins (1984)). In some embodiments, the term "conservative sequence

modifications" are used to refer to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence.

The terms "cross-block", "cross-blocked" and "cross-blocking" are used interchangeably herein to mean the ability of an antibody or other binding agent to interfere with the binding of other antibodies or binding agents to C5 in a standard competitive binding assay.

The ability or extent to which an antibody or other binding agent is able to interfere with the binding of another antibody or binding molecule to C5, and therefore whether it can be said to cross-block according to the invention, can be determined using standard competition binding assays. One suitable assay involves the use of the Biacore technology (*e.g.* by using the BIAcore 3000 instrument (Biacore, Uppsala, Sweden)), which can measure the extent of interactions using surface plasmon resonance technology. Another assay for measuring cross-blocking uses an ELISA-based approach.

The term "epitope" means a protein determinant capable of specific binding to an antibody. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and nonconformational epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents.

As used herein, the term "high affinity" for an IgG antibody refers to an antibody having a KD of 10^{-8} M or less, 10^{-9} M or less, or 10^{-10} M, or 10^{-11} M or less for a target antigen. However, "high affinity" binding can vary for other antibody isotypes. For example, "high affinity" binding for an IgM isotype refers to an antibody having a KD of 10^{-7} M or less, or 10^{-8} M or less.

The term "human antibody", as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from sequences of human origin. Furthermore, if the antibody contains a constant region, the constant region also is derived from such human sequences, *e.g.*, human germline sequences, or mutated versions of human germline sequences. The human antibodies of the invention may include amino acid residues not encoded by human sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*).

The term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human sequences. In one embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman

animal, *e.g.*, a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

A "humanized" antibody is an antibody that retains the reactivity of a non-human antibody while being less immunogenic in humans. This can be achieved, for instance, by retaining the non-human CDR regions and replacing the remaining parts of the antibody with their human counterparts (*i.e.*, the constant region as well as the framework portions of the variable region). See, *e.g.*, Morrison *et al.*, Proc. Natl. Acad. Sci. USA, 81:6851-6855, 1984; Morrison and Oi, Adv. Immunol., 44:65-92, 1988; Verhoeyen *et al.*, Science, 239:1534-1536, 1988; Padlan, Molec. Immun., 28:489-498, 1991; and Padlan, Molec. Immun., 31:169-217, 1994. Other examples of human engineering technology include, but is not limited to Xoma technology disclosed in US 5,766,886.

The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same. Two sequences are "substantially identical" if two sequences have a specified percentage of amino acid residues or nucleotides that are the same (*i.e.*, 60% identity, optionally 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identity over a specified region, or, when not specified, over the entire sequence), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Optionally, the identity exists over a region that is at least about 50 nucleotides (or 10 amino acids) in length, or more preferably over a region that is 100 to 500 or 1000 or more nucleotides (or 20, 50, 200 or more amino acids) in length.

For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith and Waterman (1970) Adv.

Appl. Math. 2:482c, by the homology alignment algorithm of Needleman and Wunsch, J. Mol. Biol. 48:443, 1970, by the search for similarity method of Pearson and Lipman, Proc. Nat'l. Acad. Sci. USA 85:2444, 1988, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (see, *e.g.*, Brent *et al.*, Current Protocols in Molecular Biology, John Wiley & Sons, Inc. (ringbou ed., 2003)).

Two examples of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.*, Nuc. Acids Res. 25:3389-3402, 1977; and Altschul *et al.*, J. Mol. Biol. 215:403-410, 1990, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, supra). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) or 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff, Proc. Natl. Acad. Sci. USA 89:10915, 1989) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, *e.g.*, Karlin and Altschul, Proc. Natl. Acad. Sci. USA 90:5873-5787, 1993). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is

considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

The percent identity between two amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller (Comput. Appl. Biosci., 4:11-17, 1988) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (J. Mol, Biol. 48:444-453, 1970) algorithm which has been incorporated into the GAP program in the GCG software package (available at www.gcg.com), using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

Other than percentage of sequence identity noted above, another indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the antibodies raised against the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions, as described below. Yet another indication that two nucleic acid sequences are substantially identical is that the same primers can be used to amplify the sequence.

The term "isolated antibody" refers to an antibody that is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that specifically binds C5 is substantially free of antibodies that specifically bind antigens other than C5). An isolated antibody that specifically binds C5 may, however, have cross-reactivity to other antigens. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

The term "isotype" refers to the antibody class (*e.g.*, IgM, IgE, IgG such as IgG1 or IgG4) that is provided by the heavy chain constant region genes. Isotype also includes modified versions of one of these classes, where modifications have been made to alter the Fc function, for example, to enhance or reduce effector functions or binding to Fc receptors.

The term "Kassoc" or "Ka", as used herein, is intended to refer to the association rate of a particular antibody-antigen interaction, whereas the term "Kdis" or "Kd," as used herein, is intended to refer to the dissociation rate of a particular antibody-antigen interaction. The term "K_D", as used herein, is intended to refer to the dissociation constant, which is obtained

from the ratio of Kd to Ka (*i.e.* Kd/Ka) and is expressed as a molar concentration (M). K_D values for antibodies can be determined using methods well established in the art. A method for determining the K_D of an antibody is by using surface plasmon resonance, or using a biosensor system such as a Biacore® system.

The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

The term "nucleic acid" is used herein interchangeably with the term "polynucleotide"and refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. The term encompasses nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, peptide-nucleic acids (PNAs).

Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (*e.g.*, degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, as detailed below, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer *et al.*, Nucleic Acid Res. 19:5081, 1991; Ohtsuka *et al.*, J. Biol. Chem. 260:2605-2608, 1985; and Rossolini *et al.*, Mol. Cell. Probes 8:91-98, 1994).

The term "operably linked" refers to a functional relationship between two or more polynucleotide (*e.g.*, DNA) segments. Typically, it refers to the functional relationship of a transcriptional regulatory sequence to a transcribed sequence. For example, a promoter or enhancer sequence is operably linked to a coding sequence if it stimulates or modulates the transcription of the coding sequence in an appropriate host cell or other expression system. Generally, promoter transcriptional regulatory sequences that are operably linked to a transcribed sequence are physically contiguous to the transcribed sequence, *i.e.*, they are cis-acting. However, some transcriptional regulatory sequences, such as enhancers, need not be physically contiguous or located in close proximity to the coding sequences whose transcription they enhance.

As used herein, the term, "optimized" means that a nucleotide sequence has been altered to encode an amino acid sequence using codons that are preferred in the production

cell or organism, generally a eukaryotic cell, for example, a cell of Pichia, a Chinese Hamster Ovary cell (CHO) or a human cell. The optimized nucleotide sequence is engineered to retain completely or as much as possible the amino acid sequence originally encoded by the starting nucleotide sequence, which is also known as the "parental" sequence. The optimized sequences herein have been engineered to have codons that are preferred in mammalian cells. However, optimized expression of these sequences in other eukaryotic cells or prokaryotic cells is also envisioned herein. The amino acid sequences encoded by optimized nucleotide sequences are also referred to as optimized.

The terms "polypeptide"and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. Unless otherwise indicated, a particular polypeptide sequence also implicitly encompasses conservatively modified variants thereof.

The term "recombinant human antibody", as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, antibodies isolated from a host cell transformed to express the human antibody, *e.g.*, from a transfectoma, antibodies isolated from a recombinant, combinatorial human antibody library, and antibodies prepared, expressed, created or isolated by any other means that involve splicing of all or a portion of a human immunoglobulin gene, sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

The term "recombinant host cell" (or simply "host cell") refers to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

The term "subject" includes human and non-human animals. Non-human animals include all vertebrates, *e.g.*, mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, and reptiles. Except when noted, the terms "patient" or "subject" are used herein interchangeably.

The term "treating" includes the administration of compositions or antibodies to prevent or delay the onset of the symptoms, complications, or biochemical indicia of a disease (*e.g.*, AMD), alleviating the symptoms or arresting or inhibiting further development of the disease, condition, or disorder. Treatment may be prophylactic (to prevent or delay the onset of the disease, or to prevent the manifestation of clinical or subclinical symptoms thereof) or therapeutic suppression or alleviation of symptoms after the manifestation of the disease.

The term "vector" is intended to refer to a polynucleotide molecule capable of transporting another polynucleotide to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

4. BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows variable-region alignments of selected antibodies with their most closely related human germline sequences.

FIG. 2 shows a hemolytic assay in which human C5 is titrated into human C5-depleted serum to determine C5 activity. FIG. 3 shows titration of cynomolgus serum into human C5-depleted serum to determine optimal cynomolgus C5 concentration for alternative pathway hemolytic assay.

FIG. 4 shows examples of classical pathway hemolytic assays with 20% human serum.

FIG. 5 shows example of alternative pathway hemolytic assays with 100pM purified human C5 added to human C5-depleted serum.

FIG. 6 shows examples of alternative patheway hemolytic assays with 0.025% cynomolgus serum added to human C5-depleted serum.

FIG. 7 shows examples of classical pathway hemolytic assays (20% human serum) with matured Fabs in comparison to their respective parentals.

FIG. 8 shows examples of classical pathway hemolytic assays (5% cynomolgus serum) with matrured Fabs.

FIG. 9 shows affinity matured Fab characterization in alternative pathway hemolytic assay using 100 pM human C5 added to 20% human C5-depleted serum.

FIG. 10 shows affinity matured Fab characteriztion in alternative pathway hemolytic assay using 20% human serum.

FIG. 11 shows affinity matured Fab characterization in alternative pathway hemolytic assay using 100 pM cynomolgus C5 added to 20% human C5-depleted serum.

FIG. 12 shows characterization of germlined IgGs in classical pathway hemolytic assay using 20% human serum.

FIG. 13 shows characterization of germlined IgGs in classical pathway hemolytic assay using 5% cynomolgus serum.

FIG. 14 shows characterization of germlined IgGs in alternative pathway hemolytic assay, 100 pM human C5.

FIG. 15 shows characterization of final germlined IgGs in alternative pathway hemolytic assay and C5a generation ELISA using 20% human serum.

FIG. 16 shows affinity matured Fab characterization in the C5a ELISA using supernatant from 20% human serum hemolytic assays.

FIG. 17 shows specificity solution ELISA on human C3, C4, C5 and cynomolgus C5 testing antibody 7091 and its derivatives.

FIG. 18 shows serum stability assays (binding to human C5 in the presence of 50% serum) with the Fabs.

FIG. 19 shows epitope binning of some affinity improved Fabs.

FIG. 20 shows an ELISA for antibody binding to mouse-human chimeric C5 or human C5 to determine alpha chain versus beta chain binders. C5 was presented by 5G1.1 to determine competition with 5G1.1.

FIG. 21 shows ELISA for testing alpha chain versus beta chain binders with 5G1.1 capture.

FIG. 22 shows results of hemolytic assay for testing alpha chain versus beta chain binders.

FIG. 23 show thermolysin proteolysis of parental Fabs at 37°C (0, 30, 60 and 90 minutes).

FIG. 24 show thermolysin proteolysis of parental Fabs at 55°C (0, 30, 60 and 90 minutes).

FIG. 25 shows thermolysin sensitivity of matured Fabs at 37°C.

FIG. 26 shows thermolysin sensitivity of matured Fabs at 55°C.

FIG. 27 shows examples of Fab inhibition of alternative pathway in MAC deposition assay.

5. DETAILED DESCRIPTION OF THE INVENTION

The present invention provides antibodies that specifically bind to complement C5 protein (*e.g.*, human C5, cynomologus C5), pharmaceutical compositions, production methods, and methods of use of such antibodies and compositions.

5.1. C5 Antibodies

The present invention provides antibodies that specifically bind to C5 (*e.g.*, human C5, cynomologus C5). In some embodiments, the present invention provides antibodies that specifically bind to both human and cynomologus C5. Antibodies of the invention include, but are not limited to, the human monoclonal antibodies, isolated as described, in the Examples (see Section 6 below).

The present invention provides antibodies that specifically bind a C5 protein (*e.g.*, human and/or cynomologus C5), said antibodies comprising a VH domain having an amino acid sequence of SEQ ID NO: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281. The present invention also provides antibodies that specifically bind to a C5 protein (*e.g.*, human and/or cynomologus C5), said antibodies comprising a VH CDR having an amino acid sequence of any one of the VH CDRs listed in Table 1, *infra*. In particular, the invention provides antibodies that specifically bind to a C5 protein (*e.g.*, human and/or cynomologus C5), said antibodies comprising (or alternatively, consisting of) one, two, three, four, five or more VH CDRs having an amino acid sequence of any of the VH CDRs listed in Table 1, *infra*.

The present invention provides antibodies that specifically bind to a C5 protein (*e.g.*, human and/or cynomologus C5), said antibodies comprising a VL domain having an amino acid sequence of SEQ ID NO: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188,

202, 211, 219, 228, 242, 261, 265, 269, 285, or 289. The present invention also provides antibodies that specifically bind to a C5 protein (*e.g.*, human and/or cynomologus C5), said antibodies comprising a VL CDR having an amino acid sequence of any one of the VL CDRs listed in Table 1, *infra*. In particular, the invention provides antibodies that specifically bind to a C5 protein (*e.g.*, human and/or cynomologus C5), said antibodies comprising (or alternatively, consisting of) one, two, three or more VL CDRs having an amino acid sequence of any of the VL CDRs listed in Table 1, *infra*.

Other antibodies of the invention include amino acids that have been mutated, yet have at least 60, 70, 80, 90 or 95 percent identity in the CDR regions with the CDR regions depicted in the sequences described in Table 1. In some embodiments, it includes mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the CDR regions when compared with the CDR regions depicted in the sequence described in Table 1.

The present invention also provides nucleic acid sequences that encode VH, VL, the full length heavy chain, and the full length light chain of the antibodies that specifically bind to a C5 protein (*e.g.*, human and/or cynomologus C5). Such nucleic acid sequences can be optimized for expression in mammalian cells (for example, Table 1 shows the optimized nucleic acid sequences for the heavy chain and light chain of antibodies 8109, 8110, 8111, 8113, 8114, 8112, 8125, 8126, 8127, 8128, 8129, 8130, 8131, 8132, and 8091).

Table 1. Examples of C5 Antibodies of the Present Invention and C5 Proteins

Antibody 8109	Sequence Identifier (SEQ ID NO:) or comments/details
CDRH1	1: SYAIS
CDRH2	2: GIGPFFGTANYAQKFQG
CDRH3	3:DTPYFDY
CDRL1	4:SGDSIPNYYVY
CDRL2	5: DDSNRPS
CDRL3	6:QSFDSSLNAEV
VH	7:EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIGPFFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSS
VL	8:SYELTQPLSVSVALGQTARITCSGDSIPNYYVYWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTISRA QAGDEADYYCQSFDSSLNAEVFGGGTKLTVL
Heavy chain	9:EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIGPFFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	10:SYELTQPLSVSVALGQTARITCSGDSIPNYYVYWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTISR AQAGDEADYYCQSFDSSLNAEVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding	11:GAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAG

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-011416- -00000-0000
Fecha: 2011-02-01 18:10:39 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASEINACIONALI
Act: 411 PRESENTACION Folios: 1085

PATENTE DE INVENCIÓN ☐ **MODELO D**

- ☐ 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 ☐

SEQ ID NO:7	CCTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGGTGCGGCCAAGGCCCCTGGGCAGGGTCTCGAGTGGAT GGGCGGTATCGGTCCGTTTTTTGGCACTGCGAATTACGCGCAGAAGTTTCAGGGCCGGGTGACCATTACCGCG GATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCGAAGATACGGCCGTGTATTATTGCG CGCGTGATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:8	12:TCCTATGAACTCACACAGCCCCTGAGCGTGAGCGTGGCCCTGGGCCAGACCGCCCGGATCACCTGCTCCG GGGACAGCATCCCCAACTACTACGTGTACTGGTACCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTA CGAGGACAGCAACCGGCCCAGCGGCATCCCCGAGCGGTTCAGCGGCAGCAACAGCGGCAACACCGCCACCC TGACCATTTCCAGAGCACAGGCAGGCGAGGCCGACTACTACTGCCAGAGCTTCGACAGCAGCCTGAACGC CGAGGTGTTCGGCGGAGGGACCAAGTTAACCGTCCTA
PN encoding SEQ ID NO:9	13:GAGGTGCAATTGGTTCAGTCTGGGGCGGAAGTGAAAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAG CCTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGGTGCGGCCAAGCCCCTGGGCAGGGTCTCGAGTGGAT GGGCGGTATCGGTCCGTTTTTTGGCACTGCGAATTACGCGCAGAAGTTTCAGGGCCGGGTGACCATTACCGCG GATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCGAAGATACGGCCGTGTATTATTGCG CGCGTGATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCCTCCACCAAGGGT CCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTC AAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTC CCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCA CCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGGGGGACCGTCAGTCTTCCTCTTC CCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCC ACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCG GGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGG CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAA GGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGC CTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAG AACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGG ACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC GCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
PN encoding SEQ ID NO:10	14:TCCTATGAACTCACACAGCCCCTGAGCGTGAGCGTGGCCCTGGGCCAGACCGCCCGGATCACCTGCTCCG GGGACAGCATCCCCAACTACTACGTGTACTGGTACCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTA CGACGACAGCAACCGGCCCAGCGGCATCCCCGAGCGGTTCAGCGGCAGCAACAGCGGCAACACCGCCACCC TGACCATTTCCAGAGCACAGGCAGGCGAGGCCGACTACTACTGCCAGAGCTTCGACAGCAGCCTGAACGC CGAGGTGTTCGGCGGAGGGACCAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTC CCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAG CCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAAC AAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTA CAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA
Optimized PN encoding SEQ ID NO:9	15:GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAGAAGCCCGGTAGCAGCGTCAAGGTGTCCTGCAAG GCCAGCGGCGGCACCTTCAGCAGCTACGCCATCAGCTGGGTGCGGCAGGCCCCAGGCCAGGGCCTGGAGTG GATGGGCGGCATCGGCCCATTCTTCGGCACCGCCAACTACGCCCAGAAGTTCCAGGGCAGGGTCACCATCAC CGCCGACGAGAGCACCAGCACCGCCTACATGGAGCTGTCCAGCCTGAGAAGCGAGGACACCGCCGTGTACTA CTGCGCCAGAGAGACCCCCTACTTCGACTACTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCTAGCAC CAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCTCCGGCGGCACAGCCGCCCTGGGCT GCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGC ACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGCAGCA GCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGA GCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCCCGAAGCTGCAGGGCGCCCTTCCGT GTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGT GGACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAA GACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGA CTGGCTGAACGGCAAAGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATC

	AGCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCTTGTCGGGAGGAGATGACCAAG AACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAAC GGGCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCA AGCTGACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGC ACAACCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAG
Optimized PN encoding SEQ ID NO:10	16:AGCTACGAGCTGACCCAGCCCCCTGAGCGTGAGCGTGGCCCTGGGCCAGACCGCCAGGATCACCTGCAGCGG GGACAGCATCCCCAACTACTACGTGTACTGGTATCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTA CGACGACAGCAACAGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACAGCGGCAACACCGCCACCCT GACCATCAGCAGAGCCCAGGCCGGCGACGAGGCCGACTACTACTGCCAGAGCTTCGACAGCTCACTGAACGC CGAGGTGTTCGGCGGAGGGACCAAGCTGACCGTGCTGGGCCAGCCTAAGGCTGCCCCCAGCGTGACCCTGTT CCCCCCCAGCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAGCGACTTCTACCCAGG CGCCGTGACCGTGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCCGGCGTGGAGACCACCACCCCCAGCA AGCAGAGCAACAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAGGT CCTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTGGCCCCAACCGAGTGCAGC
Antibody 8110	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	17: NYIS
CDRH2	18: IIDPDDSYTEYSPSFQG
CDRH3	19: YEYGGFDI
CDRL1	20: SGDNIGNSYVH
CDRL2	21: KDNDRPS
CDRL3	22: GTYDIESYV
VH	23:EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPDDSYTEYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS
VL	24:SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCGTYDIESYVFGGGTKLTVL
Heavy chain	25:EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPDDSYTEYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	26:SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCGTYDIESYVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding SEQ ID NO:23	27:GAGGTGCAATTGGTTCAGAGCGGCGCGGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCA TTATTGATCCTGATGATTCTTATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTCACCATTAGCGCGGATAAAAG CATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTATG AGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:24	28:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCGGGCCAGGCGCCAGTTCTTGTGATTTATAA GGATAATGATCGTCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGGTACTTATGATATTGAGTCTTATGTGTTTGG CGGCGGCACGAAGTTAACCGTCCTA
PN encoding SEQ ID NO:25	29:GAGGTGCAATTGGTTCAGAGCGGCGCGGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCA TTATTGATCCTGATGATTCTTATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTCACCATTAGCGCGGATAAAAG CATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTATG AGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCCTCCACCAAGGGTCCATC GGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGA

	CTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGC TGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAG ACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGA CAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGGGGGACCGTCAGTCTTCCTCTTCCCCCCA AAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAG ACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG AGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGG AGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCA GCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGAC CTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAA CTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAG AGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGA AGAGCCTCTCCCTGTCTCCGGGTAAA
PN encoding SEQ ID NO:26	30:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTGCTGTAGCGG CGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAA GGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGGTACTTATGATATTGAGTCTTATGTGTTTGG CGGCGGCACCAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCT GAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGG CCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAACA AGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGG TCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA
Optimized PN encoding SEQ ID NO:25	31:GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAGG GCAGCGGCTACAGCTTCACCAACTACATCAGCTGGGTGCGGCAGATGCCCGGCAAGGGCCTGGAGTGGATGG GCATCATCGACCCCGACGACAGCTACACCGAGTACAGCCCCAGCTTCCAGGGCCAGGTGACCATCAGCGCCG ACAAGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCAGCGACACCGCCATGTACTACTGCG CCAGATACGACTACGGCGGCTTCGACATCTGGGGCCAGGGCACCCTGGTGACCGTCAGCTCAGCTAGCACCA AGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCTCCGGCGGCACAGCCGCCCTGGGCTGC CTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCAC ACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGCAGCAGC CTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAGC CCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCCGAAGCTGCAGGCGGCCCTTCCGTGT TCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGTGG ACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGA CCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGACT GGCTGAACGGCAAAGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCAG CAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGGAGGAGATGACCAAGAA CCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGG CCAGCCCGAGAACAACTACAAGACCACCCCCCCCGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAAG CTGACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCAC AACCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAG
Optimized PN encoding SEQ ID NO:26	32:AGCTACGAGCTGACCCAGCCCCCCAGCGTGAGCGTGGCCCCAGGCCAGACCGCCAGGATCAGCTGCAGC GGCGACAACATCGGCAACAGCTACGTGCACTGGTATCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATC TACAAGGACAACGACAGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACTCCGGCAACACCGCCACC CTGACCATCAGCGGCACCCAGGCCGAGGACGAGGCCGACTACTACTGCGGCACCTACGACATCGAGTCTATAC GTGTTCGGCGGAGGGACCAAGCTGACCGTGCTGGGCCAGCCTAAGGCTGCCCCCAGCGTGACCCTGTTCCCC CCCAGCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAGCGACTTCTACCCAGGCGCC GTGACCGTGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCCGGCGTGGAGACCACCACCCCCAGCAAGCA GAGCAACAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAGGTCCTA CAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTGGCCCCAACCGAGTGCAGC
Antibody 8111	SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS

CDRH1	33: TSGGGVS
CDRH2	34: NIDDADIFDYSPSLKS
CDRH3	35:GPYGFDS
CDRL1	36:TGTSSDIGTYNYVS
CDRL2	37: DDSNRPS
CDRL3	38:QSYDSQSIV
VH	39:EVTLKESGPALVKPTQTLTLTCTFSGFSLSTSGGGVSWIRQPPGKALEWLANIDDADIFDYSPSLKSRLTISKDTSK NQVVLTMTNMDPVDTATYYCARGPYGFDSWGQGTLVTVSS
VL	40:ESALTQPASVSGSPGQSITISCTGTSSDIGTYNYVSWYQQHPGKAPKLMIYDDSNRPSGVSNRFSGSKSGNTASL TISGLQAEDEADYYCQSYDSQSIVFGGGTKLTVL
Heavy chain	41:EVTLKESGPALVKPTQTLTLTCTFSGFSLSTSGGGVSWIRQPPGKALEWLANIDDADIFDYSPSLKSRLTISKDTSK NQVVLTMTNMDPVDTATYYCARGPYGFDSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	42:ESALTQPASVSGSPGQSITISCTGTSSDIGTYNYVSWYQQHPGKAPKLMIYDDSNRPSGVSNRFSGSKSGNTASL TISGLQAEDEADYYCQSYDSQSIVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding SEQ ID NO:39	43:GAGGTGACATTGAAAGAAAGCGGCCCGGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCTT TTCCGGATTTAGCCTGTCTACTTCTGGTGGTGGTGTGTCTTGGATTGGCCAGCCGCCTGGGAAAGCCCTCGAGT GGCTGGCTAATATTGATGATGCTGATATTAAGGATTATTCTCCTTCTCTTAAGTCTCGTCTGACCATTAGCAAAGA TACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACCGCCACCTATTATTGCGCGC GTGGTCCTTATGGTTTTGATTCTTGGGGCCAAGGCACCCTGGTGACCGTTAGCTCA
PN encoding SEQ ID NO:40	44:GAAAGCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACCGGC TACTAGCAGCGATATTGGTACTTATAATTATGTGTCTTGGTACCAGCAGCATCCCGGCAAGGCGCCGAAACTTA TGATTTATGATGATTCTAATCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGCG AGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTATGATTCTCAGTCTAT TGTGTTTGGCGGCGGCACCAAGTTAACCGTCCTA
PN encoding SEQ ID NO:41	45:GAGGTGACATTGAAAGAAAGCGGCCCGGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCTT TTCCGGATTTAGCCTGTCTACTTCTGGTGGTGGTGTGTCTTGGATTGGCCAGCCGCCTGGGAAAGCCCTCGAGT GGCTGGCTAATATTGATGATGCTGATATTAAGGATTATTCTCCTTCTCTTAAGTCTCGTCTGACCATTAGCAAAGA TACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACCGCCACCTATTATTGCGCGC GTGGTCCTTATGGTTTTGATTCTTGGGGCCAAGGCACCCTGGTGACCGTTAGCTCAGCCTCCACCAAGGGTCC ATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAA GGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCC GGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACC CAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTG TGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGGGGGACCGTCAGTCTTCCTCTTCCCC CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACG AAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGG AGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCA AGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGG GCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCT GACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAA CAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGAC AAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGC AGAAGAGCCTCTCCCTGTCTCCGGGTAAA
PN encoding SEQ ID NO:42	46:GAAAGCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACCGGG TACTAGCAGCGATATTGGTACTTATAATTATGTGTCTTGGTACCAGCAGCATCCCGGCAAGGCGCCGAAACTTA TGATTTATGATGATTCTAATCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGCG

	AGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTATGATTCTCAGTCTAT TGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCG CCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCG TGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAA GCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAG CTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACACTGGCCCCTACAGAATGTTCA
Optimized PN encoding SEQ ID NO:41	47:GAGGTGACCCTGAAGGAGAGCGGCCCAGCCCTGGTGAAGCCCACCCAGACCCTGACCCTGACTTGCACCT TCAGCGGCTTCAGCCTGAGCACCAGCGGAGGGGGCGTGAGCTGGATCAGGCAGCCCCCAGGTAAGGCCCTG GAGTGGCTGGCCAATATCGACGACGCCGATATCAAGGACTACAGCCCCAGCCTGAAGAGCAGGCTGACCATCA GCAAGGACACCAGCAAGAACCAGGTGGTGCTGACCATGACCAATATGGACCCCGTGGACACCGCCACCTACTA CTGCGCCAGAGGCCCCTACGGCTTCGACAGCTGGGGCCAGGGCACCCTGGTGACCGTCAGCTCAGCTAGCAC CAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCTCCGGCGGCACAGCCGCCCTGGGCT GCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGC ACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGCAGCA GCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGA GCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCCGAAGCTGCAGGGGGCCCTTCGGT GTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGT GGACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAA GACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGA CTGGCTGAACGGCAAAGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATC AGCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGGAGGAGATGACCAAG AACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAAC GGCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCA AGCTGACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGC ACAACCACTACACCCAGAAGAGCCTGAGCCTGTCACCCGGCAAG
Optimized PN encoding SEQ ID NO:42	48:GAGGTGCAGCTGCTGGAGTCCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGACTGAGCTGCGCCG CCAGCGGCTTCACCTTCAGCGATATCGGCATGGCCTGGGTCAGACAGGCCCCCGGCAAGGGCCTGGAGTGGGTG GCCAACATCGACGACGCCGACATCAAGGACTACAGCCCCAGCCTGAAGAGCAGACTGACCATCAGCAAGGAC ACCAGCAAGAACCAGGTGGTGCTGACCATGACCAACATGGACCCCGTGGACACCGCCACCTACTACTGCGCC AGAGGCCCCTACGGCTTCGACAGCTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCTAGCACCAAGGGC CCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTG AAGGACTACTTCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTC CCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGC ACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAGCCCAAG AGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCCGAAGCTGCAGGGGGCCCTTCGGTGTTCCTG TTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGTGGACGTG AGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAG CCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTG AACGGCAAAGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCAGCAAG GCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGGAGGAGATGACCAAGAACCAG GTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAG CCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAAGCTG ACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGAGCCTGAGCCTGTCACCCGGCAAG
Antibody 8113	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:17
CDRH2	49: IIDPDDSYTRYSPSFQG
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	50:ATWGSEDQV
VH	51:EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWSWVRQMPGKGLEWMGIIDPDDSYTRYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS
VL	52:SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCATWGSEDQVFGGGTKLTVL
Heavy chain	53:EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWSWVRQMPGKGLEWMGIIDPDDSYTRYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE

	SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCATWGSEDQVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding SEQ ID NO:51	55:GAGGTGCAATTGGTTCAGAGGGGGGGGGAAGTGAAAAAAGCGGGGGGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCA TTATCGATCCGGATGATAGCTATACCCGTTATTCTCCGAGCTTTCAGGGACAGGTGACCATTAGCGCGGATAAA AGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTA TGAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:52	56:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAA GGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGCTACTTGGGGTTCTGAGGATCAGGTGTTTG GCGGCGGCACGAAGTTAACCGTCCTA
PN encoding SEQ ID NO:53	57:GAGGTGCAATTGGTTCAGAGCGGCGGCGGAAGTGAAAAAAGCGGGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCA TTATCGATCCGGATGATAGCTATACCCGTTATTCTCCGAGCTTTCAGGGACAGGTGACCATTAGCGCGGATAAA AGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTA TGAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCCTCCACCAAGGGTCCA TCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAG GACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCG GCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCC AGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGT GACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGGGGGACCGTCAGTCTTCCTCTTCCCCC CAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGGA GGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAA GGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGG CAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTG ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAAC AACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCA GAAGAGCCTCTCCCTGTCTCCGGGTAAA
PN encoding SEQ ID NO:54	58:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAA GGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGCTACTTGGGGTTCTGAGGATCAGGTGTTTG GCGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTC TGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTG GCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAAC AAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAG GTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA
Optimized PN encoding SEQ ID NO:53	59:GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAGG GCAGCGGCTACAGCTTCACCAACTACATCAGCTGGGTGCGGCAGATGCCCGGCAAGGGCCTGGAGTGGATGG GCATCATCGACCCCGACGACAGCTACACCAGGTACAGCCCCAGCTTCCAGGGCCAGGTGACCATCAGCGCCG ACAAGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCAGCGACACCGCCATGTACTACTGCG CCAGATACGAGTACGGCGGCTTCGACATCTGGGGCCAGGGCACCCTGGTGACCGTCAGCTCAGCTAGCACCA AGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCTCCGGCGGCACAGCCGCCCTGGGCTGC CTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCAC ACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGCAGCAGC CTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAGC

	CCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCCGAAGCTGCAGGCGGCCCTTCCGTGT TCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGTGGTGG ACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGA CCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGACT GGCTGAACGGCAAAGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCAG CAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGGAGGAGATGACCAAGAA CCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGG CCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAAG CTGACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCAC AACCACTACACCCAGAAGAGCCTGAGCCTGTCACCCGGCAAG
Optimized PN encoding SEQ ID NO:54	60:AGCTACGAGCTGACCCAGCCCCCCAGCGTGAGCGTGGCCCCAGGCCAGACCGCCAGGATCAGCTGCAGC GGCGACAATATCGGCAACAGCTACGTGCACTGGTATCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATC TACAAGGACAACCGACAGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACTCCGGCAACACCGCCACC CTGACAATCAGCGGCACCCAGGCCGAGGACGAGGCCGACTACTACTGCGCCACCTGGGGCCTCAGAGGACCAG GTGTTCGGCGGAGGAACCAAGCTGACCGTGCTGGGCCAGCCTAAGGCTGCCCCCAGCGTGACCCTGTTCCCC CCCAGCAGGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAGCGACTTCTACCCAGGCGCC GTGACCGTGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCCGGCGTGGAGACCACCACCCCCAGCAAGCA GAGCAACAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAGGTCCTA CAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTGGCCCCAACCGAGTGCAGC
Antibody 8114	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	61: SYYIG
CDRH2	62: IIDPTDSQTAYSPSFQG
CDRH3	63:YMMRGFDH
CDRL1	64:SGDSLGDYYAY
CDRL2	65: KDNNRPS
CDRL3	66:QTWDTGESGV
VH	67:EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWVRQMPGKGLEWMGIIDPTDSQTAYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSS
VL	68:SYELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDTGESGVFGGGTKLTVL
Heavy chain	69:EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWVRQMPGKGLEWMGIIDPTDSQTAYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	70:SYELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDTGESGVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding SEQ ID NO:67	71:GAGGTGCAATTGGTTCAGAGCGGCGCGGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGG GCATTATTGATCCTACTGATTCTCAGACTGCTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATA AAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGT TATATGATGGGTGGTTTTGATCATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:68	72:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACGGCGGGTATCTCGTGTAGCGGC GATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAA GGATAATAATCGTCCCTCAGGCATCCCGGAAGCGTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATACTGGTGAGTCTGGTGTGTT TGGCGGCGGCACGAAGTTAACCGTCCTA
PN encoding	73:GAGGTGCAATTGGTTCAGAGCGGCGCGGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAGG

SEQ ID NO:69	TTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGG GCATTATTGATCCTACTGATTCTCAGACTGCTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATA AAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGT TATATGATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCCTCCACCAAGGGTC CATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGGCCCTGGGCTGCCTGGTCA AGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCC CGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCAC CCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTT GTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGGGGGACCGTCAGTCTTCCTCTTCCC CCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCAC GAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGG GAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGC AAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAG GGCAGCCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCC TGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGA ACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGA CAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACG CAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
PN encoding SEQ ID NO:70	74:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAA GGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACC ATTACCGGCACTCAGGCGGGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATACTGGTGAGTCTGGTGTGTT TGGCGGCGGCACCAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCC TCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAG TGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACA ACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCA GGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA
Optimized PN encoding SEQ ID NO:69	75:GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAGG GCAGCGGCTACAGCTTCACCAGCTACTGGATCGGCTGGGTGCGCCAGATGCCCGGCAAGGGCCTGGAGTGGA TGGGCATCATCGACCCCACCGACAGCGACACCAGATACAGCCCCAGCTTCCAGGGCCAGGTGACCATCAGCG CCGACAAGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCAGCGACACCGCCATGTACTACT GCGCCCGGTACATGATGAGGGGCTTCGACCACTGGGGTCAGGGCACCCTGGTGACCGTCAGCTCAGCTAGCA CCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCTCCGGCGGCACAGCCGCCCTGGGC TGCCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTG CACACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGCAGC AGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGG AGCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCCGAAGCTGCAGGCGGCCCTTCCG TGTTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGT GGACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAA GACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGA CTGGCTGAACGGCAAAGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATC AGCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGGAGGAGATGACCAAG AACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAAC GGCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCA AGCTGACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGC ACAACCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAG
Optimized PN encoding SEQ ID NO:70	76:AGCTACGAGCTGACCCAGCCCCCCAGCGTGAGCGTGGCCCCAGGCCAGACCGCCAGGATCAGCTGCAGC GGCGACAGCCTGGGCGACTACTACGCCTACTGGTATCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATC TACAAGGACAACAACAGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACAGCGGCAACACCGCCACC CTGACCATCAGCGGCACCCAGGCCGAGGACGAGGCCGACTACTACTGCCAGACCTGGGACAGCGGCGAGTCA GGCGTGTTCGGCGGAGGACCAAGCTGACCGTGCTGGGTCAGCCTAAGGCTGCCCCCAGCGTGACCCTGTTC

	CCCCCCAGCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAGCGACTTCTACCCAGGC
	GCCGTGACCGTGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCCGGCGTGGAGACCACCACCCCCAGCAA
	GCAGAGCAACAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAGGTC
	CTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTGGCCCCAACCGAGTGCAGC
Antibody 8112	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:61
CDRH2	77: IIDPSDSHTTYSPSFQG
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	78:QTWDILPHGLV
VH	79:EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIDPSDSHTTYSPSFQGQVTISADKS
	ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSS
VL	80:SYELTQPPSVSVAPGQTARISCSGDSLGDYYASWYQQKPGQAPVLVIYEDNKRPSGIPERFSGSNSGNTATLTIS
	GTQAEDEADYYC QTWDILPHGLVFGGGTKLTVL
Heavy chain	81:EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIDPSDSHTTYSPSFQGQVTISADKS
	ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP
	EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP
	CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
	VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
	ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	82:SYELTQPPSVSVAPGQTARISCSGDSLGDYYASWYQQKPGQAPVLVIYEDNKRPSGIPERFSGSNSGNTATLTIS
	GTQAEDEADYYCQTWDILPHGLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA
	DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding	83:GAGGTGCAATTGGTTCAGAGCGGCGCCGAAGTGAAAAAACCCGGCGCCGAAAGCCTGAAAATTAGCTGCAAAGG
SEQ ID NO:79	TTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGG
	GCATTATCGATCCGTCTGATAGCCATACCACTTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGAT
	AAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACCGCCATGTATTATTGCGCGC
	GTTATATGATGGTGGTTTTGATCATTGGGGCCAAGGCACCCTGGTGACCGTTAGCTCA
PN encoding	84:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTGCTGTAGCGGC
SEQ ID NO:80	GATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAA
	GGATAATAATCGTCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACC
	ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATATTCTTCCTCATGGTCTTGT
	GTTTGGCGGCGGCACCAAGTTAACCGTCCTA
PN encoding	85:GAGGTGCAATTGGTTCAGAGCGGCGCCGAAGTGAAAAAACCCGGCGCCGAAAGCCTGAAAATTAGCTGCAAAGG
SEQ ID NO:81	TTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGG
	GCATTATCGATCCGTCTGATAGCCATACCACTTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGAT
	AAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACCGCCATGTATTATTGCGCGC
	GTTATATGATGGTGGTTTTGATCATTGGGGCCAAGGCACCCTGGTGACCGTTAGCTCAGCCTCCACCAAGGG
	TCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGT
	CAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTT
	CCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGC
	ACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAAT
	CTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGGGGGACCGTCAGTCTTCCTCTT
	CCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGC
	CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGC
	GGGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATG
	GCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAA
	AGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAG
	CCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGA

	GAACAAGTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTG GACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
PN encoding SEQ ID NO:82	86:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACGGCGCGTATCTGTGTAGCGG CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAA GGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATATTCTTCCTCATGGTCTTGT GTTTGGCGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCC TCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGA CAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCA ACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTG CCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA
Optimized PN encoding SEQ ID NO:81	87:GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAGG GCAGCGGCTACAGCTTCACCAGCTACTACATCGGCTGGGTGCGGCAGATGCCCGGCAAGGGCCTGGAGTGGA TGGGCATTATCGATCCGTCTGATAGCCATACCACTTATTCTCCGAGCTTTCAGGGCCAGGTGACCATCAGCGCC GACAAGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCAGCGACACCGCCATGTACTACTGC GCCCGGTACATGATGAGGGGCTTCGACCACTGGGGTCAGGGCACCCTGGTGACCGTCAGCTCAGCTAGCACC AAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCTCCGGCGGCACAGCCGCCCTGGGCTG CCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCA CACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGCAGCAG CCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAG CCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCCGAAGCTGCAGGGGGCCCTTCCGTG TTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGTG GACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAG ACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAC TGGCTGAACGGCAAAGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCA GCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGGAGGAGATGACCAAGA ACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACG GCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAA GCTGACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCA CAACCACTACACCCAGAAGAGCCTGAGCCTGTCACCCGGCAAG
Optimized PN encoding SEQ ID NO:62	88:AGCTACGAGCTGACCCAGCCCCCCAGCGTGAGCGTGGCCCCAGGCCAGACGGCCAGGATCAGCTGCAGC GGCGACAGCCTGGGCGACTACTACGCCTACTGGTATCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATC TACAAGGACAACAACAGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACAGCGGCAACACCGCCACC CTGACAATCAGCGGCACCCAGGCCGAGGACGAGGCCGACTACTACTGCCAGACTTGGGATATTCTTCCTCATG GTCTTGTGTTCGGCGGAGGGACCAAGCTGACCGTGCTGGGTCAGCCTAAGGCTGCCCCCAGCGTGACCCTGT TCCCCCCCAGCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAGCGACTTCTACCCAG GCGCCGTGACCGTGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCCGGCGTGGAGACCACCACCCCCAGC AAGCAGAGCAACAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAGG TCCTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTGGCCCCAACCGAGTGCAGC
Antibody 8125	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:77
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	89:QAWTDSPTGLV
VH	SEQ ID NO:79
VL	90:STELTQPPSVSVAPGQTARISCSGDSLGDYYATWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQAWTDSPTGLVFGGGTKLTVL
Heavy chain	SEQ ID NO:81

Light chain	91:SYELTQPPSVSVAPGQTARISCSGDSLGDYYATWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQAWTDSPTGLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWK ADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding SEQ ID NO:79	SEQ ID NO:83
PN encoding SEQ ID NO:90	92:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGGCGTATCTGGTGTAGCGG CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAA GGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGGCTTGGACTGATTCTCCTACTGGTCTTGT GTTTGGCGGCGGCACGAAGTTAACCGTCCTA
PN encoding SEQ ID NO:81	SEQ ID NO:85
PN encoding SEQ ID NO:91	93:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGGCGTATCTGGTGTAGCGG CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAA GGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGGCTTGGACTGATTCTCCTACTGGTCTTGT GTTTGGCGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCC TCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGA CAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCA ACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTG CCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA
Optimized PN encoding SEQ ID NO:81	SEQ ID NO:87
Optimized PN encoding SEQ ID NO:91	94:AGCTACGAGCTGACCCAGCCCCCCAGCGTGAGCGTGGCCCCAGGCCAGACCGCCAGGATCAGCTGCAGC GGCGACAGCCTGGGCGACTACTACGCCTACTGGTATCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATC TACAAGGACAACAACAGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACAGCGGCAACACCGCCACC CTGACAATCAGCGGCACCCAGGCCGAGGACGAGGCCGACTACTACTGCCAGGCTTGGACTGATTCTCCTACTG GTCTTGTGTTCGGCGGAGGCACCAAGCTGACCGTGCTGGGTCAGCCTAAGGCTGCCCCCAGCGTGACCCTGT TCCCCCCCAGCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAGCGACTTCTACCCAG GCGCCGTGACCGTGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCCGGCGTGGAGACCACCACCCCCAGC AAGCAGAGCAACAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAGG TCCTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTGGCCCCAACCGAGTGCAGC
Antibody 8126	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:62
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	SEQ ID NO:89
VH	SEQ ID NO:67
VL	SEQ ID NO:90
Heavy chain	SEQ ID NO:69
Light chain	SEQ ID NO:91
PN encoding SEQ ID NO:79	SEQ ID NO:71
PN encoding SEQ ID NO:90	SEQ ID NO:92
PN encoding SEQ ID NO:81	SEQ ID NO:73

PN encoding SEQ ID NO:91	SEQ ID NO:93
Optimized PN encoding SEQ ID NO:81	SEQ ID NO:75
Optimized PN encoding SEQ ID NO:91	SEQ ID NO:94
Antibody 8127	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:61
CDRH2	95: IIDPTDSYTVYSPSFQG
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	SEQ ID NO:89
VH	96:EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIDPTDSYTVYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSS
VL	SEQ ID NO:90
Heavy chain	97:EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIDPTDSYTVYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	SEQ ID NO:91
PN encoding SEQ ID NO:96	98:GAGGTGCAATTGGTTCAGAGCGGGGCGGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGG GCATTATTGATCCTACTGATTCTTATACTGTTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATAA AAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGTT ATATGATGGGTGGTTTTGATCATTGGGGCCAAGGCACCCTGGTGACCGTTAGCTCAGC
PN encoding SEQ ID NO:90	SEQ ID NO:92
PN encoding SEQ ID NO:97	99:GAGGTGCAATTGGTTCAGAGCGGGGCGGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGG GCATTATTGATCCTACTGATTCTTATACTGTTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATAA AAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGTT ATATGATGGGTGGTTTTGATCATTGGGGCCAAGGCACCCTGGTGACCGTTAGCTCAGCCTCCACCAAGGGCCCA TCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTC AAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTC CCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCA CCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGGGGGGACCGTCAGTCTTCCTCTTC CCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCC ACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCG GGAGGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGG CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAA GGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGC CTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAG AACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGG ACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC

	GCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
PN encoding SEQ ID NO:91	SEQ ID NO:93
Optimized PN encoding SEQ ID NO:97	100:GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAG GGCAGCGGCTACAGCTTCACCAGCTACTACATCGGCTGGGTGCGGCAGATGCCCGGCAAGGGCCTGGAGTGG ATGGGCATTATTGATCCTACTGATTCTTATACTGTTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATCAGCGCC GACAAGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCAGCGACACCGCCATGTACTACTGC GCCCGGTACATGATGAGGGGCTTCGACCACTGGGGTCAGGGCACCCTGGTGACCGTCAGCTCAGCTAGCACC AAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCTCCGGCGGCACAGCCGCCCTGGGCTG CCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCA CACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGCAGCAG CCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAG CCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCCGAAGCTGCAGGGGGCCCTTCGGTG TTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGTGG GACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAG ACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAC TGGCTGAACGGCAAAGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCA GCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGGAGGAGATGACCAAGA ACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACG GCCAGCCCGAGAACAACTACAAGACCACCCCCCCCGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAA GCTGACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCA CAACCACTACACCCAGAAGAGCCTGAGCCTGTCACCCGGCAAG
Optimized PN encoding SEQ ID NO:91	SEQ ID NO:94
Antibody 8128	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:49
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	101:STWDIEPTYV
VH	SEQ ID NO:51
VL	102:SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCSTWDIEPTYVFGGGTKLTVL
Heavy chain	SEQ ID NO:53
Light chain	103:SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCSTWDIEPTYVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding SEQ ID NO:51	SEQ ID NO:55
PN encoding SEQ ID NO:102	104:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACGGCGGGGTATCTCGTGTAGCG GCGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGGCCAGTTCTTGTGATTTATA AGGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGGCAACACGGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCTCTACTTGGGATATTGAGCCTACTTATGTGT TTGGCGGCGGCACGAAGTTAACCGTCCTA
PN encoding SEQ ID NO:53	SEQ ID NO:57
PN encoding SEQ ID	105:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACGGCGGGGTATCTCGTGTAGCG GCGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGGCCAGTTCTTGTGATTTATA

NO:103	AGGATAATGATGGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCTCTACTTGGGATATTGAGCCTACTTATGTGT TTGGCGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTC CTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACA GTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAAC AACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCC AGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA
Optimized PN encoding SEQ ID NO:53	SEQ ID NO:59
Optimized PN encoding SEQ ID NO:103	108:AGCTACGAGCTGACCCAGCCCCCCAGCGTGAGCGTGGCCCCAGGCCAGACCGCCAGGATCACCTGCAGC GGCGACAATATCGGCAACAGCTACGTGCACTGGTATCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATC TACAAGGACAACGACAGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACTCCGGCAACACCGCCACC CTGACAATCAGCGGCACCCAGGCCGAGGACGAGGCCGACTACTACTGCTCTACTTGGGATATTGAGCCTACTT ATGTGTTCGGCGGAGGGACCAAGCTGACCGTGCTGGGCCAGCCTAAGGCTGCCCCCAGCGTGACCCTGTTCC CCCCCAGCAGGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAGCGACTTCTACCCAGGCG CCGTGACCGTGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCCGGCGTGGAGACCACCACCCCCAGCAAG CAGAGCAACAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAGGTCC TACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTGGCCCCAACCGAGTGCAGC
Antibody 8129	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:17
CDRH2	107: IIDPQDSYTETSPSFQG
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:22
VH	108:EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWIGWVRQMPGKGLEWMGIIDPQDSYTETSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS
VL	SEQ ID NO:24
Heavy chain	109:EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWIGWVRQMPGKGLEWMGIIDPQDSYTETSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	SEQ ID NO:26
PN encoding SEQ ID NO:108	110:GAGGTGCAATTGGTTCAGAGCGGGGCGGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTCAGGATTCTTATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTCACCATTAGCGCGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTAT GAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:24	SEQ ID NO:28
PN encoding SEQ ID NO:109	111:GAGGTGCAATTGGTTCAGAGCGGGGCGGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTCAGGATTCTTATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTCACCATTAGCGCGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTAT GAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCCTCCACCAAGGGTCCAT CGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGG ACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGG

	CTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCA GACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTG ACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGGGGGACCGTCAGTCTTCCTCTTCCCCCC AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAA GACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAG GAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGC AGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGA CCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACA ACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAA GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAG AAGAGCCTCTCCCTGTCTCCGGGTAAA
PN encoding SEQ ID NO:26	SEQ ID NO:30
Optimized PN encoding SEQ ID NO:109	112GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAG GGCAGCGGCTACAGCTTCACCAACTACATCAGCTGGGTGCGCCAGATGCCCGGCAAGGGCCTGGAGTGGATG GGCATCATCGACCCCGACGACAGCTACACCGAGTACAGCCCCAGCTTCCAGGGCCAGGTGACCATCAGCGCC GACAAGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCAGCGACACCGCCATGTACTACTGC GCCAGATACGAGTACGGCGGCTTCGACATCTGGGGCCAGGGCACCCTGGTGACCGTCAGCTCAGCTAGCACC AAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCTCCGGCGGCACAGCCGCCCTGGGCTG CCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCA CACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGCAGCAG CCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAG CCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCCGAAGCTGCAGGGGGCCCTTCGTG TTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGTG GACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAG ACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAC TGGCTGAACGGCAAAGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCA GCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGGAGGAGATGACCAAGA ACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACG GCCAGCCCGAGAACAACTACAAGACCACCCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAA GCTGACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCA CAACCACTACACGCAGAAGAGCCTGAGCCTGTCACCCGGCAAG
Optimized PN encoding SEQ ID NO:26	SEQ ID NO:32
Antibody 8130	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:107
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:101
VH	SEQ ID NO:108
VL	SEQ ID NO:102
Heavy chain	SEQ ID NO:109
Light chain	SEQ ID NO:103
PN encoding SEQ ID NO:108	SEQ ID NO:110
PN encoding	SEQ ID NO:104

SEQ ID NO:102	
PN encoding SEQ ID NO:109	SEQ ID NO:111
PN encoding SEQ ID NO:103	SEQ ID NO:105
Optimized PN encoding SEQ ID NO:109	SEQ ID NO:112
Optimized PN encoding SEQ ID NO:103	SEQ ID NO:106
Antibody 8131	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:17
CDRH2	113: IIDPEDSHTEYSPSFQG
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:22
VH	114:EVQLVQSGAEVIKPGESLKISCKGSGYSFTNYWIGWVRQMPGKGLEWMGIIDPEDSHTEYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS
VL	SEQ ID NO:24
Heavy chain	115:EVQLVQSGAEVIKPGESLKISCKGSGYSFTNYWIGWVRQMPGKGLEWMGIIDPEDSHTEYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKEVEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	SEQ ID NO:26
PN encoding SEQ ID NO:114	116:GAGGTGCAATTGGTTCAGAGCGGGCGGCGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTGAGGATTCTCATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAA AGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTA TGAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:24	SEQ ID NO:28
PN encoding SEQ ID NO:115	117:GAGGTGCAATTGGTTCAGAGCGGGCGGCGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTGAGGATTCTCATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAA AGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTA TGAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCCTCCACCAAGGGTCCA TCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAG GACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCG GCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCC AGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGT GACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGGGGGACCGTCAGTCTTCCTCTTCCCCC CAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGGA

	GGAGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAA GGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGG CAGCCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTG ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAAC AACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCA GAAGAGCCTCTCCCTGTCTCCGGGTAAA
PN encoding SEQ ID NO:26	SEQ ID NO:30
Optimized PN encoding SEQ ID NO:115	116GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAG GGCAGCGGCTACAGCTTCACCAACTACATCAGCTGGGTGCGGCAGATGCCCGGCAAGGGCCTGGAGTGGATG GGCATCATCGACCCCGAGGACAGCGCCATACCGAGTACAGCCCCAGCTTCCAGGGCCAGGTGACCATCAGCGCC GACAAGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCAGCGACACCGCCATGTACTACTGC GCCAGATACGAGTACGGCGGCTTCGACATCTGGGGCCAGGGCACCCTGGTGACCGTCAGCTCAGCTAGCACC AAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCTCCGGCGGCACAGCCGCCCTGGGCTG CCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCA CACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCAGCAGCAG CCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAG CCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCCGAAGCTGCAGGCGGCCCTTCCGTG TTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGTG GACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAG ACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGCTGCACCAGGAC TGGCTGAACGGCAAAGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCA GCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGGAGGAGATGACCAAGA ACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACG GCCAGCCCGAGAACAACTACAAGACCACCCCCCCCGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAA GCTGACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCA CAACCACTACACCCAGAAGAGCCTGAGCCTGTCACCCGGCAAG
Optimized PN encoding SEQ ID NO:26	SEQ ID NO:32
Antibody 8132	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:113
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:101
VH	SEQ ID NO:114
VL	SEQ ID NO:102
Heavy chain	SEQ ID NO:115
Light chain	SEQ ID NO:103
PN encoding SEQ ID NO:114	SEQ ID NO:116
PN encoding SEQ ID NO:102	SEQ ID NO:104
PN encoding	SEQ ID NO:117

SEQ ID NO:115	
PN encoding SEQ ID NO:103	SEQ ID NO:105
Optimized PN encoding SEQ ID NO:115	SEQ ID NO:118
Optimized PN encoding SEQ ID NO:103	SEQ ID NO:106
Antibody 8091	**Sequence Identifier (SEQ ID NO:) or comments/details**
CDRH1	SEQ ID NO:1
CDRH2	119: NIGPFFGIANYAQKFQG
CDRH3	SEQ ID NO:3
CDRL1	SEQ ID NO:4
CDRL2	SEQ ID NO:5
CDRL3	120:QTYDDGSTAEV
VH	121:QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGNIGPFFGIANYAQKFQGRVTITAD ESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSS
VL	122:DIELTQPPSVSVAPGQTARISCSGDSIPNNYVYWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTYDDGSTAEVFGGGTKLTVL
Heavy chain	123:QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGNIGPFFGIANYAQKFQGRVTITAD ESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCP APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTV VHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	124:DIELTQPPSVSVAPGQTARISCSGDSIPNNYVYWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTYDDGSTAEVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding SEQ ID NO:121	125:CAGGTGCAATTGGTTCAGTCTGGGGCGGAAGTGAAAAAACCGGGCAGCAGCGGTGAAAGTGAGCTGCAAAG GCTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGGTGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGAT GGGCAATATCGGTCCGTTTTTTGGCATTGCGAATTACGCGCAGAAGTTTCAGGGCCGGGTGACCATTACCGCG GATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCGAAGATACGGCCGTGTATTATTGCG CGCGTGATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:122	126:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACGGCGCGTATCTCGTGTAGCGG GCGATTCTATTCCTAATTATTATGTTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATG ATGATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTATGATGATGGTTCTACTGCTGAGG TGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO:123	127:CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGCAGCAGCGGTGAAAGTGAGCTGCAAAG GCTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGGTGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGAT GGGCAATATCGGTCCGTTTTTTGGCATTGCGAATTACGCGCAGAAGTTTCAGGGCCGGGTGACCATTACCGCG GATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCGAAGATACGGCCGTGTATTATTGCG CGCGTGATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCTTCCACCAAGGGC CCCAGCGTGTTCCCCCTGGCCCCCTGCAGCAGAAGCACCAGCGGAGAGCACAGCGCCCTGGGCTGCCTGGTG AAGGACTACTTCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTC CCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAACTTCGGC ACCCAGACCTACACCTGCAACGTGGACCACAAGCCCAGCAACACCAAGGTGGACAAGACCGTGGAGCGGAAG TGCTGCGTGGAGTGCCCCCCCTGCCCTGCCCCTCCTGTGGCGGACCCTCCGTGTTCCTGTTCCCCCCCAAG

	CCCAAGGACACCCTGATGATCAGCCGGACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGAC CCCGAGGTGCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCCCGGGAGGAA CAGTTCAACAGCACCTTCCGGGTGGTGTCCGTGCTGACCGTGGTGCACCAGGACTGGCTGAACGGCAAAGAAT ACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTGCCCCCATCGAGAAAACCATCAGCAAGACAAAGGGCCAGCC CAGGGAACCCCAGGTGTACACCCTGCCCCCCAGCCGGGAGGAAATGACCAAGAACCAGGTGTCCCTGACCTG TCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTA CAAGACCACCCCCCCCATGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAAGCTGACAGTGGACAAGAGC CGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAG AGCCTGAGCCTGTCCCCCGGCAAA
PN encoding SEQ ID NO:124	128:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGGGGTATCTGCTGTAGCG GCGATTCTATTCCTAATTATTATGTTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATG ATGATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGAGTTATGATGATGGTTCTACTGCTGAGG TGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCC CTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTG ACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGC AACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCT GCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA
Optimized PN encoding SEQ ID NO:123	129:CAGGTGCAGCTGGTGCAGTCCGGCGCCGAGGTGAAGAAGCCCGGCTCCTCCGTGAAGGTGTCCTGCAAG GCCTCCGGCGGCACCTTCTCCTCCTACGCCATCTCCTGGGTGCGCCAGGCCCCCGGCCAGGGCCTGGAGTGG ATGGGCAACATCGGCCCCTTCTTCGGCATCGCCAACTACGCCCAGAAGTTCCAGGGCCGCGTGACCATCACCG CCGACGAGTCCACCTCCACCGCCTACATGGAGCTGTCCTCCCTGCGCTCCGAGGACACCGCCGTGTACTACTG CGCCCGCGGACACCCCCTACTTCGACTACTGGGGCCAGGGCACCCTGGTGACCGTGTCCTCCGCCTCCACCAA GGGCCCCTCCGTGTTCCCCCTGGCCCCCTGCTCCCGGTCCACCTCCGAGTCCACCGCCGCCCTGGGCTGCCT GGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACTCCGGCGCCCTGACCTCCGGCGTGCACAC CTTCCCCGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTGGTGACCGTGCCCTCCTCCAACTTC GGCACCCAGACCTACACCTGCAACGTGGACCACAAGCCCTCCAACACCAAGGTGGACAAGACCGTGGAGCGG AAGTGCTGCGTGGAGTGCCCCCCCCTGCCCCGCCCCCCCCGTGGCCGGCCCCTCCGTGTTCCTGTTCCCCCCC AAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGTCCCACGAG GACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCCCGGGAG GAGCAGTTCAACTCCACCTTCCGGGTGGTGTCCGTGCTGACCGTGGTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCCGCCCCCATCGAGAAGACCATCTCCAAGACCAAGGGC CAGCCCCGGGAGCCCCAGGTGTACACCCTGCCCCCCTCCCGGGAGGAGATGACCAAGAACCAGGTGTCCCTG ACCTGCCTGGTGAAGGGCTTCTACCCCTCCGACATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCCGAGAAC AACTACAAGACCACCCCCCCCATGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCCAAGCTGACCGTGGACAA GTCCCGGTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCA GAAGTCCCTGTCCCTGTCCCCCGGCAAG
Optimized PN encoding SEQ ID NO:124	130:GACATCGAGCTGACCCAGCCCCCCTCCGTGTCCGTGGCCCCCGGCCAGACCGCCCGGATCTCCTGCTCC GGCGACTCCATCCCCAACTACTACGTGTACTGGTACCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCT ACGACGACTCCAACCGGCCCTCCGGCATCCCCGAGCGGTTCTCCGGCTCCAACTCCGGCAACACCGCCACCC TGACCATCTCCGGCACCCAGGCCGAGGACGAGGCCGACTACTACTGCCAGACCTACGACGACGGCTCCACCG CCGAGGTGTTCGGCGGCGGCACCAAGCTGACCGTGCTGGGCCAGCCTAAGGCTGCCCCCAGCGTGACCCTGT TCCCCCCCAGCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCCTGATCAGCGACTTCTACCCAG GGGCCGTGACCGTGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCCGGCGTGGAGACCACCACCCCCAGC AAGCAGAGCAACAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACAGG TCCTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTGGCCCCTACCGAGTGCAGC
Antibody 6525	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	131: SYWIS
CDRH2	132: IIDPDDSKTNYSPSFQG
CDRH3	133:RSYYPMDY
CDRL1	134:TGTSSDVVGVYNFVS

CDRL2	135: YVDNRPS
CDRL3	136:QSFDGFGIDMV
VH	137:QVQLVQSGAEVIKPGESLKISCKGSGYSFTSYWISWVRQMPGKGLEWMGIIDPDDSETTYSPSFQGQVTISAD KSISTAYLQWSSLKASDTAMYYCARRSYYPMDYWGQGTLVTVSS
VL	138:DIALTQPASVSGSPGQSITISCTGTSSDVVGVYNFVSWYQQHPGKAPKLMIYYVDNRPSGVSNRFSGSKSGNTA SLTISGLQAEDEADYYCQSFDGFGIDMVFGGGTKLTVL
Heavy chain	139:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWISWVRQMPGKGLEWMGIIDPDDSETTYSPSFQGQVTISAD KSISTAYLQWSSLKASDTAMYYCARRSYYPMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	140:DIALTQPASVSGSPGQSITISCTGTSSDVVGVYNFVSWYQQHPGKAPKLMIYYVDNRPSGVSNRFSGSKSGNTA SLTISGLQAEDEADYYCQSFDGFGIDMVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTV AWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO:137	141:CAGGTGCAATTGGTTCAGAGCGGGCGCGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTGGATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG GGCATTATCGATCCGGATGATAGCAAGACCAATTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGA TAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGC GTCGTTCTTATTATCCTATGGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:138	142:GATATCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACGG GTACTAGCAGCGATGTTGTTGGTGTTTATAATTTTGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAA CTTATGATTTATTATGTTGATAATCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACC GCGAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTTTGATGGTTTTGG TATTGATATGGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO:139	143:CAGGTGCAATTGGTTCAGAGCGGGCGCGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTGGATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG GGCATTATCGATCCGGATGATAGCAAGACCAATTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGA TAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGC GTCGTTCTTATTATCCTATGGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCGTCGACCAAAGGT CCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACAGCGGCTGCCCTGGGCTGCCTGGTT AAAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCATACCTTTC CGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGCA CTCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAACCGAAAAGC X (X can be TGC, GAATTC or TGCGAATTC)
PN encoding SEQ ID NO:140	144:GATATCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACGG GTACTAGCAGCGATGTTGTTGGTGTTTATAATTTTGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAA CTTATGATTTATTATGTTGATAATCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACC GCGAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTTTGATGGTTTTGG TATTGATATGGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCGGCACCGAGTGTGACG CTGTTTCCGCCGAGCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATC CGGGAGCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCC TCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACA GAAGCTACAGCTGCCAGGTCACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGGCGACTGAGX (X can be TGCAGC or GCC)
Antibody 6756	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	145: SYWIA
CDRH2	146: IIYPGDSDTNYSPSFQG
CDRH3	147:SKYGSFDY
CDRL1	148:TGTSSDVGGYNYVS
CDRL2	149: NVNSRPS
CDRL3	150:QSYDDGQDNEV

VH	151:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIAWVRQMPGKGLEWMGIIYPGDSDTNYSPSFQGQVTISAD KSISTAYLQWSSLKASDTAMYYCARSKYGSFDYWGQGTLVTVSS
VL	152:DIALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYNVNSRPSGVSNRFSGSKSGNTAS LTISGLQAEDEADYYCQSYDDGQDNEVFGGGTKLTVL
Heavy chain	153:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIAWVRQMPGKGLEWMGIIYPGDSDTNYSPSFQGQVTISAD KSISTAYLQWSSLKASDTAMYYCARSKYGSFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	154:DIALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYNVNSRPSGVSNRFSGSKSGNTAS LTISGLQAEDEADYYCQSYDDGQDNEVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTV AWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO:151	155:CAGGTGCAATTGGTTCAGAGGGGGGGGGGAAGTGAAAAAACCGGGGGGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTGGATTGCTTGGGTGGGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG GGCATTATCTATCCGGGTGATAGCGATACCAATTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGGGGA TAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGGCC GTTCTAAGTATGGTTCTTTTGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:152	156:GATATCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACAGG GTACTAGCAGCGATGTTGGTGGTTATAATTATGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTT ATGATTTATAATGTTAATTCTCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGC GAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTATGATGATGGTCAG GATAATGAGGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO:153	157:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTGGATTGCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG GGCATTATCTATCCGGGTGATAGCGATACCAATTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGA TAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGGCC GTTCTAAGTATGGTTCTTTTGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCGTCGACCAAAGGT CCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACAGCTGCCCTGGGCTGCCTGGTT AAAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGCGCCTGACCAGCGGCGTGCATACCTTTC CGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGCA CTCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAACCGAAAAGC X (X can be TGC, GAATTC or TGCGAATTC)
PN encoding SEQ ID NO:154	158:GATATCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACAGG GTACTAGCAGCGATGTTGGTGGTTATAATTATGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTT ATGATTTATAATGTTAATTCTCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGC GAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTATGATGATGGTCAG GATAATGAGGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCGGCACCGAGTGTGACGC TGTTTCCGCCGAGCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCC GGGAGCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCT CCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAG AAGCTACAGCTGCCAGGTCACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGAGX (X can be TGCAGC or GCC)
Antibody 6757	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	159: SYAMH
CDRH2	160: AISSSGSSTYYADSVKG
CDRH3	161:ESWFLDL
CDRL1	162:RASQSISNWLA
CDRL2	163: LASSLQS
CDRL3	164:QQYYDFSDT
VH	165:QVQLVESGGGLVQPGGSLRLSCAASGFTFTSYAMHWVRQAPGKGLEWVSAISSSGSSTYYADSVKGRFTISRD

	NSKNTLYLQMNSLRAEDTAVYYCARESWFLDLWGQGTLVTVSS
VL	166:DIQMTQSPSSLSASVGDRVTITCRASQSISNWLAWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTI SSLQPEDFAVYYCQQYYDFSDTFGQGTKVEIK
Heavy chain	167:QVQLVESGGGLVQPGGSLRLSCAASGFTFTSYAMHWVRQAPGKGLEWVSAISSSGSSTYYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCARESWFLDLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	168:DIQMTQSPSSLSASVGDRVTITCRASQSISNWLAWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTI SSLQPEDFAVYYCQQYYDFSDTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEX (X can be C or A)
PN encoding SEQ ID NO:165	169:CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGC GGCCTCCGGATTTACCTTTACTTCTTATGCTATGCATTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGG GTGAGCGCTATCTCTTCTTCTGGTAGCTCTACCTATTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCACGT GATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGC GCGTGAGTCTTGGTTTCTTGATCTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:166	170:GATATCCAGATGACCCAGAGCCCGTCTAGCCTGAGCGCGAGCGTGGGTGATCGTGTGACCATTACCTGCA GAGCGAGCCAGTCTATTTCTAATTGGCTGGCTTGGTACCAGCAGAAACCAGGTAAAGCACCGAAACTATTAATT TATCTTGCTTCTTCTTTGCAAAGCGGGGTCCCGTCCCGTTTTAGCGGCTCTGGATCCGGCACTGATTTTACCCT GACCATTAGCAGCCTGCAACCTGAAGACTTTGCGGTTTATTATTGCCAGCAGTATTATGATTTTTCTGATACCTTT GGCCAGGGTACCAAAGTTGAAATTAAA
PN encoding SEQ ID NO:167	171:CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGC GGCCTCCGGATTTACCTTTACTTCTTATGCTATGCATTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGG GTGAGCGCTATCTCTTCTTCTGGTAGCTCTACCTATTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCACGT GATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGC GCGTGAGTCTTGGTTTCTTGATCTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCGTGCGACCAAAGGT CCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACAGCGCTGCCCTGGGCTGCCTGGTT AAAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGCGCTGACCAGCGGCGTGCATACCTTTC CGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGCA CTCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAACCGAAAAGC X (X can be TGC, GAATTC or TGCGAATTC)
PN encoding SEQ ID NO:168	172:GATATCCAGATGACCCAGAGCCCGTCTAGCCTGAGCGCGAGCGTGGGTGATCGTGTGACCATTACCTGCA GAGCGAGCCAGTCTATTTCTAATTGGCTGGCTTGGTACCAGCAGAAACCAGGTAAAGCACCGAAACTATTAATT TATCTTGCTTCTTCTTTGCAAAGCGGGGTCCCGTCCCGTTTTAGCGGCTCTGGATCCGGCACTGATTTTACCCT GACCATTAGCAGCCTGCAACCTGAAGACTTTGCGGTTTATTATTGCCAGCAGTATTATGATTTTTCTGATACCTTT GGCCAGGGTACCAAAGTTGAAATTAAACGTACGGTGGCTGCTCCGAGCGTGTTTATTTTTCCGCCGAGCGATGA ACAACTGAAAAGCGGCACCGCGAGCGTGGTGTGCCTGCTGAACAACTTTTATCCGCGTGAAGCGAAAGTTCAG TGGAAAGTAGACAACGCGCTGCAAAGCGGCAACAGCCAGGAAAGCGTGACCGAACAGGATAGCAAAGATAGCA CCTATTCTCTGAGCAGCACCCTGACCCTGAGCAAAGCGGATTATGAAAAACATAAAGTGTATGCGTGCGAAGTG ACCCATCAAGGTCTGAGCAGCCCGGTGACTAAATCTTTTAATCGTGGCGAGX (X can be TGC or GCC)
Antibody 6763	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	173: NYGMH
CDRH2	174: VSYAGSFTNYADSVKG
CDRH3	175:SWLFGYPDIFDY
CDRL1	176:TGTSSDVGGYNYVS
CDRL2	177: DVNNRPS
CDRL3	178:SSYDKFQTV
VH	179:QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVSVSYAGSFTNYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCARSWLFGYPDIFDYWGQGTLVTVSS
VL	180:DIALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVNNRPSGVSNRFSGSKSGNTA SLTISGLQAEDEADYYCSSYDKFQTVFGGGTKLTVL

Heavy chain	181:QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVSVSTAGSFTNYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCARSWLFGYPDIFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	182:DIALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVNNRPSGVSNRFSGSKSGNTA SLTISGLQAEDEADYYCSSYTDKFQTVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO:179	183:CAGGTGCAATTGGTGGAAAGCGGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGC GGCCTCCGGATTTACCTTTTCTAATTATGGTATGCATTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGG GTGAGCGTTTCTTATGCTGGTAGCTTTACCAATTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCACGTGAT AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGCGCG TTCTTGGCTTTTTGGTTATCCTGATATTTTTGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:180	184:GATATCCAGCTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACGG GTACTAGCAGCGATGTTGGTGGTTATAATTATGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTT ATGATTTATGATGTTAATAATCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGCC GAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCTCTTCTTATGATAAGTTTCAGA CTGTGTTTGGCGGCGGCACGAAGTTAACCGTT
PN encoding SEQ ID NO:181	185:CAGGTGCAATTGGTGGAAAGCGGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGC GGCCTCCGGATTTACCTTTTCTAATTATGGTATGCATTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGG GTGAGCGTTTCTTATGCTGGTAGCTTTACCAATTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCACGTGAT AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGATACGGCCGTGTATTATTGCGCGCG TTCTTGGCTTTTTGGTTATCCTGATATTTTTGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCGTC GACCAAAGGTCCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACAGCGCTGCCCTGGG CTGCCTGGTTAAAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTG CATACCTTTCCGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCA GCTTAGGCACTCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAA CCGAAAAGCX (X can be TGC, GAATTC or TGCGAATTC)
PN encoding SEQ ID NO:182	186:GATATCCAGCTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACGG GTACTAGCAGCGATGTTGGTGGTTATAATTATGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTT ATGATTTATGATGTTAATAATCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGCC GAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCTCTTCTTATGATAAGTTTCAGA CTGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACGCTGTTTCCC GCCGAGCAGCGAAGAATTGCAGGCGAACAAAGCGACCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCC GTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAA AGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACA GCTGCCAGGTCACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGAGX (X can be TGCAGC or GCC)
Antibody 7086	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:1
CDRH2	SEQ ID NO:2
CDRH3	SEQ ID NO:3
CDRL1	SEQ ID NO:4
CDRL2	SEQ ID NO:5
CDRL3	SEQ ID NO:6
VH	187:QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIGPFFGTANYAQKFQGRVTITA DESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSS
VL	188:DIELTQPPSVSVAPGQTARISCSGDSIPNYYVYWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQSFDSSLNAEVFGGGTKLTVL
Heavy chain	189:QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIGPFFGTANYAQKFQGRVTITA DESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY

	FPEFVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	190:DIELTQPPSVSVAPGQTARISCSGDSIPTKYVYWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQSFDSSLNAEVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO:187	191:CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGGCAGCAGCGTGAAAGTGAGCTGCAAAG CCTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGGTGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGAT GGGCGGTATCGGTCCGTTTTTTGGCACTGCGAATTACGCGCAGAAGTTTCAGGGCCGCGTGACCATTACCGCG GATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCGAAGATACGGCCGTGTATTATTGCG CGCGTGATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCTGGTGACCGTTAGCTCA
PN encoding SEQ ID NO:188	192:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGGATTCTATTCCTAATTATTATGTTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATG ATGATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTTTGATTCTTCTCTTAATGCTGAGGT GTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO:189	193:CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGGCAGCAGCGTGAAAGTGAGCTGCAAAG CCTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGGTGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGAT GGGCGGTATCGGTCCGTTTTTTGGCACTGCGAATTACGCGCAGAAGTTTCAGGGCCGCGTGACCATTACCGCG GATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCGAAGATACGGCCGTGTATTATTGCG CGCGTGATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCTGGTGACCGTTAGCTCAGCGTCGACCAAAGGT CCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACAGCGCTGCCCTGGGCTGCCTGGTT AAAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGCGCCTGACCAGCGGCGTGCATACCTTTC CGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGCA CTCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAACCGAAAAGC X (X can be TGC, GAATTC or TGCGAATTC)
PN encoding SEQ ID NO:190	194:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGGATTCTATTCCTAATTATTATGTTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATG ATGATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTTTGATTCTTCTCTTAATGCTGAGGT GTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACGCTGTTTCCGCCC GAGCAGCTGGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCGTG ACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGC AACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCT GCCAGGTCACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGAGX (X can be TGCAGC or GCC)
Antibody 7037	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	195: SYYIS
CDRH2	196: GIIPIFGTANYAQKFQG
CDRH3	197: GEIWHVHQPYYSGVYGAAT
CDRL1	198: RASQGISNWLN
CDRL2	199: GTSSLQS
CDRL3	200: QQLDSFPAT
VH	201:QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARGEIWHVHQPYYSGVYGAATWGQGTLVTVSS
VL	202:DIQMTQSPSSLSASVGDRVTITCRASQGISNWLNWYQQKPGKAPKLLIYGTSSLQSGVPSRFSGSGSGTDFTLTI SSLQPEDFATYYCQQLDSFPATFGQGTKVEIK
Heavy chain	203:QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARGEIWHVHQPYYSGVYGAATWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSX (X can be C, EF or CEF)
Light chain	204:DIQMTQSPSSLSASVGDRVTITCRASQGISNWLNWYQQKPGKAPKLLIYGTSSLQSGVPSRFSGSGSGTDFTLTI SSLQPEDFATYYCQQLDSFPATFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN

	ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEX (X can be C or A)
PN encoding SEQ ID NO:201	205:CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGGCAGCAGCGTGAAAGTGAGCTGCAAAG CCTCCGGAGGCACTTTTTCTTCTTATTATATTTCTTGGGTGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGATG GGCGGTATCATTCCGATTTTTGGCACTGCGAATTACGCGCAGAAGTTTCAGGGCCGGGTGACCATTACCGCGG ATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCGAAGATACGGCCGTGTATTATTGCGC GCGTGGTGAGATTTGGCATGTTCATCAGCCTTATAAGTCTGGTGTTTATGGTGCTGCTTATTGGGGCCAAGGCA CCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:202	206:GATATCCAGATGACCCAGAGCCCGTCTAGCCTGAGCGCGAGCGTGGGTGATCGTGTGACCATTACCTGCA GAGCGAGCCAGGGTATTTCTAATTGGCTGAATTGGTACCAGCAGAAACCAGGTAAAGCACCGAAACTATTAATT TATGGTACTTCTTCTTTGCAAAGCGGGGTCCCGTCCCGTTTTAGCGGCTCTGGATCCGGCACTGATTTTACCCT GACCATTAGCAGCCTGCAACCTGAAGACTTTGCGACTTATTATTGCCAGCAGCTTGATTCTTTTCCTGCTACCTT TGGCCAGGGTACGAAAGTTGAAATTAAA
PN encoding SEQ ID NO:203	207:CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGGCAGCAGCGTGAAAGTGAGCTGCAAAG CCTCCGGAGGCACTTTTTCTTCTTATTATATTTCTTGGGTGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGATG GGCGGTATCATTCCGATTTTTGGCACTGCGAATTACGCGCAGAAGTTTCAGGGCCGGGTGACCATTACCGCGG ATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCGAAGATACGGCCGTGTATTATTGCGC GCGTGGTGAGATTTGGCATGTTCATCAGCCTTATAAGTCTGGTGTTTATGGTGCTGCTTATTGGGGCCAAGGCA CCCTGGTGACGGTTAGCTCAGCGTCGACCAAAGGTCCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCAC CAGCGGCGGCACGGCTGCCCTGGGCTGCCTGGTTAAAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAAC AGCGGCGCCCTGACCAGCGGCGTGCATACCTTTCCGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGC AGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGCACTCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAA CACCAAAGTGGATAAAAAAGTGGAACCGAAAAGCX (X can be TGC, GAATTC or TGCGAATTC)
PN encoding SEQ ID NO:204	208:GATATCCAGATGACCCAGAGCCCGTCTAGCCTGAGCGCGAGCGTGGGTGATCGTGTGACCATTACCTGCA GAGCGAGCCAGGGTATTTCTAATTGGCTGAATTGGTACCAGCAGAAACCAGGTAAAGCACCGAAACTATTAATT TATGGTACTTCTTCTTTGCAAAGCGGGGTCCCGTCCCGTTTTAGCGGCTCTGGATCCGGCACTGATTTTACCCT GACCATTAGCAGCCTGCAACCTGAAGACTTTGCGACTTATTATTGCCAGCAGCTTGATTCTTTTCCTGCTACCTT TGGCCAGGGTACGAAAGTTGAAATTAAACGTACGGTGGCTGCTCCGAGCGTGTTTATTTTTCCGCCGAGCGATG AACAACTGAAAAGCGGCACGGCGAGCGTGGTGTGCCTGCTGAACAACTTTTATCCGCGTGAAGCGAAAGTTCA GTGGAAAGTAGACAACGCGCTGCAAAGCGGCAACAGCCAGGAAAGCGTGACCGAACAGGATAGCAAAGATAG CACCTATTCTCTGAGCAGCACCCTGACCCTGAGCAAAGCGGATTATGAAAAACATAAAGTGTATGCGTGCGAAG TGACCCATCAAGGTCTGAGCAGCCCGGTGACTAAATCTTTTAATCGTGGCGAGX (X can be TGC or GCC)
Antibody 7091	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:77
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	209:QSWTDSPNTLV
VH	210:QVQLVQSGAEVIKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIDPSDSHTTYSPSFQGQVTISADK SISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSS
VL	211:DIELTQPPSVSVAPGQTARISCSGDSLGDYYATWYQQKPGQAPVLVIYEDNKRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQSWTDSPNTLVFGGGTKLTVL
Heavy chain	212:QVQLVQSGAEVIKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIDPSDSHTTYSPSFQGQVTISADK SISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	213:DIELTQPPSVSVAPGQTARISCSGDSLGDYYATWYQQKPGQAPVLVIYEDNKRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQSWTDSPNTLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID	214:CAGGTGCAATTGGTTCAGAGCGGGCGCGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG

NO:210	GGCATTATCGATCCGTCTGATAGCCATACCACTTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGA TAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGC GTTATATGATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:211	215:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTGGACTGATTCTCCTAATACTCTTG TGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO:212	216:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG GGCATTATCGATCCGTCTGATAGCCATACCACTTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGA TAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGC GTTATATGATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGGGTCGACCAAAGG TCCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACAGCCTGCCCTGGGCTGCCTGGT TAAAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCATACCTTT CCGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGC ACTCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAACCGAAAAG CX (X can be TGC, GAATTC or TGCGAATTC)
PN encoding SEQ ID NO:213	217:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTGGACTGATTCTCCTAATACTCTTG TGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCCCACCGAGTGTGACGCTGTTTCCGCC GAGCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCGTG ACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGC AACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCT GCCAGGTCACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGAGX (X can be TGCAGC or GCC)
Antibody 7032	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:49
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:22
VH	218:QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWVRQMPGKGLEWMGIIDPDDSYTRYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS
VL	219:DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCGTYDIESYVFGGGTKLTVL
Heavy chain	220:QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWVRQMPGKGLEWMGIIDPDDSYTRYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	221:DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCGTYDIESYVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO:218	222:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATCGATCCGGATGATAGCTATACCCGTTATTCTCCGAGCTTTCAGGGACAGGTGACCATTAGCGCGGATAA AAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGTT ATGAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA

PN encoding SEQ ID NO:219	223:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGGGTATCTCGTGTAGCG GCGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGGTACTTATGATATTGAGTCTTATGTGTTTG GCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO:220	224:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGCAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATCGATCCGGATGATAGCTATACCCGTTATTCTCCGAGCTTTCAGGGACAGGTGACCATTAGCGCGGATAA AAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGGTT ATGAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCGTCGACCAAAGGTCC AAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACAGCGCTGCCCTGGGCTGCCTGGTTAA AGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCATACCTTTCCG GCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGCACT CAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAACCGAAAAGCX (X can be TGC, GAATTC or TGCGAATTC)
PN encoding SEQ ID NO:221	225:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGGGTATCTCGTGTAGCG GCGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGGTACTTATGATATTGAGTCTTATGTGTTTG GCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCGGCACCGAGTGTGACGCTGTTTCCGCCGAGCA GCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACAA CAAGTACGCGGCGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCA GGTCACGCATGAGGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGAGX (X can be TGCAGC or GCC)
Antibody 7093	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:33
CDRH2	226: HIFSDDDKYYSTSLKT
CDRH3	SEQ ID NO:35
CDRL1	SEQ ID NO:36
CDRL2	SEQ ID NO:37
CDRL3	SEQ ID NO:38
VH	227:QVQLTESGPALVKPTQTLTLTCTFSGFSLSTSGGGVSWIRQPPGKALEWLAHIFSDDDKYYSTSLKTRLTISKDT SKNQVVLTMTNMDPVDTATYYCARGPYGFDSWGQGTLVTVSS
VL	228:DIALTQPASVSGSPGQSITISCTGTSSDIGTYNYVSWYQQHPGKAPKLMIYDDSNRPSGVSNRFSGSKSGNTAS LTISGLQAEDEADYYCQSYDSQSIVFGGGTKLTVL
Heavy chain	229:QVQLTESGPALVKPTQTLTLTCTFSGFSLSTSGGGVSWIRQPPGKALEWLAHIFSDDDKYYSTSLKTRLTISKDT SKNQVVLTMTNMDPVDTATYYCARGPYGFDSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	230:DIALTQPASVSGSPGQSITISCTGTSSDIGTYNYVSWYQQHPGKAPKLMIYDDSNRPSGVSNRFSGSKSGNTAS LTISGLQAEDEADYYCQSYDSQSIVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWK ADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO:227	231:CAGGTGCAATTGAAAGAAAGGGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCT TTTCCGGATTTAGCCTGTCTACTTCTGGTGGTGGTGTGTCTTGGATTCGCCAGCCGCCTGGGAAAGCCCTGGAG TGGCTGGCTCATATCTTTTCTGATGATGATAAGTATTATAGCACCAGCCTGAAAACCCGTCTGACCATTAGCAAA GATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACCGCCACCTATTATTGCGC GCGTGGTCCTTATGGTTTTGATTCTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:228	232:GATATCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACCGG GTACTAGCAGCGATATTGGTAGTTATAATTATGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAAGTT ATGATTTATGATGATTCTAATCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGC

	GAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTATGATTCTCAGTCTA TTGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO:229	233:CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCT TTTCCGGATTTAGCCTGTCTACTTCTGGTGGTGGTGTCTTGGATTGGCCAGCCGCCTGGGAAAGCCCTGGAG TGGCTGGCTCATATCTTTTCTGATGATGATAAGTATTATAGCACCAGCCTGAAAACCGGTCTGACCATTAGCAAA GATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACCGCCACCTATTATTGCGC GCGTGGTGCTTATGGTTTTGATTCTTGGGGCCAAGGCACCCTGGTGACCGTTAGCTCAGCGTCGACCAAAGGT CCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACAGCTGCCCTGGGCTGCCTGGTT AAAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCATACCTTTC CGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGCA CTCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAACCGAAAAGC X (X can be TGC, GAATTC or TGCGAATTC)
PN encoding SEQ ID NO:230	234:GATATCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACCGG GTACTAGCAGCGATATTGGTACTTATAATTATGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCCGAAACTT ATGATTTATGATGATTCTAATCGTCCCCTCAGGGGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGCC GAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTATGATTCTCAGTCTA TTGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACGCTGTTTCC GCCGAGCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCC GTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAA AGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACA GCTGCCAGGTCACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGGCCGACTGAGX (X can be TGCAGC or GCC)
Antibody 7094	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	235: TSGMSVG
CDRH2	236: LIDWDEDKSYSTSLKT
CDRH3	237:YNWYNPPGFDN
CDRL1	238:SGSSSNIGSNYVS
CDRL2	239: RNDKRPS
CDRL3	240: QSADSSSMV
VH	241:QVQLKESGPALVKPTQTLTLTCTFSGFSLSTSGMSVGWIRQPPGKALEWLALIDWDEDKSYSTSLKTRLTISKDT SKNQVVLTMTNMDPVDTATYYCARYNWYNPPGFDNWGQGTLVTVSS
VL	242:DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSNYVSWYQQLPGTAPKLLIYRNDKRPSGVPDRFSGSKSGTSASL AITGLQSEDEADYYCQSADSSSMVFGGGTKLTVL
Heavy chain	243:QVQLKESGPALVKPTQTLTLTCTFSGFSLSTSGMSVGWIRQPPGKALEWLALIDWDEDKSYSTSLKTRLTISKDT SKNQVVLTMTNMDPVDTATYYCARYNWYNPPGFDNWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	244:DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSNYVSWYQQLPGTAPKLLIYRNDKRPSGVPDRFSGSKSGTSASL AITGLQSEDEADYYCQSADSSSMVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWK ADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO:241	245:CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCT TTTCCGGATTTAGCCTGTCTACTTCTGGTATGTCTGTGGGTTGGATTGGCCAGCCGCCTGGGAAAGCCCTGGAG TGGCTGGCTCTTATCGATTGGGATGACGATAAGTCTTATAGCACCAGCCTGAAAACCGGTCTGACCATTAGCAA AGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACCGCCACCTATTATTGCG CGCGTTATAATTGGTATAATCCTCCTGGTTTTGATAATTGGGGCCAAGGCACCCTGGTGACCGTTAGCTCA
PN encoding SEQ ID NO:242	246:GATATCGTGCTGACCCAGCCGCCTTCAGTGAGTGGCGCACCAGGTCAGCGTGTGACCATCTCGTGTAGCGG CAGCAGCAGCAACATTGGTTCTAATTATGTGTCTTGGTACCAGCAGTTGCCCGGGACGGCGCCGAAACTTCT GATTTATCGTAATGATAAGCGTCCCCTCAGGCGTGCCGGATCGTTTTAGCGGATCCAAAAGCGGCACCAGCGCG AGCCTTGCGATTACGGGCCTGCAAAGCGAAGACGAAGCGGATTATTATTGCCAGTCTGCTGATTCTTCTTCTAT GGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTT

PN encoding SEQ ID NO:243	247:CAGGTGCAATTGAAAGAAAGGGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCT TTTCCGGATTTAGCCTGTCTACTTCTGGTATGTCTGTGGGTTGGATTCGCCAGCCGCCTGGGAAAGCCCTGGAG TGGCTGGCTCTTATCGATTGGGATGATGATAAGTCTTATAGCACCAGCCTGAAAACGGGTCTGACCATTAGCAA AGATACTTCGAAAAATCAGGTGGTCCTGACTATGACCAACATGGACCCGGTGGATACGGCCACCTATTATTGCG CGCGTTATAATTGGTATAATCCTCCTGGTTTTGATAATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCG TCGACCAAAGGTCCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACAGCCTGCCCTG GGCTGCCTGGTTAAAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGC GTGCATACCTTTCCGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCA GCAGCTTAGGCACTCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAGTG GAACCGAAAAGCX (X can be TGC, GAATTC or TGCGAATTC)
PN encoding SEQ ID NO:244	248:GATATCGTGCTGACCCAGCCGCCTTCAGTGAGTGGGCCACCAGGTCAGCGTGTGACCATCTCGTGTAGCGG GCAGCAGCAGCAACATTGGTTCTAATTATGTGTCTTGGTACCAGCAGTTGCCCGGGACGGCGCCGAAACTTCT GATTTATCGTAATGATAAGCGTCCCTCAGGCGTGCCGGATCGTTTTAGCGGATCCAAAAGCGGCACCAGCGCG AGCCTTGCGATTACGGGCCTGCAAAGCGAAGACGAAGCGGATTATTATTGCCAGTCTGCTGATTCTTCTTCTAT GGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACGCTGTTTCCG CCGAGCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCG TGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAA GCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAG CTGCCAGGTCACGCATGAGGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGAGX (X can be TGCAGC or GCC)
Antibody 7821	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:1
CDRH2	SEQ ID NO:119
CDRH3	SEQ ID NO:3
CDRL1	SEQ ID NO:4
CDRL2	SEQ ID NO:5
CDRL3	SEQ ID NO:6
VH	SEQ ID NO:121
VL	SEQ ID NO:188
Heavy chain	249:QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGRIIPFFGIANYAQKFQGRVTITAD ESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	SEQ ID NO:190
PN encoding SEQ ID NO:121	SEQ ID NO:125
PN encoding SEQ ID NO:188	SEQ ID NO:192
PN encoding SEQ ID NO:249	250:CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAG CCTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGGTGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGAT GGGCAATATCGGTCCGTTTTTTGGCATTGCGAATTACGCGCAGAAGTTTCAGGGCCGGGTGACCATTACCGCG GATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCGAAGATACGGCCGTGTATTATTGCG CGCGTGATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCGTCGACCAAAGGT CCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACAGCCTGCCCTGGGCTGCCTGGTT AAAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCATACCTTTC CGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGCA CTCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAACCGAAAAGC X (X can be TGC, GAATTC or TGCGAATTC)

PN encoding SEQ ID NO:190	SEQ ID NO:194
Antibody 7865	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:1
CDRH2	SEQ ID NO:2
CDRH3	SEQ ID NO:3
CDRL1	SEQ ID NO:4
CDRL2	SEQ ID NO:5
CDRL3	SEQ ID NO:120
VH	SEQ ID NO:187
VL	SEQ ID NO:122
Heavy chain	SEQ ID NO:189
Light chain	251:DIELTQPPSVSVAPGQTARISCSGDSIPNYYVTWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDDGSTAEVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEC (X can be CS or A)
PN encoding SEQ ID NO:187	SEQ ID NO:191
PN encoding SEQ ID NO:122	SEQ ID NO:126
PN encoding SEQ ID NO:189	SEQ ID NO:193
PN encoding SEQ ID NO:251	252:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCCACCAGGTCAGAACGCGCGTATCTCGTGTAGCG GCGATTCTATTCCTAATTATTATGTTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATG ATGATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTATGATGATGGTTCTACTGCTGAGG TGTTTGGCGGCGGCACCAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACCCTGTTTCCGCCC GAGCAGCCGAAGAATTGCAGCCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCGTG ACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGC AACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCT GCCAGGTCACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGAGC (X can be TGCAGC or GCC)
Antibody 7829	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:62
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	SEQ ID NO:209
VH	253:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIDPTDSQTAYSPSFQGQVTISADK SISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSS
VL	SEQ ID NO:211
Heavy chain	254:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIDPTDSQTAYSPSFQGQVTISADK SISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC (X can be C, EF or CEF)
Light chain	SEQ ID NO:213
PN encoding	255:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG

SEQ ID NO:253	GTTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGGCAGATGCCTGGGAAGGGTCTCGAGTGGATG GGCATTATTGATCCTACTGATTCTCAGACTGCTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGAT AAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGC GTTATATGATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:211	SEQ ID NO:215
PN encoding SEQ ID NO:254	256:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG GGCATTATTGATCCTACTGATTCTCAGACTGCTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGAT AAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGC GTTATATGATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCGTCGACCAAAGG TCCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACAGGCTGCCCTGGGCTGCCTGGT TAAAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGGGCGCTGACCAGCGGCGTGCATACCTTT CCGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGC ACCCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAACCGAAAAG CX (X can be TGC, GAATTC or TGCGAATTC)
PN encoding SEQ ID NO:213	SEQ ID NO:217
Antibody 7830	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:95
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	SEQ ID NO:209
VH	257:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIDPTDSYTVYSPSFQGQVTISADK SISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSS
VL	SEQ ID NO:211
Heavy chain	258:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIDPTDSYTVYSPSFQGQVTISADK SISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	SEQ ID NO:213
PN encoding SEQ ID NO:257	259:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG GGCATTATTGATCCTACTGATTCTTATACTGTTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATA AAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGT TATATGATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:211	SEQ ID NO:215
PN encoding SEQ ID NO:258	260:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG GGCATTATTGATCCTACTGATTCTTATACTGTTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATA AAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGT TATATGATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCGTCGACCAAAGGTC CAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACAGGCTGCCCTGGGCTGCCTGGTTA AAGATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGGGCGCTGACCAGCGGCGTGCATACCTTTCC

	GGCGGTGCTGCAAAGCAGGGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGCAC TCAGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAACCGAAAAGCX (X can be TGC, GAATTC or TGCGAATTC)
PN encoding SEQ ID NO:213	SEQ ID NO:217
Antibody 7871	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:77
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	SEQ ID NO:66
VH	SEQ ID NO:210
VL	261:DIELTQPPSVSVAPGQTARISCSGDSLGDYYASWYQQKPGQAPVLVIYEDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDTGESGVFGGGTKLTVL
Heavy chain	SEQ ID NO:212
Light chain	262:DIELTQPPSVSVAPGQTARISCSGDSLGDYYASWYQQKPGQAPVLVIYEDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDTGESGVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO:210	SEQ ID NO:214
PN encoding SEQ ID NO:261	263:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTGTGTAGCG GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATACTGGTGAGTCTGGTGTG TTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO:212	SEQ ID NO:216
PN encoding SEQ ID NO:262	264:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTGTGTAGCG GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATACTGGTGAGTCTGGTGTG TTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACCGCTGTTTCCGGCGGA GCAGCGAAGAATTGCAGGCGAACAAAGCGGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCGTGAC AGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAA CAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGC CAGGTCACGCATGAGGGAGCACCGTGGAAAAACCCGTTGCGCCGACTGAGX (X can be TGCAGC or GCC)
Antibody 7872	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:77
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	SEQ ID NO:78
VH	SEQ ID NO:210
VL	265:DIELTQPPSVSVAPGQTARISCSGDSLGDYYASWYQQKPGQAPVLVIYEDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDILPHGLVFGGGTKLTVL

Heavy chain	SEQ ID NO:212
Light chain	266:DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYEDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDILPHGLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO:210	SEQ ID NO:214
PN encoding SEQ ID NO:265	267:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGGCGTATCTCGTGTAGCG GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATATTCTTCCTCATGGTCTTG TGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO:212	SEQ ID NO:216
PN encoding SEQ ID NO:266	268:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGGCGTATCTCGTGTAGCG GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATATTCTTCCTCATGGTCTTG TGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCGGCACCGAGTGTGACGCTGTTTCCGCCC GAGCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCGTG ACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGC AACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCT GCCAGGTCACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGGCGACTGAGX (X can be TGCAGC or GCC)
Antibody 7873	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:77
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	SEQ ID NO:89
VH	SEQ ID NO:210
VL	269:DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYEDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQAWTDSPTGLVFGGGTKLTVL
Heavy chain	SEQ ID NO:212
Light chain	270:DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYEDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQAWTDSPTGLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA ADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO:210	SEQ ID NO:214
PN encoding SEQ ID NO:269	271:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGGCGTATCTCGTGTAGCG GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGGCTTGGACTGATTCTCCTACTGGTCTTG TGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO:212	SEQ ID NO:216
PN encoding	272:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGGCGTATCTCGTGTAGCG

SEQ ID NO:270	GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGGCCAGTTCTTGTGATTTATA AGGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGGCTTGGACTGATTCTCCTACTGGTCTTG TGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACGCTGTTTCCGCC GAGCAGCGAAGAATTGCAGGCGAACAAAGCGGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCGTG ACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGC AACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCT GCCAGGTCACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGAGX (X can be TGCAGC or GCC)
Antibody 7832	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:18
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:22
VH	273:QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWVRQMPGKGLEWMGIIDPDDSYTEYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS
VL	SEQ ID NO:219
Heavy chain	274:QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWVRQMPGKGLEWMGIIDPDDSYTEYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be G, EF or CEF)
Light chain	SEQ ID NO:221
PN encoding SEQ ID NO:273	275:CAGGTGCAATTGGTTCAGAGCGGGGCGGTGGAAGTGAAAAAACCGGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTGATGATTCTTATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTCACCATTAGCGCGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGGCGCGTTAT GAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCGTCGACCAAAGGTCCAA GCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGGCGGCACGGCTGCCCTGGGCTGCCTGGTTAAAG ATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGGGCGCTGACCAGCGGCGTGCATACCTTTCCGGCC GTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGCACCCA GACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAACCGAAAAGCX (X can be TGC, GAATTC or TGCGAATTC)
Antibody 7009	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:107
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:22
VH	277:QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWVRQMPGKGLEWMGIIDPQDSYTEYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS

VL	SEQ ID NO:219
Heavy chain	278:QVQLVQSGAEVHKPGESLHISCHGSGYSFTNYWVRQMPGHGLEWMGIIDPQDSYTEYSPSFQGQVTISADHS ISTAYLQWSSLHASDTAMYYCARYEYGGFDIWGQGTLVTVSSASTHGPSVFPLAPSSHSTSGGTAALGCLVHDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHHPSNTHVDHHVEPHSX (X can be G, EF or CEF)
Light chain	SEQ ID NO:221
PN encoding SEQ ID NO:277	279:CAGGTGCAATTGGTTCAGAGCGGGCGCGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTCAGGATTCTTATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTCACCATTAGCGCGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTAT GAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:219	SEQ ID NO:223
PN encoding SEQ ID NO:278	280:CAGGTGCAATTGGTTCAGAGCGGGCGCGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTCAGGATTCTTATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTCACCATTAGCGCGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTAT GAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCGTCGACCAAAGGTCCAA GCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGGCACAGCGCTGCCCTGGGCTGCCTGGTTAAAG ATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGGGCGCTGACCAGCGGCGTGCATACCTTTCCGGCC GGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGCACTCA GACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAACCGAAAAGCX (X can be TGC, GAATTC or TGCGAATTC)
Antibody 7910	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:113
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:22
VH	281:QVQLVQSGAEVHKPGESLHISCHGSGYSFTNYWVRQMPGHGLEWMGIIDPEDSHTEYSPSFQGQVTISADHS ISTAYLQWSSLHASDTAMYYCARYEYGGFDIWGQGTLVTVSS
VL	SEQ ID NO:219
Heavy chain	282:QVQLVQSGAEVHKPGESLHISCHGSGYSFTNYWVRQMPGHGLEWMGIIDPEDSHTEYSPSFQGQVTISADHS ISTAYLQWSSLHASDTAMYYCARYEYGGFDIWGQGTLVTVSSASTHGPSVFPLAPSSHSTSGGTAALGCLVHDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHHPSNTHVDHHVEPHSX (X can be G, EF or CEF)
Light chain	SEQ ID NO:221
PN encoding SEQ ID NO:281	283:CAGGTGCAATTGGTTCAGAGCGGGCGCGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTGAGGATTCTCATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAA AGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTA TGAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:219	SEQ ID NO:223
PN encoding SEQ ID NO:282	284:CAGGTGCAATTGGTTCAGAGCGGGCGCGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTGAGGATTCTCATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAA

	AGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCGATACGGCCATGTATTATTGCGGCGGTTA TGAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACCGTTAGCTCAGCGTCGACCAAAGGTCCA AGCGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGGCGGCACGGCTGCCCTGGGCTGCCTGGTTAAA GATTATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGGGCGCTGACCAGCGGCGTGCATACCTTTCCGG CGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGCACTC AGACCTATATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTGGATAAAAAAGTGGAACCGAAAAGCX (X can be TGC, GAATTC or TGCGAATTC)
Antibody 7876	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:49
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:50
VH	SEQ ID NO:218
VL	285:DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYEDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCATWGSEDQVFGGGTKLTVL
Heavy chain	SEQ ID NO:220
Light chain	286:DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYEDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCATWGSEDQVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO:218	SEQ ID NO:222
PN encoding SEQ ID NO:285	287:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG GCGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATGATCGTCCCTCAGGCATCCCGGAAGGCTTTAGCGGATCCAACAGCGGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGCTACTTGGGGTTCTGAGGATCAGGTGTTT GGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO:220	SEQ ID NO:224
PN encoding SEQ ID NO:286	288:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG GCGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATGATCGTCCCTCAGGCATCCCGGAAGGCTTTAGCGGATCCAACAGCGGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGCTACTTGGGGTTCTGAGGATCAGGTGTTT GGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCGGCACCGAGTGTGACGCTGTTTCCGCCGAGC AGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCGTGACAG TGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAACA ACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCA GGTCACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGAGX (X can be TGCAGC or GCC)
Antibody 7878	**SEQUENCE IDENTIFIER (SEQ ID NO:) OR COMMENTS/DETAILS**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:49
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:101
VH	SEQ ID NO:218
VL	289:DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYEDNDRPSGIPERFSGSNSGNTATLTIS

	GTQAEDEADYYCSTWDIEPTYVFGGGTKLTVL
Heavy chain	SEQ ID NO:220
Light chain	290:DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYEDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCSTWDIEPTYVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEC (X can be CS or A)
PN encoding SEQ ID NO:218	SEQ ID NO:222
PN encoding SEQ ID NO:289	291:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACGGCGGGTATCTCGTGTAGCGG GCGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCTCTACTTGGGATATTGAGCCTACTTATGTGT TTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO:220	SEQ ID NO:224
PN encoding SEQ ID NO:290	292:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACGGCGGGTATCTCGTGTAGCGG GCGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCTCTACTTGGGATATTGAGCCTACTTATGTGT TTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACGCTGTTTCCGCCGA GCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCGTGAC AGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGCAA CAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGC CAGGTCACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGAGX (X can be TGCAGC or GCC)
Human (*Homo sapiens*) C5	296:MGLLGILCFLIFLGKTWGQEQTYVISAPKIFRVGASENIVIQVYGYTEAFDATISITSYPDKKFSYSSGHVHLSSENK FQNSAILTIQPKQLPGGQNPVSYVYLEVVSKHFSKSKRMPITYDNGFLFIHTDNPVYTPDQSVKVRVYSLNDDLKPAK RETVLTFIDPEGSEVDMVEEIDHIGIISFPDFKIPSNPRYGMWTIKARYKEDFSTTGTAYFEVKEYVLPHFSVSIEPEYNF IGYKNFKNFEITIKARYFYNKVVTEADVYITFGIREDLKDDQKEMMQTAMQNTMLINGIAQVTFDSETAVKELSYYSLED LNNKYLYIAVTVIESTGGFSEEAEIPGIKYVLSPYKLNLVATPLFLKPGIPYPIKVQVKDSLDQLVGGVPVTLNAQTIDVN QETSDLDPSKSVTRVDDGVASFVLNLPSGVTVLEFNVKTDAPDLPEENQAREGYRAIAYSSLSQSYLYIDWTDNHKA LLVGEHLNIIVTPKSPYIDKITHYNYLILSKGKIIHFGTREKFSDASYQSINIPVTQNMVPSSRLLVYYIVTGEQTAELVSD SVWLNIEEKCGNQLQVHLSPDADAYSPGQTVSLNMATGMDSWVALAAVDSAVYGVQRGAKKPLERVFQFLEKSDL GCGAGGGLNNANVFHLAGLTFLTNANADDSQENDEPCKEILRPRRTLQKKIEEIAAKYKHSVVKKCCYDGACVNNDE TCEQRAARISLGPRCIKAFTECCVVASQLRANISHKDMQLGRLHMKTLLPVSKPEIRSYFPESWLWEVHLVPRRKQL QFALPDSLTTWEIQGVGISNTGICVADTVKAKVFKDVFLEMNIPYSVVRGEQIQLKGTVYNYRTSGMQFCVKMSAVE GICTSESPVIDHQGTKSSKCVRQKVEGSSSHLVTFTVLPLEIGLHNINFSLETWFGKEILVKTLRVVPEGVKRESYSGV TLDPRGIYGTISRRKEFPYRIPLDLVPKTEIKRILSVKGLLVGEILSAVLSQEGINILTHLPKGSAEAELMSVVPVFYVFHY LETGNHWNIFHSDPLIEKQKLKKKLKEGMLSIMSYRNADYSYSVWKGGSASTWLTAFALRVLGQVNKYVEQNQNSIC NSLLWLVENYLQLDNGRFKENSQYQPIKLQGTLPVEARENSLYLTAFTVIGIRKAFDICPLVKIDTALIKADNFLLENTLPA QSTFTLAISAYALSLGDKTHPQFRSIVSALKREALVKGNPPIYRFWKDNLQHKDSSVPNTGTARMVETTAYALLTSLNL KDINYVNPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLVKQLRLSMDIDVSYKHKGALHNYKMTDKNFLGRPVE VLLNDDLIVSTGFGSGLATVHVTTVVHKTSTSEEVCSFYLKIDTQDIEASHYRGYGNSDYKRIVACASYKPSREESSSG SSHAVMDISLPTGISANEEDLKALVEGVDQLFTDYQIKDGHVILQLNSIPSSDFLCVRFRIFELFEVGFLSPATFTVYEY HRPDKQCTMFYSTSNIKIQKVCEGAACKCVEADCGQMQEELDLTISAETRKQTACKPEIAYAYKVSITSITVENVFVKY KATLLDIYKTGEAVAEKDSEITFIKKVTCTNAELVKGRQYLIMGKEALQIKYNFSFRYIYPLDSLTWIEYWPRDTTCSSC QAFLANLDEFAEDIFLNGC
Cynomolgus Macaque (*Macaca fascicularis*)	297:MGLLGILCFLIFLGKTWGQEQTYVISAPKIFRVGASENIVIQVYGYTEAFDATISITSYPDKKFSYSSGHVHLSSENK FQNSAVLTIQPKQLPGGQNQVSYVYLEVVSKHFSKSKRIPITYDNGFLFIHTDKPVYTPDQSVKVRVYSLNDDLKPAK RETVLTFIDPEGSEIDMVEEIDHIGIISFPDFKIPSNPRYGMWTIQAKYKEDFSTTGTAFFEVKEYVLPHFSVSVEPESNF IGYKNFKNFEITIKARYFYNKVVTEADVYITFGIREDLKDDQKEMMQTAMQNTMLINGIAQVTFDSETAVKELSYYSLED

C5	LNNITLTAVTVIESTGGFSEEAEIFGIAVLSPVTLNLVATPLFLDPGIPVSIEVQVRDALDQLVGGVPVTLNAQTIDVN QETSDLEPARSVTRVDDGVASFVVNLPSGVTVLEFNVRTDAPDLFDENQAREGYRAIAYSSLSQSYLTIDWTDNHFA LLVGEVLNIIVTPLSPVIDRITHVNVLILSIGSHIIHFGTREILSDASVQSIIIPVTQNIMVFSSRLLVTVIVTGEQTAELVSDS VWLNIEEHCGNQLQVHLSPDADTVSPGQTVSLNMVTGMDSWVALTAVDSAVVGVQRFAKRLERVFQFLERSDLG CGAGGGLNNANVFHLAGLTFLTNANADDSQENDEPCREIIRPRRRMLQERIEEIAARVLHLVVRECCVDGVRINHDETC EQRAARISVGPRCVRAFTECCVVASQLRANNSHRDLQLGRLHMRTLLPVSRPEIRSVFPESWLWEVHLVPRRRQLQ FALPDSVTTWEIQGVGISNSGICVADTIRARVFRDVFLEMNIPYSVVRGEQVQLRGTVYNVFTSGMQFCVRMSAVEGI CTSESPVIDHQGTKSSKCVRQRVEGSSTIHLVTFTVLPLEIGLQNINFSLETSFGREILVRGLRVVPEGVRRESYSGITLD PPGNVGTISRRREFPYRIRLDLVPETEIRRILSVRGLLVGEILSAVLSREGINILTHLPEGSAEAELMSVVPVFVVFHVLET GNHWNIFHSDPLIEERNLEELLEGMVSIMSYRNADYSYSVWEGGSASTWLTAFALRVLGQVHRYVEQNQNSICNS LLWLVENYQLDNGSFREDSQYQPILQGTLPVEARENSLYLTAFTVIGIRKAFDICPLVRINTALIRADTFLLENTLPAQS TFTLAISAYALSLGDLTHPQFRSIVSALREEALVKGNPPIYRFWRDSLQHIDSSVPNTGTARMVETTAYALLTSLNLKD ITYVNPIIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLVKQLRLNMDIDVAYKHKGPLHNFKMTDKNFLGRPVEVLL NDDLVVSTGFGSGLATVHVTTVVHKTSTSEEVCSFYLKIDTQDIEASHYRGYGNSDYKRIVACASYKPSKEESSSGSS HAVMDISLPTGINANEEDLKALVEGVDQLFTDYQIKDGHVILQLNSIPSSDFLQVRFRIFELFEVGFLSPATFTVYEYHR PDKQCTMFYSTSNIKIQKVCEGATCKIIEADCGQMQKELDLTISAETRLSQTAGNFEIAYAYLVIITSITTENVFVKYTAT LLDIYKTGEAVAEKDSEITFIKKVTCTNAELVKGRQYLIMGKEALQIKYNFTFRYQYPLDSLTWIEYWPRDTTCSSCQAF LANLDEFAEDIFLNGC

Other antibodies of the invention include those where the amino acids or nucleic acids encoding the amino acids have been mutated, yet have at least 60, 70, 80, 90 or 95 percent identity to the sequences described in Table 1. In some embodiments, it include mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the variable regions when compared with the variable regions depicted in the sequence described in Table 1, while retaining substantially the same therapeutic activity.

Since each of these antibodies can bind to C5, the VH, VL, full length light chain, and full length heavy chain sequences (amino acid sequences and the nucleotide sequences encoding the amino acid sequences) can be "mixed and matched" to create other C5-binding antibodies of the invention. Such "mixed and matched" C5-binding antibodies can be tested using the binding assays known in the art (*e.g.*, ELISAs, and other assays described in the Example section). When these chains are mixed and matched, a VH sequence from a particular VH/VL pairing should be replaced with a structurally similar VH sequence. Likewise a full length heavy chain sequence from a particular full length heavy chain / full length light chain pairing should be replaced with a structurally similar full length heavy chain sequence. Likewise, a VL sequence from a particular VH/VL pairing should be replaced with a structurally similar VL sequence. Likewise a full length light chain sequence from a particular full length heavy chain / full length light chain pairing should be replaced with a structurally similar full length light chain sequence. Accordingly, in one aspect, the invention provides an isolated monoclonal antibody or antigen binding region thereof having: a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, and 281; and a light chain variable region comprising an

amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, and 289; wherein the antibody specifically binds to C5 (*e.g.*, human and/or cynomologus C5).

In another aspect, the invention provides (i) an isolated monoclonal antibody having: a full length heavy chain comprising an amino acid sequence that has been optimized for expression in the cell of a mammalian selected from the group consisting of SEQ ID NOs: 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, and 282; and a full length light chain comprising an amino acid sequence that has been optimized for expression in the cell of a mammalian selected from the group consisting of SEQ ID NOs: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, and 290; or (ii) a functional protein comprising an antigen binding portion thereof.

In another aspect, the present invention provides C5-binding antibodies that comprise the heavy chain and light chain CDR1s, CDR2s and CDR3s as described in Table 1, or combinations thereof. The amino acid sequences of the VH CDR1s of the antibodies are shown in SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235. The amino acid sequences of the VH CDR2s of the antibodies and are shown in SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236. The amino acid sequences of the VH CDR3s of the antibodies are shown in SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237. The amino acid sequences of the VL CDR1s of the antibodies are shown in SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238. The amino acid sequences of the VL CDR2s of the antibodies are shown in SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239. The amino acid sequences of the VL CDR3s of the antibodies are shown in SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240. The CDR regions are delineated using the Kabat system (Kabat, E. A., *et al.*, 1991 Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242).

Given that each of these antibodies can bind to C5 and that antigen-binding specificity is provided primarily by the CDR1, 2 and 3 regions, the VH CDR1, 2 and 3 sequences and VL CDR1, 2 and 3 sequences can be "mixed and matched" (*i.e.*, CDRs from different antibodies can be mixed and match, although each antibody must contain a VH CDR1, 2 and 3 and a VL CDR1, 2 and 3 to create other C5-binding binding molecules of the invention. Such "mixed and matched" C5-binding antibodies can be tested using the binding assays known in the art and those described in the Examples (*e.g.*, ELISAs). When VH CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VH sequence should be replaced with a structurally similar CDR sequence(s). Likewise, when VL CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3

sequence from a particular VL sequence should be replaced with a structurally similar CDR sequence(s). It will be readily apparent to the ordinarily skilled artisan that novel VH and VL sequences can be created by substituting one or more VH and/or VL CDR region sequences with structurally similar sequences from the CDR sequences shown herein for monoclonal antibodies of the present invention.

Accordingly, the present invention provides an isolated monoclonal antibody or antigen binding region thereof comprising a heavy chain variable region CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 17, 33, 81, 131, 145, 159, 173, 195, and 235; a heavy chain variable region CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236; a heavy chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237; a light chain variable region CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238; a light chain variable region CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239; and a light chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240; wherein the antibody specifically binds C5.

In a specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO:1; a heavy chain variable region CDR2 of SEQ ID NO: 2; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR1 of SEQ ID NO: 4; a light chain variable region CDR2 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 6. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR2 of SEQ ID NO: 18; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 22.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 33; a heavy chain variable region CDR2 of SEQ ID NO: 34; a heavy chain variable region CDR3 of SEQ ID NO: 35; a light chain variable region CDR1 of SEQ ID NO: 36; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 38. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR2 of SEQ ID NO: 49; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of

SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 50.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR2 of SEQ ID NO: 62; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 66. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR2 of SEQ ID NO: 77; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 78.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR2 of SEQ ID NO: 77; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 89. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR2 of SEQ ID NO: 62; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 89.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR2 of SEQ ID NO: 95; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 89. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR2 of SEQ ID NO: 49; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 101.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR2 of SEQ ID NO: 107; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO:

21; and a light chain variable region CDR3 of SEQ ID NO: 22. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR2 of SEQ ID NO: 107; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 101.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR2 of SEQ ID NO: 113; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 22. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR2 of SEQ ID NO: 113; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 101.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 119; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR1 of SEQ ID NO: 4; a light chain variable region CDR2 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 120. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 131; a heavy chain variable region CDR2 of SEQ ID NO: 132; a heavy chain variable region CDR3 of SEQ ID NO: 133; a light chain variable region CDR1 of SEQ ID NO: 134; a light chain variable region CDR2 of SEQ ID NO: 135; and a light chain variable region CDR3 of SEQ ID NO: 136.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 145; a heavy chain variable region CDR2 of SEQ ID NO: 146; a heavy chain variable region CDR3 of SEQ ID NO: 147; a light chain variable region CDR1 of SEQ ID NO: 148; a light chain variable region CDR2 of SEQ ID NO: 149; and a light chain variable region CDR3 of SEQ ID NO: 150. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 159; a heavy chain variable region CDR2 of SEQ ID NO: 160; a heavy chain variable region CDR3 of SEQ ID NO: 161; a light chain variable region CDR1 of SEQ ID NO: 162; a light chain variable region CDR2 of SEQ ID NO: 163; and a light chain variable region CDR3 of SEQ ID NO: 164.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 173; a heavy chain variable region CDR2 of SEQ ID NO: 174; a heavy chain variable region CDR3 of SEQ ID NO: 175; a light chain variable region CDR1 of SEQ ID NO: 176; a light chain variable region CDR2 of SEQ ID NO: 177; and a light chain variable region CDR3 of SEQ ID NO: 178. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 195; a heavy chain variable region CDR2 of SEQ ID NO: 196; a heavy chain variable region CDR3 of SEQ ID NO: 197; a light chain variable region CDR1 of SEQ ID NO: 198; a light chain variable region CDR2 of SEQ ID NO: 199; and a light chain variable region CDR3 of SEQ ID NO: 200.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR2 of SEQ ID NO: 77; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 209. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR2 of SEQ ID NO: 49; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 22.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 33; a heavy chain variable region CDR2 of SEQ ID NO: 226; a heavy chain variable region CDR3 of SEQ ID NO: 35; a light chain variable region CDR1 of SEQ ID NO: 36; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 38. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 235; a heavy chain variable region CDR2 of SEQ ID NO: 236; a heavy chain variable region CDR3 of SEQ ID NO: 237; a light chain variable region CDR1 of SEQ ID NO: 238; a light chain variable region CDR2 of SEQ ID NO: 239; and a light chain variable region CDR3 of SEQ ID NO: 240.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 119; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR1 of SEQ ID NO: 4; a light chain variable region CDR2 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 6. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 2; a heavy chain variable

region CDR3 of SEQ ID NO: 3; a light chain variable region CDR1 of SEQ ID NO: 4; a light chain variable region CDR2 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 120.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR2 of SEQ ID NO: 62; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 209. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR2 of SEQ ID NO: 95; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 209.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR2 of SEQ ID NO: 77; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 66. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR2 of SEQ ID NO: 77; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 78.

In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR2 of SEQ ID NO: 77; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 89. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR2 of SEQ ID NO: 107; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 22.

In certain embodiments, an antibody that specifically binds to C5 is an antibody that is described in Table 1.

As used herein, a human antibody comprises heavy or light chain variable regions or full length heavy or light chains that are "the product of" or "derived from" a particular germline sequence if the variable regions or full length chains of the antibody are obtained from a system that uses human germline immunoglobulin genes. Such systems include immunizing a transgenic mouse carrying human immunoglobulin genes with the antigen of interest or screening a human immunoglobulin gene library displayed on phage with the antigen of interest. A human antibody that is "the product of" or "derived from" a human germline immunoglobulin sequence can be identified as such by comparing the amino acid sequence of the human antibody to the amino acid sequences of human germline immunoglobulins and selecting the human germline immunoglobulin sequence that is closest in sequence (*i.e.*, greatest % identity) to the sequence of the human antibody. A human antibody that is "the product of" or "derived from" a particular human germline immunoglobulin sequence may contain amino acid differences as compared to the germline sequence, due to, for example, naturally occurring somatic mutations or intentional introduction of site-directed mutations. However, in the VH or VL framework regions, a selected human antibody typically is at least 90% identical in amino acids sequence to an amino acid sequence encoded by a human germline immunoglobulin gene and contains amino acid residues that identify the human antibody as being human when compared to the germline immunoglobulin amino acid sequences of other species (*e.g.*, murine germline sequences). In certain cases, a human antibody may be at least 60%, 70%, 80%, 90%, or at least 95%, or even at least 96%, 97%, 98%, or 99% identical in amino acid sequence to the amino acid sequence encoded by the germline immunoglobulin gene. Typically, a recombinant human antibody will display no more than 10 amino acid differences from the amino acid sequence encoded by the human germline immunoglobulin gene in the VH or VL framework regions. In certain cases, the human antibody may display no more than 5, or even no more than 4, 3, 2, or 1 amino acid difference from the amino acid sequence encoded by the germline immunoglobulin gene.

Homologous antibodies

In yet another embodiment, the present invention provides an antibody or an antigen-binding fragment thereof comprising amino acid sequences that are homologous to the sequences described in Table 1, and said antibody binds to a C5 protein (*e.g.*, human and/or cynomologus C5), and retains the desired functional properties of those antibodies described in Table 1.

For example, the invention provides an isolated monoclonal antibody (or a functional antigen binding fragment thereof) comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence that is at least 80%, at least 90%, or at lest 95% identical to an amino acid sequence

selected from the group consisting of SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281; the light chain variable region comprises an amino acid sequence that is at least 80%, at least 90%, or at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 226, 242, 261, 265, 269, 285, or 289; the antibody specifically binds to C5 (*e.g.*, human and/or cynomologus C5), and the antibody can inhibit red blood cell lysis in a hemolytic assay. In a specific example, such antibodies have an IC_{50} value in a hemolytic assay of 20-200 pM when using human C5-depleted serum that is reconstituted with 100 pM human C5.

In other embodiments, the VH and/or VL amino acid sequences may be 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the sequences set forth in Table 1. In other embodiments, the VH and/or VL amino acid sequences may be identical except an amino acid substitution in no more than 1,2,3,4 or 5 amino acid position. An antibody having VH and VL regions having high (*i. e.*, 80% or greater) identity to the VH and VL regions of those described in Table 1 can be obtained by mutagenesis (*e.g.*, site-directed or PCR-mediated mutagenesis) of nucleic acid molecules encoding SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281; and 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, or 289 respectively, followed by testing of the encoded altered antibody for retained function using the functional assays described herein.

In other embodiments, the full length heavy chain and/or full length light chain amino acid sequences may be 50% 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the sequences set forth in Table 1. An antibody having a full length heavy chain and full length light chain having high (*i.e.*, 80% or greater) identity to the full length heavy chains of any of SEQ ID NOs : 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, and 282 and full length light chains of any of SEQ ID NOs 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, and 290 respectively, can be obtained by mutagenesis (*e.g.*, site-directed or PCR-mediated mutagenesis) of nucleic acid molecules encoding such polypeptides respectively, followed by testing of the encoded altered antibody for retained function using the functional assays described herein.

In other embodiments, the full length heavy chain and/or full length light chain nucleotide sequences may be 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the sequences set forth above.

In other embodiments, the variable regions of heavy chain and/or light chain nucleotide sequences may be 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the sequences set forth above

As used herein, the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity equals number of identical positions/total number of positions x 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

Additionally or alternatively, the protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identify related sequences. For example, such searches can be performed using the BLAST program (version 2.0) of Altschul, *et al.*, 1990 J.Mol. Biol. 215:403-10.

Antibodies with Conservative Modifications

In certain embodiments, an antibody of the invention has a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein one or more of these CDR sequences have specified amino acid sequences based on the antibodies described herein or conservative modifications thereof, and wherein the antibodies retain the desired functional properties of the C5-binding antibodies of the invention. Accordingly, the invention provides an isolated monoclonal antibody, or a functional antigen binding fragment thereof, consisting of a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein: the heavy chain variable region CDR1 amino acid sequences are selected from the group consisting of SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235, and conservative modifications thereof; the heavy chain variable region CDR2 amino acid sequences are selected from the group consisting of SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236, and conservative modifications thereof; the heavy chain variable region CDR3 amino acid sequences are selected from the group consisting of SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237, and conservative modifications thereof; the light chain variable regions CDR1 amino acid sequences are selected from the group consisting of SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238, and conservative modifications thereof; the light chain variable regions CDR2 amino acid sequences are selected from the group consisting of SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239, and conservative modifications thereof; the light chain

variable regions of CDR3 amino acid sequences are selected from the group consisting of SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240, and conservative modifications thereof; the antibody or the antigen-bindign fragment thereof specifically binds to C5, and inhibits red blood cell lysis in a hemolytic assay as described herein.

In other embodiments, an antibody of the invention optimized for expression in a mammalian cell has a full length heavy chain sequence and a full length light chain sequence, wherein one or more of these sequences have specified amino acid sequences based on the antibodies described herein or conservative modifications thereof, and wherein the antibodies retain the desired functional properties of the C5-binding antibodies of the invention. Accordingly, the invention provides an isolated monoclonal antibody optimized for expression in a mammalian cell consisting of a full length heavy chain and a full length light chain wherein: the full length heavy chain has amino acid sequences selected from the group of SEQ ID NOs: : 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, and 282, and conservative modifications thereof; and the full length light chain has amino acid sequences selected from the group of SEQ ID NOs: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, and 290, and conservative modifications thereof; the antibody specifically binds to C5 (*e.g.*, human and/or cynomologus C5); and the antibody inhibits red blood cell lysis in a hemolytic assay as described herein. In a specific embodiment, such antibodies have an IC_{50} value in a hemolytic assay of 20-200 pM when using human C5-depleted serum that is reconstituted with 100 pM human C5.

Antibodies That Bind to the Same Epitope

The present invention provides antibodies that bind to the same epitope as do the C5-binding antibodies described in Table 1. Additional antibodies can therefore be identified based on their ability to cross-compete (*e.g.*, to competitively inhibit the binding of, in a statistically significant manner) with other antibodies of the invention in C5 binding assays. The ability of a test antibody to inhibit the binding of antibodies of the present invention to a C5 protein (*e.g.*, human and/or cynomolgus C5) demonstrates that the test antibody can compete with that antibody for binding to C5; such an antibody may, according to non-limiting theory, bind to the same or a related (*e.g.*, a structurally similar or spatially proximal) epitope on the C5 protein as the antibody with which it competes. In a certain embodiment, the antibody that binds to the same epitope on C5 as the antibodies of the present invention is a human monoclonal antibody. Such human monoclonal antibodies can be prepared and isolated as described herein.

Engineered and Modified Antibodies

An antibody of the invention further can be prepared using an antibody having one or more of the VH and/or VL sequences shown herein as starting material to engineer a modified antibody, which modified antibody may have altered properties from the starting antibody. An antibody can be engineered by modifying one or more residues within one or both variable regions (*i. e.*, VH and/or VL), for example within one or more CDR regions and/or within one or more framework regions. Additionally or alternatively, an antibody can be engineered by modifying residues within the constant region(s), for example to alter the effector function(s) of the antibody.

One type of variable region engineering that can be performed is CDR grafting. Antibodies interact with target antigens predominantly through amino acid residues that are located in the six heavy and light chain complementarity determining regions (CDRs). For this reason, the amino acid sequences within CDRs are more diverse between individual antibodies than sequences outside of CDRs. Because CDR sequences are responsible for most antibody-antigen interactions, it is possible to express recombinant antibodies that mimic the properties of specific naturally occurring antibodies by constructing expression vectors that include CDR sequences from the specific naturally occurring antibody grafted onto framework sequences from a different antibody with different properties (see, *e.g.*, Riechmann, L. *et al.*, 1998 Nature 332:323-327; Jones, P. *et al.*, 1986 Nature 321:522-525; Queen, C. *et al.*, 1989 Proc. Natl. Acad., U.S.A. 86:10029-10033; U.S. Patent No. 5,225,539 to Winter, and U.S. Patent Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen *et al.*)

Accordingly, another embodiment of the invention pertains to an isolated monoclonal antibody, or an antigen binding fragment thereof, comprising a heavy chain variable region comprising CDR1 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 17, 33, 81, 131, 145, 159, 173, 195, and 235; CDR2 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236; CDR3 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237, respectively; and a light chain variable region having CDR1 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238; CDR2 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239; and CDR3 sequences consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240, respectively. Thus, such antibodies contain the VH and VL CDR sequences of monoclonal antibodies, yet may contain different framework sequences from these antibodies.

Such framework sequences can be obtained from public DNA databases or published references that include germline antibody gene sequences. For example, germline DNA sequences for human heavy and light chain variable region genes can be found in the "VBase" human germline sequence database (available on the Internet at www.mrc-cpe.cam.ac.uk/vbase), as well as in Kabat, E. A., *et al.*, 1991 Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Tomlinson, I. M., *et al.*, 1992 J. fol. Biol. 227:776-798; and Cox, J. P. L. *et al.*, 1994 Eur. J Immunol. 24:827-836; the contents of each of which are expressly incorporated herein by reference.

An example of framework sequences for use in the antibodies of the invention are those that are structurally similar to the framework sequences used by selected antibodies of the invention, *e.g.*, consensus sequences and/or framework sequences used by monoclonal antibodies of the invention. The VH CDR1, 2 and 3 sequences, and the VL CDR1, 2 and 3 sequences, can be grafted onto framework regions that have the identical sequence as that found in the germline immunoglobulin gene from which the framework sequence derive, or the CDR sequences can be grafted onto framework regions that contain one or more mutations as compared to the germline sequences. For example, it has been found that in certain instances it is beneficial to mutate residues within the framework regions to maintain or enhance the antigen binding ability of the antibody (see *e.g.*, U.S. Patent Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen et al).

Another type of variable region modification is to mutate amino acid residues within the VH and/or VL CDR1, CDR2 and/or CDR3 regions to thereby improve one or more binding properties (*e.g.*, affinity) of the antibody of interest, known as "affinity maturation." Site-directed mutagenesis or PCR-mediated mutagenesis can be performed to introduce the mutation(s) and the effect on antibody binding, or other functional property of interest, can be evaluated in *in vitro* or *in vivo* assays as described herein and provided in the Examples. Conservative modifications (as discussed above) can be introduced. The mutations may be amino acid substitutions, additions or deletions. Moreover, typically no more than one, two, three, four or five residues within a CDR region are altered.

Accordingly, in another embodiment, the invention provides isolated C5-binding monoclonal antibodies, or an antigen binding fragment thereof, consisting of a heavy chain variable region having: a VH CDR1 region consisting of an amino acid sequence selected from the group having SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235 or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235; a VH CDR2 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236, or

an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236; a VH CDR3 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237; a VL CDR1 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238; a VL CDR2 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239; and a VL CDR3 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240.

Grafting Antigen-binding Domains Into Alternative Frameworks or Scaffolds

A wide variety of antibody/ immunoglobulin frameworks or scaffolds can be employed so long as the resulting polypeptide includes at least one binding region which specifically binds to C5. Such frameworks or scaffolds include the 5 main idiotypes of human immunoglobulins, or fragments thereof, and include immunoglobulins of other animal species, preferably having humanized aspects. Single heavy-chain antibodies such as those identified in camelids are of particular interest in this regard. Novel frameworks, scaffolds and fragments continue to be discovered and developed by those skilled in the art.

In one aspect, the invention pertains to generating non-immunoglobulin based antibodies using non- immunoglobulin scaffolds onto which CDRs of the invention can be grafted. Known or future non-immunoglobulin frameworks and scaffolds may be employed, as long as they comprise a binding region specific for the target C5 protein (*e.g.*, human and/or cynomolgus C5). Known non-immunoglobulin frameworks or scaffolds include, but are not limited to, fibronectin (Compound Therapeutics, Inc., Waltham, MA), ankyrin (Molecular Partners AG, Zurich, Switzerland), domain antibodies (Domantis, Ltd., Cambridge, MA, and Ablynx nv, Zwijnaarde, Belgium), lipocalin (Pieris Proteolab AG, Freising, Germany), small modular immuno-pharmaceuticals (Trubion Pharmaceuticals Inc.,

Seattle, WA), maxybodies (Avidia, Inc., Mountain View, CA), Protein A (Affibody AG, Sweden), and affilin (gamma-crystallin or ubiquitin) (Scil Proteins GmbH, Halle, Germany).

The fibronectin scaffolds are based on fibronectin type III domain (*e.g.*, the tenth module of the fibronectin type III (10 Fn3 domain)). The fibronectin type III domain has 7 or 8 beta strands which are distributed between two beta sheets, which themselves pack against each other to form the core of the protein, and further containing loops (analogous to CDRs) which connect the beta strands to each other and are solvent exposed. There are at least three such loops at each edge of the beta sheet sandwich, where the edge is the boundary of the protein perpendicular to the direction of the beta strands (see US 6,818,418). These fibronectin-based scaffolds are not an immunoglobulin, although the overall fold is closely related to that of the smallest functional antibody fragment, the variable region of the heavy chain, which comprises the entire antigen recognition unit in camel and llama IgG. Because of this structure, the non-immunoglobulin antibody mimics antigen binding properties that are similar in nature and affinity to those of antibodies. These scaffolds can be used in a loop randomization and shuffling strategy *in vitro* that is similar to the process of affinity maturation of antibodies *in vivo*. These fibronectin-based molecules can be used as scaffolds where the loop regions of the molecule can be replaced with CDRs of the invention using standard cloning techniques.

The ankyrin technology is based on using proteins with ankyrin derived repeat modules as scaffolds for bearing variable regions which can be used for binding to different targets. The ankyrin repeat module is a 33 amino acid polypeptide consisting of two anti-parallel α-helices and a β-turn. Binding of the variable regions is mostly optimized by using ribosome display.

Avimers are derived from natural A-domain containing protein such as LRP-1. These domains are used by nature for protein-protein interactions and in human over 250 proteins are structurally based on A-domains. Avimers consist of a number of different "A-domain" monomers (2-10) linked via amino acid linkers. Avimers can be created that can bind to the target antigen using the methodology described in, for example, U.S. Patent Application Publication Nos. 20040175756; 20050053973; 20050048512; and 20060008844.

Affibody affinity ligands are small, simple proteins composed of a three-helix bundle based on the scaffold of one of the IgG-binding domains of Protein A. Protein A is a surface protein from the bacterium Staphylococcus aureus. This scaffold domain consists of 58 amino acids, 13 of which are randomized to generate affibody libraries with a large number of ligand variants (See *e.g.*, US 5,831,012). Affibody molecules mimic antibodies, they have a molecular weight of 6 kDa, compared to the molecular weight of antibodies, which is 150

kDa. In spite of its small size, the binding site of affibody molecules is similar to that of an antibody.

Anticalins are products developed by the company Pieris ProteoLab AG. They are derived from lipocalins, a widespread group of small and robust proteins that are usually involved in the physiological transport or storage of chemically sensitive or insoluble compounds. Several natural lipocalins occur in human tissues or body liquids. The protein architecture is reminiscent of immunoglobulins, with hypervariable loops on top of a rigid framework. However, in contrast with antibodies or their recombinant fragments, lipocalins are composed of a single polypeptide chain with 160 to 180 amino acid residues, being just marginally bigger than a single immunoglobulin domain. The set of four loops, which makes up the binding pocket, shows pronounced structural plasticity and tolerates a variety of side chains. The binding site can thus be reshaped in a proprietary process in order to recognize prescribed target molecules of different shape with high affinity and specificity. One protein of lipocalin family, the bilin-binding protein (BBP) of Pieris Brassicae has been used to develop anticalins by mutagenizing the set of four loops. One example of a patent application describing anticalins is in PCT Publication No. WO 199916873.

Affilin molecules are small non-immunoglobulin proteins which are designed for specific affinities towards proteins and small molecules. New affilin molecules can be very quickly selected from two libraries, each of which is based on a different human derived scaffold protein. Affilin molecules do not show any structural homology to immunoglobulin proteins. Currently, two affilin scaffolds are employed, one of which is gamma crystalline, a human structural eye lens protein and the other is "ubiquitin" superfamily proteins. Both human scaffolds are very small, show high temperature stability and are almost resistant to pH changes and denaturing agents. This high stability is mainly due to the expanded beta sheet structure of the proteins. Examples of gamma crystalline derived proteins are described in WO200104144 and examples of "ubiquitin-like" proteins are described in WO2004106368.

Protein epitope mimetics (PEM) are medium-sized, cyclic, peptide-like molecules (MW 1-2kDa) mimicking beta-hairpin secondary structures of proteins, the major secondary structure involved in protein-protein interactions.

In some embodiments, the Fabs are converted to silent IgG1 format by changing the Fc region. For example, antibodies 6525-7910 in Table 1 can be converted to silent IgG1 formate by substituting the "X" in the amino acid sequences for the heavy chain with:

CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG

QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 293)

and substituting the "X" in the amino acid sequence for the light chain with: CS if the light chain is lambda, or C if the light chain is kappa. As used herein, a "silent IgG1" is an IgG1 Fc sequence in which the amino acid sequence has been altered to reduce Fc-mediated effector functions (for example ADCC and/or CDC). Such an antibody will typically have reduced binding to Fc receptors and/or C1q.

In some other embodiments, the Fabs are converted to IgG2 format. For example, antibodies 6525-7910 in Table 1 can be converted to IgG2 format by substituting the constant sequence

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (SEQ ID NO: 294)

with the constant sequence for the heavy chain of IgG2:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVV
SVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFS
CSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 295)

and substituting the "X" in the amino acid sequence for the light chain with CS if the light chain is lambda, or C if the light chain is kappa.

Human or humanized antibodies

The present invention provides fully human antibodies that specifically bind to a C5 protein (*e.g.*, human and/or cynomolgus C5). Compared to the chimeric or humanized antibodies, the human C5-binding antibodies of the invention have further reduced antigenicity when administered to human subjects.

The human C5-binding antibodies can be generated using methods that are known in the art. For example, the humaneering technology used to converting non-human antibodies into engineered human antibodies. U.S. Patent Publication No. 20050008625 describes an *in vivo* method for replacing a nonhuman antibody variable region with a human variable region in an antibody while maintaining the same or providing better binding characteristics relative to that of the nonhuman antibody. The method relies on epitope guided replacement of variable regions of a non-human reference antibody with a fully human antibody. The resulting human antibody is generally unrelated structurally to the reference nonhuman antibody, but binds to the same epitope on the same antigen as the reference antibody.

Briefly, the serial epitope-guided complementarity replacement approach is enabled by setting up a competition in cells between a "competitor" and a library of diverse hybrids of the reference antibody ("test antibodies") for binding to limiting amounts of antigen in the presence of a reporter system which responds to the binding of test antibody to antigen. The competitor can be the reference antibody or derivative thereof such as a single-chain Fv fragment. The competitor can also be a natural or artificial ligand of the antigen which binds to the same epitope as the reference antibody. The only requirements of the competitor are that it binds to the same epitope as the reference antibody, and that it competes with the reference antibody for antigen binding. The test antibodies have one antigen-binding V-region in common from the nonhuman reference antibody, and the other V-region selected at random from a diverse source such as a repertoire library of human antibodies. The common V-region from the reference antibody serves as a guide, positioning the test antibodies on the same epitope on the antigen, and in the same orientation, so that selection is biased toward the highest antigen-binding fidelity to the reference antibody.

Many types of reporter system can be used to detect desired interactions between test antibodies and antigen. For example, complementing reporter fragments may be linked to antigen and test antibody, respectively, so that reporter activation by fragment complementation only occurs when the test antibody binds to the antigen. When the test antibody- and antigen-reporter fragment fusions are co-expressed with a competitor, reporter activation becomes dependent on the ability of the test antibody to compete with the competitor, which is proportional to the affinity of the test antibody for the antigen. Other reporter systems that can be used include the reactivator of an auto-inhibited reporter reactivation system (RAIR) as disclosed in U.S. Patent Application Ser. No. 10/208,730 (Publication No. 20030198971), or competitive activation system disclosed in U.S. Patent Application Ser. No. 10/076,845 (Publication No. 20030157579).

With the serial epitope-guided complementarity replacement system, selection is made to identify cells expresses a single test antibody along with the competitor, antigen, and reporter components. In these cells, each test antibody competes one-on-one with the competitor for binding to a limiting amount of antigen. Activity of the reporter is proportional to the amount of antigen bound to the test antibody, which in turn is proportional to the affinity of the test antibody for the antigen and the stability of the test antibody. Test antibodies are initially selected on the basis of their activity relative to that of the reference antibody when expressed as the test antibody. The result of the first round of selection is a set of "hybrid" antibodies, each of which is comprised of the same non-human V-region from the reference antibody and a human V-region from the library, and each of which binds to the same epitope on the antigen as the reference antibody. One of more of the hybrid antibodies

selected in the first round will have an affinity for the antigen comparable to or higher than that of the reference antibody.

In the second V-region replacement step, the human V-regions selected in the first step are used as guide for the selection of human replacements for the remaining non-human reference antibody V-region with a diverse library of cognate human V-regions. The hybrid antibodies selected in the first round may also be used as competitors for the second round of selection. The result of the second round of selection is a set of fully human antibodies which differ structurally from the reference antibody, but which compete with the reference antibody for binding to the same antigen. Some of the selected human antibodies bind to the same epitope on the same antigen as the reference antibody. Among these selected human antibodies, one or more binds to the same epitope with an affinity which is comparable to or higher than that of the reference antibody.

Using one of the mouse or chimeric C5-binding antibodies described above as the reference antibody, this method can be readily employed to generate human antibodies that bind to human C5 with the same binding specificity and the same or better binding affinity. In addition, such human C5-binding antibodies can also be commercially obtained from companies which customarily produce human antibodies, *e.g.*, KaloBios, Inc. (Mountain View, CA).

Camelid antibodies

Antibody proteins obtained from members of the camel and dromedary (Camelus bactrianus and Calelus dromaderius) family including new world members such as llama species (Lama paccos, Lama glama and Lama vicugna) have been characterized with respect to size, structural complexity and antigenicity for human subjects. Certain IgG antibodies from this family of mammals as found in nature lack light chains, and are thus structurally distinct from the typical four chain quaternary structure having two heavy and two light chains, for antibodies from other animals. See PCT/EP93/02214 (WO 94/04678 published 3 March 1994).

A region of the camelid antibody which is the small single variable domain identified as VHH can be obtained by genetic engineering to yield a small protein having high affinity for a target, resulting in a low molecular weight antibody-derived protein known as a "camelid nanobody". See U.S. patent number 5,759,808 issued June 2, 1998; see also Stijlemans, B. *et al.*, 2004 J Biol Chem 279: 1256-1261; Dumoulin, M. *et al.*, 2003 Nature 424: 783-788; Pleschberger, M. *et al.* 2003 Bioconjugate Chem 14: 440-448; Cortez-Retamozo, V. *et al.* 2002 Int J Cancer 89: 456-62; and Lauwereys, M. *et al.* 1998 EMBO J 17: 3512-3520. Engineered libraries of camelid antibodies and antibody fragments are commercially available, for example, from Ablynx, Ghent, Belgium. As with other antibodies of non-human

origin, an amino acid sequence of a camelid antibody can be altered recombinantly to obtain a sequence that more closely resembles a human sequence, *i.e.*, the nanobody can be "humanized". Thus the natural low antigenicity of camelid antibodies to humans can be further reduced.

The camelid nanobody has a molecular weight approximately one-tenth that of a human IgG molecule, and the protein has a physical diameter of only a few nanometers. One consequence of the small size is the ability of camelid nanobodies to bind to antigenic sites that are functionally invisible to larger antibody proteins, *i.e.*, camelid nanobodies are useful as reagents detect antigens that are otherwise cryptic using classical immunological techniques, and as possible therapeutic agents. Thus yet another consequence of small size is that a camelid nanobody can inhibit as a result of binding to a specific site in a groove or narrow cleft of a target protein, and hence can serve in a capacity that more closely resembles the function of a classical low molecular weight drug than that of a classical antibody.

The low molecular weight and compact size further result in camelid nanobodies being extremely thermostable, stable to extreme pH and to proteolytic digestion, and poorly antigenic. Another consequence is that camelid nanobodies readily move from the circulatory system into tissues, and even cross the blood-brain barrier and can treat disorders that affect nervous tissue. Nanobodies can further facilitated drug transport across the blood brain barrier. See U.S. patent application 20040161738 published August 19, 2004. These features combined with the low antigenicity to humans indicate great therapeutic potential. Further, these molecules can be fully expressed in prokaryotic cells such as E. coli and are expressed as fusion proteins with bacteriophage and are functional.

Accordingly, a feature of the present invention is a camelid antibody or nanobody having high affinity for C5. In certain embodiments herein, the camelid antibody or nanobody is naturally produced in the camelid animal, *i.e.*, is produced by the camelid following immunization with C5 or a peptide fragment thereof, using techniques described herein for other antibodies. Alternatively, the C5-binding camelid nanobody is engineered, *i.e.*, produced by selection for example from a library of phage displaying appropriately mutagenized camelid nanobody proteins using panning procedures with C5 as a target as described in the examples herein. Engineered nanobodies can further be customized by genetic engineering to have a half life in a recipient subject of from 45 minutes to two weeks. In a specific embodiment, the camelid antibody or nanobody is obtained by grafting the CDRs sequences of the heavy or light chain of the human antibodies of the invention into nanobody or single domain antibody framework sequences, as described for example in PCT/EP93/02214.

Bispecific Molecules and Multivalent Antibodies

In another aspect, the present invention features bispecific or multispecific molecules comprising an C5-binding antibody, or a fragment thereof, of the invention. An antibody of the invention, or antigen-binding regions thereof, can be derivatized or linked to another functional molecule, *e.g.*, another peptide or protein (*e.g.*, another antibody or ligand for a receptor) to generate a bispecific molecule that binds to at least two different binding sites or target molecules. The antibody of the invention may in fact be derivatized or linked to more than one other functional molecule to generate multi-specific molecules that bind to more than two different binding sites and/or target molecules; such multi-specific molecules are also intended to be encompassed by the term "bispecific molecule" as used herein. To create a bispecific molecule of the invention, an antibody of the invention can be functionally linked (*e.g.*, by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other binding molecules, such as another antibody, antibody fragment, peptide or binding mimetic, such that a bispecific molecule results.

Accordingly, the present invention includes bispecific molecules comprising at least one first binding specificity for C5 and a second binding specificity for a second target epitope. For example, the second target epitope is another epitope of C5 different from the first target epitope.

Additionally, for the invention in which the bispecific molecule is multi-specific, the molecule can further include a third binding specificity, in addition to the first and second target epitope.

In one embodiment, the bispecific molecules of the invention comprise as a binding specificity at least one antibody, or an antibody fragment thereof, including, *e.g.*, an Fab, Fab', F(ab')2, Fv, or a single chain Fv. The antibody may also be a light chain or heavy chain dimer, or any minimal fragment thereof such as a Fv or a single chain construct as described in Ladner *et al.* U.S. Patent No. 4,946,778.

Diabodies are bivalent, bispecific molecules in which VH and VL domains are expressed on a single polypeptide chain, connected by a linker that is too short to allow for pairing between the two domains on the same chain. The VH and VL domains pair with complementary domains of another chain, thereby creating two antigen binding sites (see e.g., Holliger *et al.*, 1993 Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak *et al.*, 1994 Structure 2:1121-1123). Diabodies can be produced by expressing two polypeptide chains with either the structure VHA-VLB and VHB-VLA (VH-VL configuration), or VLA-VHB and VLB-VHA (VL-VH configuration) within the same cell. Most of them can be expressed in soluble form in bacteria. Single chain diabodies (scDb) are produced by connecting the two diabody-forming polypeptide chains with linker of approximately 15 amino acid residues (see

Holliger and Winter, 1997 Cancer Immunol. Immunother., 45(3-4):128-30; Wu *et al.*, 1996 Immunotechnology, 2(1):21-36). scDb can be expressed in bacteria in soluble, active monomeric form (see Holliger and Winter, 1997 Cancer Immunol. Immunother., 45(34): 128-30; Wu *et al.*, 1996 Immunotechnology, 2(1):21-36; Pluckthun and Pack, 1997 Immunotechnology, 3(2): 83-105; Ridgway *et al.*, 1996 Protein Eng., 9(7):617-21). A diabody can be fused to Fc to generate a "di-diabody" (see Lu *et al.*, 2004 J. Biol. Chem., 279(4):2856-65).

Other antibodies which can be employed in the bispecific molecules of the invention are murine, chimeric and humanized monoclonal antibodies.

The bispecific molecules of the present invention can be prepared by conjugating the constituent binding specificities, using methods known in the art. For example, each binding specificity of the bispecific molecule can be generated separately and then conjugated to one another. When the binding specificities are proteins or peptides, a variety of coupling or cross-linking agents can be used for covalent conjugation. Examples of cross-linking agents include protein A, carbodiimide, N-succinimidyl-S-acetyl-thioacetate (SATA), 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), o-phenylenedimaleimide (oPDM), N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), and sulfosuccinimidyl 4-(N-maleimidomethyl) cyclohaxane-l-carboxylate (sulfo-SMCC) (see *e.g.*, Karpovsky *et al.*, 1984 J. Exp. Med. 160:1686; Liu, MA *et al.*, 1985 Proc. Natl. Acad. Sci. USA 82:8648). Other methods include those described in Paulus, 1985 Behring Ins. Mitt. No. 78,118-132; Brennan *et al.*, 1985 Science 229:81-83), and Glennie *et al.*, 1987 J. Immunol. 139: 2367-2375). Conjugating agents are SATA and sulfo-SMCC, both available from Pierce Chemical Co. (Rockford, IL).

When the binding specificities are antibodies, they can be conjugated by sulfhydryl bonding of the C-terminus hinge regions of the two heavy chains. In a particularly embodiment, the hinge region is modified to contain an odd number of sulfhydryl residues, for example one, prior to conjugation.

Alternatively, both binding specificities can be encoded in the same vector and expressed and assembled in the same host cell. This method is particularly useful where the bispecific molecule is a mAb x mAb, mAb x Fab, Fab x F(ab')2 or ligand x Fab fusion protein. A bispecific molecule of the invention can be a single chain molecule comprising one single chain antibody and a binding determinant, or a single chain bispecific molecule comprising two binding determinants. Bispecific molecules may comprise at least two single chain molecules. Methods for preparing bispecific molecules are described for example in U.S. Patent Number 5,260,203; U.S. Patent Number 5,455,030; U.S. Patent Number 4,881,175; U.S. Patent Number 5,132,405; U.S. Patent Number 5,091,513; U.S. Patent Number

5,476,786; U.S. Patent Number 5,013,653; U.S. Patent Number 5,258,498; and U.S. Patent Number 5,482,858.

Binding of the bispecific molecules to their specific targets can be confirmed by, for example, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (REA), FACS analysis, bioassay (*e.g.*, growth inhibition), or Western Blot assay. Each of these assays generally detects the presence of protein-antibody complexes of particular interest by employing a labeled reagent (*e.g.*, an antibody) specific for the complex of interest.

In another aspect, the present invention provides multivalent compounds comprising at least two identical or different antigen-binding portions of the antibodies of the invention binding to C5. The antigen-binding portions can be linked together via protein fusion or covalent or non covalent linkage. Alternatively, methods of linkage has been described for the bispecific molecules. Tetravalent compounds can be obtained for example by cross-linking antibodies of the antibodies of the invention with an antibody that binds to the constant regions of the antibodies of the invention, for example the Fc or hinge region.

Trimerizing domain are described for example in Borean patent EP 1 012 280B1. Pentamerizing modules are described for example in PCT/EP97/05897.

Antibodies with Extended Half Life

The present invention provides for antibodies that specifically bind to C5 protein which have an extended half-life *in vivo*.

Many factors may affect a protein's half life *in vivo*. For examples, kidney filtration, metabolism in the liver, degradation by proteolytic enzymes (proteases), and immunogenic responses (*e.g.*, protein neutralization by antibodies and uptake by macrophages and dentritic cells). A variety of strategies can be used to extend the half life of the antibodies of the present invention. For example, by chemical linkage to polyethyleneglycol (PEG), reCODE PEG, antibody scaffold, polysialic acid (PSA), hydroxyethyl starch (HES), albumin-binding ligands, and carbohydrate shields; by genetic fusion to proteins binding to serum proteins, such as albumin, IgG, FcRn, and transferring; by coupling (genetically or chemically) to other binding moieties that bind to serum proteins, such as nanobodies, Fabs, DARPins, avimers, affibodies, and anticalins; by genetic fusion to rPEG, albumin, domain of albumin, albumin-binding proteins, and Fc; or by incorporation into nancarriers, slow release formulations, or medical devices.

To prolong the serum circulation of antibodies *in vivo*, inert polymer molecules such as high molecular weight PEG can be attached to the antibodies or a fragment thereof with or without a multifunctional linker either through site-specific conjugation of the PEG to the N- or C-terminus of the antibodies or via epsilon-amino groups present on lysine residues. To

pegylate an antibody, the antibody, or fragment thereof, typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. The pegylation can be carried out by an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C1-C10) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. In certain embodiments, the antibody to be pegylated is an aglycosylated antibody. Linear or branched polymer derivatization that results in minimal loss of biological activity will be used. The degree of conjugation can be closely monitored by SDS-PAGE and mass spectrometry to ensure proper conjugation of PEG molecules to the antibodies. Unreacted PEG can be separated from antibody-PEG conjugates by size-exclusion or by ion-exchange chromatography. PEG-derivatized antibodies can be tested for binding activity as well as for *in vivo* efficacy using methods well-known to those of skill in the art, for example, by immunoassays described herein. Methods for pegylating proteins are known in the art and can be applied to the antibodies of the invention. See for example, EP 0 154 316 by Nishimura *et al.* and EP 0 401 384 by Ishikawa *et al.*

Other modified pegylation technologies include reconstituting chemically orthogonal directed engineering technology (ReCODE PEG), which incorporates chemically specified side chains into biosynthetic proteins via a reconstituted system that includes tRNA synthetase and tRNA. This technology enables incorporation of more than 30 new amino acids into biosynthetic proteins in E.coli, yeast, and mammalian cells. The tRNA incorporates a nonnative amino acid any place an amber codon is positioned, converting the amber from a stop codon to one that signals incorporation of the chemically specified amino acid.

Recombinant pegylation technology (rPEG) can also be used for serum halflife extension. This technology involves genetically fusing a 300-600 amino acid unstructured protein tail to an existing pharmaceutical protein. Because the apparent molecular weight of such an unstructured protein chain is about 15-fold larger than its actual molecular weight, the serum halflife of the protein is greatly increased. In contrast to traditional PEGylation, which requires chemical conjugation and repurification, the manufacturing process is greatly simplified and the product is homogeneous.

Polysialytion is another technology, which uses the natural polymer polysialic acid (PSA) to prolong the active life and improve the stability of therapeutic peptides and proteins. PSA is a polymer of sialic acid (a sugar). When used for protein and therapeutic peptide drug delivery, polysialic acid provides a protective microenvironment on conjugation. This increases the active life of the therapeutic protein in the circulation and prevents it from being

recognized by the immune system. The PSA polymer is naturally found in the human body. It was adopted by certain bacteria which evolved over millions of years to coat their walls with it. These naturally polysialylated bacteria were then able, by virtue of molecular mimicry, to foil the body's defence system. PSA, nature's ultimate stealth technology, can be easily produced from such bacteria in large quantities and with predetermined physical characteristics. Bacterial PSA is completely non-immunogenic, even when coupled to proteins, as it is chemically identical to PSA in the human body.

Another technology include the use of hydroxyethyl starch ("HES") derivatives linked to antibodies. HES is a modified natural polymer derived from waxy maize starch and can be metabolized by the body's enzymes. HES solutions are usually administered to substitute deficient blood volume and to improve the rheological properties of the blood. Hesylation of an antibody enables the prolongation of the circulation half-life by increasing the stability of the molecule, as well as by reducing renal clearance, resulting in an increased biological activity. By varying different parameters, such as the molecular weight of HES, a wide range of HES antibody conjugates can be customized.

Antibodies having an increased half-life *in vivo* can also be generated introducing one or more amino acid modifications (*i.e.*, substitutions, insertions or deletions) into an IgG constant domain, or FcRn binding fragment thereof (preferably a Fc or hinge Fc domain fragment). See, *e.g.*, International Publication No. WO 98/23289; International Publication No. WO 97/34631; and U.S. Patent No. 6,277,375.

Further, antibodies can be conjugated to albumin in order to make the antibody or antibody fragment more stable *in vivo* or have a longer half life *in vivo*. The techniques are well-known in the art, see, *e.g.*, International Publication Nos. WO 93/15199, WO 93/15200, and WO 01/77137; and European Patent No. EP 413,622.

The strategies for increasing half life is especially useful in nanobodies, fibronectin-based binders, and other antibodies or proteins for which increased in vivo half life is desired.

Antibody Conjugates

The present invention provides antibodies or fragments thereof that specifically bind to a C5 protein recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous protein or polypeptide (or fragment thereof, preferably to a polypeptide of at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids) to generate fusion proteins. In particular, the invention provides fusion proteins comprising an antigen-binding fragment of an antibody described herein (*e.g.*, a Fab fragment, Fd fragment, Fv fragment, F(ab)2 fragment, a VH domain, a VH CDR, a VL domain or a VL CDR) and a heterologous protein, polypeptide, or peptide. Methods for fusing or conjugating proteins, polypeptides, or

peptides to an antibody or an antibody fragment are known in the art. See, *e.g.*, U.S. Patent Nos. 5,336,603, 5,622,929, 5,359,046, 5,349,053, 5,447,851, and 5,112,946; European Patent Nos. EP 307,434 and EP 367,166; International Publication Nos. WO 96/04388 and WO 91/06570; Ashkenazi *et al.*, 1991, Proc. Natl. Acad. Sci. USA 85: 10535-10539; Zheng *et al.*, 1995, J. Immunol. 154:5590-5600; and Vil *et al.*, 1992, Proc. Natl. Acad. Sci. USA 89:11337- 11341.

Additional fusion proteins may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of antibodies of the invention or fragments thereof (*e.g.*, antibodies or fragments thereof with higher affinities and lower dissociation rates). See, generally, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458; Patten *et al.*, 1997, Curr. Opinion Biotechnol. 8:724-33; Harayama, 1998, Trends Biotechnol. 16(2):76-82; Hansson, *et al.*, 1999, J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, 1998, Biotechniques 24(2):308- 313 (each of these patents and publications are hereby incorporated by reference in its entirety). Antibodies or fragments thereof, or the encoded antibodies or fragments thereof, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. A polynucleotide encoding an antibody or fragment thereof that specifically binds to a C5 protein may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Moreover, the antibodies or fragments thereof can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz *et al.*, 1989, Proc. Natl. Acad. Sci. USA 86:821-824, for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin ("HA") tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson *et al.*, 1984, Cell 37:767), and the "flag" tag.

In other embodiments, antibodies of the present invention or fragments thereof conjugated to a diagnostic or detectable agent. Such antibodies can be useful for monitoring or prognosing the onset, development, progression and/or severity of a disease or disorder as part of a clinical testing procedure, such as determining the efficacy of a particular therapy. Such diagnosis and detection can accomplished by coupling the antibody to detectable substances including, but not limited to, various enzymes, such as, but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as, but not limited to, streptavidin/biotin and

avidin/biotin; fluorescent materials, such as, but not limited to, umbelliferone, fluorescein, fluorescein isothiocynate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as, but not limited to, luminol; bioluminescent materials, such as but not limited to, luciferase, luciferin, and aequorin; radioactive materials, such as, but not limited to, iodine (131I, 125I, 123I, and 121I,), carbon (14C), sulfur (35S), tritium (3H), indium (115In, 113In, 112In, and 111In,), technetium (99Tc), thallium (201Ti), gallium (68Ga, 67Ga), palladium (103Pd), molybdenum (99Mo), xenon (133Xe), fluorine (18F), 153Sm, 177Lu, 159Gd, 149Pm, 140La, 175Yb, 166Ho, 90Y, 47Sc, 186Re, 188Re,142 Pr, 105Rh, 97Ru, 68Ge, 57Co, 65Zn, 85Sr, 32P, 153Gd, 169Yb, 51Cr, 54Mn, 75Se, 113Sn, and 117Tin; and positron emitting metals using various positron emission tomographies, and noradioactive paramagnetic metal ions.

The present invention further encompasses uses of antibodies or fragments thereof conjugated to a therapeutic moiety. An antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, *e.g.*, a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, *e.g.*, alpha-emitters. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells.

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety or drug moiety that modifies a given biological response. Therapeutic moieties or drug moieties are not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein, peptide, or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin; a protein such as tumor necrosis factor, α-interferon, β-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, an anti-angiogenic agent; or, a biological response modifier such as, for example, a lymphokine.

Moreover, an antibody can be conjugated to therapeutic moieties such as a radioactive metal ion, such as alph-emiters such as 213Bi or macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, 131In, 131LU, 131Y, 131Ho, 131Sm, to polypeptides. In certain embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) which can be attached to the antibody via a linker molecule. Such linker molecules are commonly known in the art and described in Denardo *et al.*, 1998, Clin Cancer Res. 4(10):2483-90; Peterson *et al.*, 1999, Bioconjug. Chem. 10(4):553-7; and Zimmerman *et al.*, 1999, Nucl. Med. Biol. 26(8):943-50, each incorporated by reference in their entireties.

Techniques for conjugating therapeutic moieties to antibodies are well known, see, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer

Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies 84: Biological And Clinical Applications, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, 1982, Immunol. Rev. 62:119-58.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

5.2. Methods of Producing Antibodies of the Invention

5.2.1. Nucleic Acids Encoding the Antibodies

The invention provides substantially purified nucleic acid molecules which encode polypeptides comprising segments or domains of the C5-binding antibody chains described above. Some of the nucleic acids of the invention comprise the nucleotide sequence encoding the heavy chain variable region shown in SEQ ID NO: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281, and/or the nucleotide sequence encoding the light chain variable region shown in SEQ ID NO: 8, 24, 40, 52, 68, 80, 90, 102, 122, 136, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, or 289. In a specific embodiment, the nucleic acid molecules are those identified in Table 1. Some other nucleic acid molecules of the invention comprise nucleotide sequences that are substantially identical (*e.g.*, at least 65, 80%, 95%, or 99%) to the nucleotide sequences of those identified in Table 1. When expressed from appropriate expression vectors, polypeptides encoded by these polynucleotides are capable of exhibiting C5 antigen binding capacity.

Also provided in the invention are polynucleotides which encode at least one CDR region and usually all three CDR regions from the heavy or light chain of the C5-binding antibody set forth above. Some other polynucleotides encode all or substantially all of the variable region sequence of the heavy chain and/or the light chain of the C5-binding antibody set forth above. Because of the degeneracy of the code, a variety of nucleic acid sequences will encode each of the immunoglobulin amino acid sequences.

The nucleic acid molecules of the invention can encode both a variable region and a constant region of the antibody. Some of nucleic acid sequences of the invention comprise

nucleotides encoding a mature heavy chain variable region sequence that is substantially identical (*e.g.*, at least 80%, 90%, or 99%) to the mature heavy chain variable region sequence set forth in SEQ ID NO: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281. Some other nucleic acid sequences comprising nucleotide encoding a mature light chain variable region sequence that is substantially identical (*e.g.*, at least 80%, 90%, or 99%) to the mature light chain variable region sequence set forth in SEQ ID NO: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, or 289.

The polynucleotide sequences can be produced by de novo solid-phase DNA synthesis or by PCR mutagenesis of an existing sequence (*e.g.*, sequences as described in the Examples below) encoding an C5-binding antibody or its binding fragment. Direct chemical synthesis of nucleic acids can be accomplished by methods known in the art, such as the phosphotriester method of Narang *et al.*, 1979, Meth. Enzymol. 68:90; the phosphodiester method of Brown *et al.*, Meth. Enzymol. 68:109, 1979; the diethylphosphoramidite method of Beaucage *et al.*, Tetra. Lett., 22:1859, 1981; and the solid support method of U.S. Patent No. 4,458,066. Introducing mutations to a polynucleotide sequence by PCR can be performed as described in, *e.g.*, PCR Technology: Principles and Applications for DNA Amplification, H.A. Erlich (Ed.), Freeman Press, NY, NY, 1992; PCR Protocols: A Guide to Methods and Applications, Innis *et al.* (Ed.), Academic Press, San Diego, CA, 1990; Mattila *et al.*, Nucleic Acids Res. 19:967, 1991; and Eckert *et al.*, PCR Methods and Applications 1:17, 1991.

Also provided in the invention are expression vectors and host cells for producing the C5-binding antibodies described above. Various expression vectors can be employed to express the polynucleotides encoding the C5-binding antibody chains or binding fragments. Both viral-based and nonviral expression vectors can be used to produce the antibodies in a mammalian host cell. Nonviral vectors and systems include plasmids, episomal vectors, typically with an expression cassette for expressing a protein or RNA, and human artificial chromosomes (see, *e.g.*, Harrington *et al.*, Nat Genet 15:345, 1997). For example, nonviral vectors useful for expression of the C5-binding polynucleotides and polypeptides in mammalian (*e.g.*, human) cells include pThioHis A, B & C, pcDNA3.1/His, pEBVHis A, B & C, (Invitrogen, San Diego, CA), MPSV vectors, and numerous other vectors known in the art for expressing other proteins. Useful viral vectors include vectors based on retroviruses, adenoviruses, adenoassociated viruses, herpes viruses, vectors based on SV40, papilloma virus, HBP Epstein Barr virus, vaccinia virus vectors and Semliki Forest virus (SFV). See, Brent *et al.*, supra; Smith, Annu. Rev. Microbiol. 49:807, 1995; and Rosenfeld *et al.*, Cell 68:143, 1992.

The choice of expression vector depends on the intended host cells in which the vector is to be expressed. Typically, the expression vectors contain a promoter and other regulatory sequences (*e.g.*, enhancers) that are operably linked to the polynucleotides encoding an C5-binding antibody chain or fragment. In some embodiments, an inducible promoter is employed to prevent expression of inserted sequences except under inducing conditions. Inducible promoters include, *e.g.*, arabinose, lacZ, metallothionein promoter or a heat shock promoter. Cultures of transformed organisms can be expanded under noninducing conditions without biasing the population for coding sequences whose expression products are better tolerated by the host cells. In addition to promoters, other regulatory elements may also be required or desired for efficient expression of an C5-binding antibody chain or fragment. These elements typically include an ATG initiation codon and adjacent ribosome binding site or other sequences. In addition, the efficiency of expression may be enhanced by the inclusion of enhancers appropriate to the cell system in use (see, *e.g.*, Scharf *et al.*, Results Probl. Cell Differ. 20:125, 1994; and Bittner *et al.*, Meth. Enzymol., 153:516, 1987). For example, the SV40 enhancer or CMV enhancer may be used to increase expression in mammalian host cells.

The expression vectors may also provide a secretion signal sequence position to form a fusion protein with polypeptides encoded by inserted C5-binding antibody sequences. More often, the inserted C5-binding antibody sequences are linked to a signal sequences before inclusion in the vector. Vectors to be used to receive sequences encoding C5-binding antibody light and heavy chain variable domains sometimes also encode constant regions or parts thereof. Such vectors allow expression of the variable regions as fusion proteins with the constant regions thereby leading to production of intact antibodies or fragments thereof. Typically, such constant regions are human.

The host cells for harboring and expressing the C5-binding antibody chains can be either prokaryotic or eukaryotic. E. coli is one prokaryotic host useful for cloning and expressing the polynucleotides of the present invention. Other microbial hosts suitable for use include bacilli, such as Bacillus subtilis, and other enterobacteriaceae, such as Salmonella, Serratia, and various Pseudomonas species. In these prokaryotic hosts, one can also make expression vectors, which typically contain expression control sequences compatible with the host cell (*e.g.*, an origin of replication). In addition, any number of a variety of well-known promoters will be present, such as the lactose promoter system, a tryptophan (trp) promoter system, a beta-lactamase promoter system, or a promoter system from phage lambda. The promoters typically control expression, optionally with an operator sequence, and have ribosome binding site sequences and the like, for initiating and completing transcription and translation. Other microbes, such as yeast, can also be

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employed to express C5-binding polypeptides of the invention. Insect cells in combination with baculovirus vectors can also be used.

In some preferred embodiments, mammalian host cells are used to express and produce the C5-binding polypeptides of the present invention. For example, they can be either a hybridoma cell line expressing endogenous immunoglobulin genes (*e.g.*, the 1D6.C9 myeloma hybridoma clone as described in the Examples) or a mammalian cell line harboring an exogenous expression vector (*e.g.*, the SP2/0 myeloma cells exemplified below). These include any normal mortal or normal or abnormal immortal animal or human cell. For example, a number of suitable host cell lines capable of secreting intact immunoglobulins have been developed including the CHO cell lines, various Cos cell lines, HeLa cells, myeloma cell lines, transformed B-cells and hybridomas. The use of mammalian tissue cell culture to express polypeptides is discussed generally in, *e.g.*, Winnacker, FROM GENES TO CLONES, VCH Publishers, N.Y., N.Y., 1987. Expression vectors for mammalian host cells can include expression control sequences, such as an origin of replication, a promoter, and an enhancer (see, *e.g.*, Queen, *et al.*, Immunol. Rev. 89:49-68, 1986), and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences. These expression vectors usually contain promoters derived from mammalian genes or from mammalian viruses. Suitable promoters may be constitutive, cell type-specific, stage-specific, and/or modulatable or regulatable. Useful promoters include, but are not limited to, the metallothionein promoter, the constitutive adenovirus major late promoter, the dexamethasone-inducible MMTV promoter, the SV40 promoter, the MRP polIII promoter, the constitutive MPSV promoter, the tetracycline-inducible CMV promoter (such as the human immediate-early CMV promoter), the constitutive CMV promoter, and promoter-enhancer combinations known in the art.

Methods for introducing expression vectors containing the polynucleotide sequences of interest vary depending on the type of cellular host. For example, calcium chloride transfection is commonly utilized for prokaryotic cells, whereas calcium phosphate treatment or electroporation may be used for other cellular hosts. (See generally Sambrook, *et al.*, supra). Other methods include, *e.g.*, electroporation, calcium phosphate treatment, liposome-mediated transformation, injection and microinjection, ballistic methods, virosomes, immunoliposomes, polycation:nucleic acid conjugates, naked DNA, artificial virions, fusion to the herpes virus structural protein VP22 (Elliot and O'Hare, Cell 88:223, 1997), agent-enhanced uptake of DNA, and ex vivo transduction. For long-term, high-yield production of recombinant proteins, stable expression will often be desired. For example, cell lines which stably express C5-binding antibody chains or binding fragments can be prepared using expression vectors of the invention which contain viral origins of replication or endogenous expression elements and a selectable marker gene. Following the introduction of the vector,

cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth of cells which successfully express the introduced sequences in selective media. Resistant, stably transfected cells can be proliferated using tissue culture techniques appropriate to the cell type.

5.2.2. Generation of monoclonal antibodies of the invention

Monoclonal antibodies (mAbs) can be produced by a variety of techniques, including conventional monoclonal antibody methodology *e.g.*, the standard somatic cell hybridization technique of Kohler and Milstein, 1975 Nature 256: 495. Many techniques for producing monoclonal antibody can be employed *e.g.*, viral or oncogenic transformation of B lymphocytes.

An animal system for preparing hybridomas is the murine system. Hybridoma production in the mouse is a well established procedure. Immunization protocols and techniques for isolation of immunized splenocytes for fusion are known in the art. Fusion partners (*e.g.*, murine myeloma cells) and fusion procedures are also known.

Chimeric or humanized antibodies of the present invention can be prepared based on the sequence of a murine monoclonal antibody prepared as described above. DNA encoding the heavy and light chain immunoglobulins can be obtained from the murine hybridoma of interest and engineered to contain non-murine (*e.g.*,. human) immunoglobulin sequences using standard molecular biology techniques. For example, to create a chimeric antibody, the murine variable regions can be linked to human constant regions using methods known in the art (see *e.g.*, U.S. Patent No. 4,816,567 to Cabilly *et al.*). To create a humanized antibody, the murine CDR regions can be inserted into a human framework using methods known in the art. See *e.g.*, U.S. Patent No. 5225539 to Winter, and U.S. Patent Nos. 5530101; 5585089; 5693762 and 6180370 to Queen *et al.*

In a certain embodiment, the antibodies of the invention are human monoclonal antibodies. Such human monoclonal antibodies directed against C5 can be generated using transgenic or transchromosomic mice carrying parts of the human immune system rather than the mouse system. These transgenic and transchromosomic mice include mice referred to herein as HuMAb mice and KM mice, respectively, and are collectively referred to herein as "human Ig mice."

The HuMAb mouse® (Medarex, Inc.) contains human immunoglobulin gene miniloci that encode un-rearranged human heavy (μ and γ) and κ light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous μ and κ chain loci (see *e.g.*, Lonberg, *et al.*, 1994 Nature 368(6474): 856-859). Accordingly, the mice exhibit reduced expression of mouse IgM or κ, and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic

mutation to generate high affinity human IgGκ monoclonal (Lonberg, N. *et al.*, 1994 supra; reviewed in Lonberg, N., 1994 Handbook of Experimental Pharmacology 113:49-101; Lonberg, N. and Huszar, D., 1995 Intern. Rev. Immunol.13: 65-93, and Harding, F. and Lonberg, N., 1995 Ann. N. Y. Acad. Sci. 764:536-546). The preparation and use of HuMAb mice, and the genomic modifications carried by such mice, is further described in Taylor, L. *et al.*, 1992 Nucleic Acids Research 20:6287-6295; Chen, J. et at., 1993 International Immunology 5: 647-656; Tuaillon *et al.*, 1993 Proc. Natl. Acad. Sci. USA 94:3720-3724; Choi *et al.*, 1993 Nature Genetics 4:117-123; Chen, J. *et al.*, 1993 EMBO J. 12: 821-830; Tuaillon *et al.*, 1994 J. Immunol. 152:2912-2920; Taylor, L. *et al.*, 1994 International Immunology 579-591; and Fishwild, D. *et al.*, 1996 Nature Biotechnology 14: 845-851, the contents of all of which are hereby specifically incorporated by reference in their entirety. See further, U.S. Patent Nos. 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,789,650; 5,877,397; 5,661,016; 5,814,318; 5,874,299; and 5,770,429; all to Lonberg and Kay; U.S. Patent No. 5,545,807 to Surani *et al.*; PCT Publication Nos. WO 92103918, WO 93/12227, WO 94/25585, WO 97113852, WO 98/24884 and WO 99/45962, all to Lonberg and Kay; and PCT Publication No. WO 01/14424 to Korman *et al.*

In another embodiment, human antibodies of the invention can be raised using a mouse that carries human immunoglobulin sequences on transgenes and transchomosomes such as a mouse that carries a human heavy chain transgene and a human light chain transchromosome. Such mice, referred to herein as "KM mice", are described in detail in PCT Publication WO 02/43478 to Ishida *et al.*

Still further, alternative transgenic animal systems expressing human immunoglobulin genes are available in the art and can be used to raise C5-binding antibodies of the invention. For example, an alternative transgenic system referred to as the Xenomouse (Abgenix, Inc.) can be used. Such mice are described in, *e.g.*, U.S. Patent Nos. 5,939,598; 6,075,181; 6,114,598; 6, 150,584 and 6,162,963 to Kucherlapati *et al.*

Moreover, alternative transchromosomic animal systems expressing human immunoglobulin genes are available in the art and can be used to raise C5-binding antibodies of the invention. For example, mice carrying both a human heavy chain transchromosome and a human light chain tranchromosome, referred to as "TC mice" can be used; such mice are described in Tomizuka *et al.*, 2000 Proc. Natl. Acad. Sci. USA 97:722-727. Furthermore, cows carrying human heavy and light chain transchromosomes have been described in the art (Kuroiwa *et al.*, 2002 Nature Biotechnology 20:889-894) and can be used to raise C5-binding antibodies of the invention.

Human monoclonal antibodies of the invention can also be prepared using phage display methods for screening libraries of human immunoglobulin genes. Such phage display methods for isolating human antibodies are established in the art or described in the

examples below. See for example: U.S. Patent Nos. 5,223,409; 5,403,484; and 5,571,698 to Ladner *et al.*; U.S. Patent Nos. 5,427,908 and 5,580,717 to Dower *et al.*; U.S. Patent Nos. 5,969,108 and 6,172,197 to McCafferty *et al.*; and U.S. Patent Nos. 5,885,793; 6,521,404; 6,544,731; 6,555,313; 6,582,915 and 6,593,081 to Griffiths *et al.*

Human monoclonal antibodies of the invention can also be prepared using SCID mice into which human immune cells have been reconstituted such that a human antibody response can be generated upon immunization. Such mice are described in, for example, U.S. Patent Nos. 5,476,996 and 5,698,767 to Wilson *et al.*

5.2.3. Framework or Fc engineering

Engineered antibodies of the invention include those in which modifications have been made to framework residues within VH and/or VL, *e.g.* to improve the properties of the antibody. Typically such framework modifications are made to decrease the immunogenicity of the antibody. For example, one approach is to "backmutate" one or more framework residues to the corresponding germline sequence. More specifically, an antibody that has undergone somatic mutation may contain framework residues that differ from the germline sequence from which the antibody is derived. Such residues can be identified by comparing the antibody framework sequences to the germline sequences from which the antibody is derived. To return the framework region sequences to their germline configuration, the somatic mutations can be "backmutated" to the germline sequence by, for example, site-directed mutagenesis. Such "backmutated" antibodies are also intended to be encompassed by the invention.

Another type of framework modification involves mutating one or more residues within the framework region, or even within one or more CDR regions, to remove T cell -epitopes to thereby reduce the potential immunogenicity of the antibody. This approach is also referred to as "deimmunization" and is described in further detail in U.S. Patent Publication No. 20030153043 by Carr *et al.*

In addition or alternative to modifications made within the framework or CDR regions, antibodies of the invention may be engineered to include modifications within the Fc region, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity. Furthermore, an antibody of the invention may be chemically modified (*e.g.*, one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody. Each of these embodiments is described in further detail below. The numbering of residues in the Fc region is that of the EU index of Kabat.

In one embodiment, the hinge region of CH1 is modified such that the number of cysteine residues in the hinge region is altered, *e.g.*, increased or decreased. This approach is described further in U.S. Patent No. 5,677,425 by Bodmer *et al.* The number of cysteine residues in the hinge region of CH1 is altered to, for example, facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody.

In another embodiment, the Fc hinge region of an antibody is mutated to decrease the biological half-life of the antibody. More specifically, one or more amino acid mutations are introduced into the CH2-CH3 domain interface region of the Fc-hinge fragment such that the antibody has impaired Staphylococcyl protein A (SpA) binding relative to native Fc-hinge domain SpA binding. This approach is described in further detail in U.S. Patent No. 6,165,745 by Ward *et al.*

In another embodiment, the antibody is modified to increase its biological half-life. Various approaches are possible. For example, one or more of the following mutations can be introduced: T252L, T254S, T256F, as described in U.S. Patent No. 6,277,375 to Ward. Alternatively, to increase the biological half life, the antibody can be altered within the CH1 or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Patent Nos. 5,869,046 and 6,121,022 by Presta *et al.*

In yet other embodiments, the Fc region is altered by replacing at least one amino acid residue with a different amino acid residue to alter the effector functions of the antibody. For example, one or more amino acids can be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Patent Nos. 5,624,821 and 5,648,260, both by Winter *et al.*

In another embodiment, one or more amino acids selected from amino acid residues can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Patent Nos. 6,194,551 by Idusogie *et al.*

In another embodiment, one or more amino acid residues are altered to thereby alter the ability of the antibody to fix complement. This approach is described further in PCT Publication WO 94/29351 by Bodmer *et al.*

In yet another embodiment, the Fc region is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the antibody for an Fcγ receptor by modifying one or more amino acids. This approach is described further in PCT Publication WO 00/42072 by Presta. Moreover, the

binding sites on human IgG1 for FcγRI, FcγRII, FcγRIII and FcRn have been mapped and variants with improved binding have been described (see Shields, R.L. *et al.*, 2001 J. Biol. Chen. 276:6591-6604).

In still another embodiment, the glycosylation of an antibody is modified. For example, an aglycoslated antibody can be made (*i.e.*, the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for "antigen'. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affinity of the antibody for antigen. Such an approach is described in further detail in U.S. Patent Nos. 5,714,350 and 6,350,861 by Co *et al.*

Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. For example, EP 1,176,195 by Hang *et al.* describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation. PCT Publication WO 03/035835 by Presta describes a variant CHO cell line, Lec13 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields, R.L. *et al.*, 2002 J. Biol. Chem. 277:26733-26740). PCT Publication WO 99/54342 by Umana *et al.* describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (*e.g.*, beta(1,4)-N acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNac structures which results in increased ADCC activity of the antibodies (see also Umana *et al.*, 1999 Nat. Biotech. 17:176-180).

5.2.4. Methods of Engineering Altered Antibodies

As discussed above, the C5-binding antibodies having VH and VL sequences or full length heavy and light chain sequences shown herein can be used to create new C5-binding antibodies by modifying full length heavy chain and/or light chain sequences, VH and/or VL sequences, or the constant region(s) attached thereto. Thus, in another aspect of the

invention, the structural features of a C5-binding antibody of the invention are used to create structurally related C5-binding antibodies that retain at least one functional property of the antibodies of the invention, such as binding to human C5 and also inhibiting one or more functional properties of C5 (*e.g.*, inhibit red blood cell lysis in a hemolytic assay).

For example, one or more CDR regions of the antibodies of the present invention, or mutations thereof, can be combined recombinantly with known framework regions and/or other CDRs to create additional, recombinantly-engineered, C5-binding antibodies of the invention, as discussed above. Other types of modifications include those described in the previous section. The starting material for the engineering method is one or more of the VH and/or VL sequences provided herein, or one or more CDR regions thereof. To create the engineered antibody, it is not necessary to actually prepare (*i.e.*, express as a protein) an antibody having one or more of the VH and/or VL sequences provided herein, or one or more CDR regions thereof. Rather, the information contained in the sequence(s) is used as the starting material to create a "second generation" sequence(s) derived from the original sequence(s) and then the "second generation" sequence(s) is prepared and expressed as a protein.

Accordingly, in another embodiment, the invention provides a method for preparing an C5-binding antibody consisting of: a heavy chain variable region antibody sequence having a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235, a CDR2 sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236, and/or a CDR3 sequence selected from the group consisting of SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237; and a light chain variable region antibody sequence having a CDR1 sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238, a CDR2 sequence selected from the group consisting of SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239, and/or a CDR3 sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240; altering at least one amino acid residue within the heavy chain variable region antibody sequence and/or the light chain variable region antibody sequence to create at least one altered antibody sequence; and expressing the altered antibody sequence as a protein.

Accordingly, in another embodiment, the invention provides a method for preparing an C5-binding antibody optimized for expression in a mammalian cell consisting of: a full length heavy chain antibody sequence having a sequence selected from the group of SEQ ID NOs: 9, 25, 41, 53, 69, 91, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, and 282; and a full length light chain antibody sequence having a sequence selected from the group of 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154,

168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, and 290; altering at least one amino acid residue within the full length heavy chain antibody sequence and/or the full length light chain antibody sequence to create at least one altered antibody sequence; and expressing the altered antibody sequence as a protein.

The altered antibody sequence can also be prepared by screening antibody libraries having fixed CDR3 sequences or minimal essential binding determinants as described in US20050255552 and diversity on CDR1 and CDR2 sequences. The screening can be performed according to any screening technology appropriate for screening antibodies from antibody libraries, such as phage display technology.

Standard molecular biology techniques can be used to prepare and express the altered antibody sequence. The antibody encoded by the altered antibody sequence(s) is one that retains one, some or all of the functional properties of the C5-binding antibodies described herein, which functional properties include, but are not limited to, specifically binding to human and/or cynomolgus C5; and the antibody inhibit red blood cell lysis in a hemolytic assay.

The functional properties of the altered antibodies can be assessed using standard assays available in the art and/or described herein, such as those set forth in the Examples (*e.g.*, ELISAs).

In certain embodiments of the methods of engineering antibodies of the invention, mutations can be introduced randomly or selectively along all or part of an C5-binding antibody coding sequence and the resulting modified C5-binding antibodies can be screened for binding activity and/or other functional properties as described herein. Mutational methods have been described in the art. For example, PCT Publication WO 02/092780 by Short describes methods for creating and screening antibody mutations using saturation mutagenesis, synthetic ligation assembly, or a combination thereof. Alternatively, PCT Publication WO 03/074679 by Lazar *et al.* describes methods of using computational screening methods to optimize physiochemical properties of antibodies.

5.3. Characterization of the Antibodies of the Invention

The antibodies of the invention can be characterized by various functional assays. For example, they can be characterized by their ability to inhibit red blood cell lysis in hemolytic assays, their affinity to a C5 protein (*e.g.*, human and/or cynomolgus C5), the epitope binning, their resistance to proteolysis, and their ability to block the complement cascade, for example, their ability to inhibit MAC formation.

Various methods can be used to measure presence of complement pathway molecules and activation of the complement system (see, *e.g.*, U.S. Pat. No. 6,087,120; and

Newell *et al.*, J Lab Clin Med, 100:437-44, 1982). For example, the complement activity can be monitored by (i) measurement of inhibition of complement-mediated lysis of red blood cells (hemolysis); (ii) measurement of ability to inhibit cleavage of C3 or C5; and (iii) inhibition of alternative pathway mediated hemolysis.

The two most commonly used techniques are hemolytic assays (see, *e.g.*, Baatrup *et al.*, Ann Rheum Dis, 51:892-7, 1992) and immunological assays (see, *e.g.*, Auda *et al.*, Rheumatol Int, 10:185-9, 1990). The hemolytic techniques measure the functional capacity of the entire sequence-either the classical or alternative pathway. Immunological techniques measure the protein concentration of a specific complement component or split product. Other assays that can be employed to detect complement activation or measure activities of complement components in the methods of the present invention include, *e.g.*, T cell proliferation assay (Chain *et al.*, J Immunol Methods, 99:221-8, 1987), and delayed type hypersensitivity (DTH) assay (Forstrom *et al.*, 1983, Nature 303:627-629; Hallidaye*t al.*, 1982, in Assessment of Immune Status by the Leukocyte Adherence Inhibition Test, Academic, New York pp. 1-26; Koppi *et al.*, 1982, Cell. Immunol. 66:394-406; and U.S. Pat. No. 5,843,449).

In hemolytic techniques, all of the complement components must be present and functional. Therefore hemolytic techniques can screen both functional integrity and deficiencies of the complement system (see, *e.g.*, Dijk *et al.*, J Immunol Methods 36: 29-39, 1980; Minh *et al.*, Clin Lab Haematol. 5:23-34 1983; and Tanaka *et al.*, J Immunol 86: 161-170, 1986). To measure the functional capacity of the classical pathway, sheep red blood cells coated with hemolysin (rabbit IgG to sheep red blood cells) or chicken red blood cells that are sensitized with rabbit anti-chicken antibodies are used as target cells (sensitized cells). These Ag-Ab complexes activate the classical pathway and result in lysis of the target cells when the components are functional and present in adequate concentration. To determine the functional capacity of the alternative pathway, rabbit red blood cells are used as the target cell (see, *e.g.*, U.S. Pat. No. 6,087,120).

To test the ability of an antibody to inhibit MAC (membrance attack complex) formation, a MAC deposition assay can be performed. Briefly, zymosan can be used to activate the alternative pathway and IgM can be used to active the classic pathway . Fabs are pre-incubated with human serum and added to plates coated with zymosan or IgM. Percentage inhibition of MAC deposition can be calculated for each sample relative to baseline (EDTA treated human serum) and positive control (human serum).

The ability of an antibody to bind to C5 can be detected by labelling the antibody of interest directly, or the antibody may be unlabelled and binding detected indirectly using various sandwich assay formats known in the art.

In some embodiments, the C5-binding antibodies of the invention block or compete with binding of a reference C5-binding antibody to a C5 polypeptide. These can be fully human C5-binding antibodies described above. They can also be other mouse, chimeric or humanized C5-binding antibodies which bind to the same epitope as the reference antibody. The capacity to block or compete with the reference antibody binding indicates that a C5-binding antibody under test binds to the same or similar epitope as that defined by the reference antibody, or to an epitope which is sufficiently proximal to the epitope bound by the reference C5-binding antibody. Such antibodies are especially likely to share the advantageous properties identified for the reference antibody. The capacity to block or compete with the reference antibody may be determined by, *e.g.*, a competition binding assay. With a competition binding assay, the antibody under test is examined for ability to inhibit specific binding of the reference antibody to a common antigen, such as a C5 polypeptide. A test antbody competes with the reference antibody for specific binding to the antigen if an excess of the test antibody substantially inhibits binding of the reference antibody. Substantial inhibition means that the test antibody reduces specific binding of the reference antibody usually by at least 10%, 25%, 50%, 75%, or 90%.

There are a number of known competition binding assays that can be used to assess competition of a C5-binding antibody with the reference C5-binding antibody for binding to a C5 protein. These include, *e.g.*, solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see Stahli *et al.*, Methods in Enzymology 9:242-253, 1983); solid phase direct biotin-avidin EIA (see Kirkland *et al.*, J. Immunol. 137:3614-3619, 1986); solid phase direct labeled assay, solid phase direct labeled sandwich assay (see Harlow & Lane, supra); solid phase direct label RIA using I-125 label (see Morel *et al.*, Molec. Immunol. 25:7-15, 1988); solid phase direct biotin-avidin EIA (Cheung *et al.*, Virology 176:546-552, 1990); and direct labeled RIA (Moldenhauer *et al.*, Scand. J. Immunol. 32:77-82, 1990). Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing either of these, an unlabelled test C5-binding antibody and a labelled reference antibody. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test antibody. Usually the test antibody is present in excess. Antibodies identified by competition assay (competing antibodies) include antibodies binding to the same epitope as the reference antibody and antibodies binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antibody for steric hindrance to occur.

To determine if the selected C5-binding monoclonal antibodies bind to unique epitopes, each antibody can be biotinylated using commercially available reagents (*e.g.*, reagents from Pierce, Rockford, IL). Competition studies using unlabeled monoclonal

antibodies and biotinylated monoclonal antibodies can be performed using a C5 polypeptide coated-ELISA plates. Biotinylated MAb binding can be detected with a strep-avidin-alkaline phosphatase probe. To determine the isotype of a purified C5-binding antibody, isotype ELISAs can be performed. For example, wells of microtiter plates can be coated with 1 µg/ml of anti-human IgG overnight at 4°C. After blocking with 1% BSA, the plates are reacted with 1 µg/ml or less of the monoclonal C5-binding antibody or purified isotype controls, at ambient temperature for one to two hours. The wells can then be reacted with either human IgGl or human IgM-specific alkaline phosphatase-conjugated probes. Plates are then developed and analyzed so that the isotype of the purified antibody can be determined.

To demonstrate binding of monoclonal C5-binding antibodies to live cells expressing a C5 polypeptide, flow cytometry can be used. Briefly, cell lines expressing C5 (grown under standard growth conditions) can be mixed with various concentrations of a C5-binding antibody in PBS containing 0.1% BSA and 10% fetal calf serum, and incubated at 37°C for 1 hour. After washing, the cells are reacted with Fluorescein-labeled anti-human IgG antibody under the same conditions as the primary antibody staining. The samples can be analyzed by FACScan instrument using light and side scatter properties to gate on single cells. An alternative assay using fluorescence microscopy may be used (in addition to or instead of) the flow cytometry assay. Cells can be stained exactly as described above and examined by fluorescence microscopy. This method allows visualization of individual cells, but may have diminished sensitivity depending on the density of the antigen.

C5-binding antibodies of the invention can be further tested for reactivity with a C5 polypeptide or antigenic fragment by Western blotting. Briefly, purified C5 polypeptides or fusion proteins, or cell extracts from cells expressing C5 can be prepared and subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis. After electrophoresis, the separated antigens are transferred to nitrocellulose membranes, blocked with 10% fetal calf serum, and probed with the monoclonal antibodies to be tested. Human IgG binding can be detected using anti-human IgG alkaline phosphatase and developed with BCIP/NBT substrate tablets (Sigma Chem. Co., St. Louis, MO).

Examples of functional assays are also described in the Example section below.

5.4. Prophylactic and Therapeutic Uses

The present invention provides methods of treating a disease or disorder associated with increased complement activity by administering to a subject in need thereof an effective amount of the antibodies of the invention. In a specific embodiment, the present invention provides a method of treating age-related macular degeneration (AMD) by administering to a subject in need thereof an effective amount of the antibodies of the invention.

The antibodies of the invention can be used, *inter alia*, to prevent progression of dry AMD to wet AMD, to slow and/or prevent progression of geographic atrophy, and to improve vision lost due to dry AMD progression. It can also be used in combination with anti-VEGF therapies for the treatement of wet AMD patients.

In some embodiments, the present invention provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the antibodies of the invention. Examples of known complement related diseases or disorders include: neurological disorders, multiple sclerosis, stroke, Guillain Barre Syndrome, traumatic brain injury, Parkinson's disease, disorders of inappropriate or undesirable complement activation, hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, Crohn's disease, adult respiratory distress syndrome, thermal injury including burns or frostbite, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, hemodialysis, renal ischemia, mesenteric artery reperfusion after acrotic reconstruction, infectious disease or sepsis, immune complex disorders and autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus (SLE), SLE nephritis, proliferative nephritis, hemolytic anemia, and myasthenia gravis. In addition, other known complement related disease are lung disease and disorders such as dyspnea, hemoptysis, ARDS, asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, inert dusts and minerals (*e.g.*, silicon, coal dust, beryllium, and asbestos), pulmonary fibrosis, organic dust diseases, chemical injury (due to irritant gasses and chemicals, *e.g.*, chlorine, phosgene, sulfur dioxide, hydrogen sulfide, nitrogen dioxide, ammonia, and hydrochloric acid), smoke injury, thermal injury (*e.g.*, burn, freeze), asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, and immune complex-associated inflammation.

In a specific embodiment, the present invention provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the antibodies of the invention, wherein said disease or disorder is asthma, arthritis (*e.g.*, rheumatoid arthritis), autoimmune heart disease, multiple sclerosis, inflammatory bowel disease, ischemia-reperfusion injuries, Barraquer-Simons Syndrome, hemodialysis, systemic lupus, lupus erythematosus, psoriasis, multiple sclerosis, transplantation, diseases of the central nervous system such as Alzheimer's disease and other neurodegenerative conditions, aHUS, glomerulonephritis, bullous pemphigoid or MPGN II.

In a specific embodiment, the present invention provides methods of treating glomerulonephritis by administering to a subject in need thereof an effective amount of a composition comprising an antibody of the present invention. Symptoms of glomerulonephritis include, but not limited to, proteinuria; reduced glomerular filtration rate (GFR); serum electrolyte changes including azotemia (uremia, excessive blood urea nitrogen--BUN) and salt retention, leading to water retention resulting in hypertension and edema; hematuria and abnormal urinary sediments including red cell casts; hypoalbuminemia; hyperlipidemia; and lipiduria. In a specific embodiment, the present invention provides methods of treating paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of a composition comprising an antibody of the present invention.

In a specific embodiment, the present invention provides methods of reducing the dysfunction of the immune and hemostatic systems associated with extracorporeal circulation by administering to a subject in need thereof an effective amount of a composition comprising an antibody of the present invention. The antibodies of the present invention can be used in any procedure which involves circulating the patient's blood from a blood vessel of the patient, through a conduit, and back to a blood vessel of the patient, the conduit having a luminal surface comprising a material capable of causing at least one of complement activation, platelet activation, leukocyte activation, or platelet-leukocyte adhesion. Such procedures include, but are not limited to, all forms of ECC, as well as procedures involving the introduction of an artifical or foreign organ, tissue, or vessel into the blood circuit of a patient.

Subjects to be treated with therapeutic agents of the present invention can also be administered other therapeutic agents with know methods of treating conditions associated with macular degeneration, such as antibiotic treatments as described in U.S. Pat. No. 6,218,368. In other treatments, immunosuppressive agents such as cyclosporine, are agents capable of suppressing immune responses. These agents include cytotoxic drugs, corticosteriods, nonsteroidal anti-inflammatory drugs (NSAIDs), specific T-lymphocyte immunosuppressants, and antibodies or fragments thereof (see Physicians' Desk Reference, 53rd edition, Medical Economics Company Inc., Montvale, N.J. (1999). Immunosuppressive treatment is typically continued at intervals for a period of a week, a month, three months, six months or a year. In some patients, treatment is administered for up to the rest of a patient's life.

When the therapeutic agents of the present invention are administered together with another agent, the two can be administered sequentially in either order or simultaneously. In some aspects, an antibody of the present invention is administered to a subject who is also

receiving therapy with a second agent (e.g., verteporfin). In other aspects, the binding molecule is administered in conjunction with surgical treatments.

Suitable agents for combination treatment with C5-binding antibodies include agents known in the art that are able to modulate the activities of complement components (see, e.g., U.S. Pat. No. 5,808,109). Other agents have been reported to diminish complement-mediated activity. Such agents include: amino acids (Takada, Y. *et al.* Immunology 1978, 34, 509); phosphonate esters (Becker, L. Biochem. Biophy. Acta 1967, 147, 289); polyanionic substances (Conrow, R. B. *et al.* J. Med. Chem. 1980, 23, 242); sulfonyl fluorides (Hansch, C.; Yoshimoto, M. J. Med. Chem. 1974, 17, 1160, and references cited therein); polynucleotides (DeClercq, P. F. *et al.* Biochem. Biophys. Res. Commun. 1975, 67, 255); pimaric acids (Glovsky, M. M. *et al.* J. Immunol. 1969, 102, 1); porphines (Lapidus, M. and Tomasco, J. Immunopharmacol. 1981, 3, 137); several antiinflammatories (Burge, J. J. *et al.* J. Immunol. 1978, 120, 1625); phenols (Muller-Eberhard, H. J. 1978, in Molecular Basis of Biological Degradative Processes, Berlin, R. D. *et al.*, eds. Academic Press, New York, p. 65); and benzamidines (Vogt, W. *et al* Immunology 1979, 36, 138). Some of these agents function by general inhibition of proteases and esterases. Others are not specific to any particular intermediate step in the complement pathway, but, rather, inhibit more than one step of complement activation. Examples of the latter compounds include the benzamidines, which block C1, C4 and C5 utilization (see, e.g., Vogt *et al.* Immunol. 1979, 36, 138).

Additional agents known in the art that can inhibit activity of complement components include K-76, a fungal metabolite from Stachybotrys (Corey *et al.*, J. Amer. Chem. Soc. 104: 5551, 1982). Both K-76 and K-76 COOH have been shown to inhibit complement mainly at the C5 step (Hong *et al.*, J. Immunol. 122: 2418, 1979; Miyazaki *et al.*, Microbiol. Immunol. 24: 1091, 1980), and to prevent the generation of a chemotactic factor from normal human complement (Bumpers *et al.*, Lab. Clinc. Med. 102: 421, 1983). At high concentrations of K-76 or K-76 COOH, some inhibition of the reactions of C2, C3, C6, C7, and C9 with their respective preceding intermediaries is exhibited. K-76 or K-76 COOH has also been reported to inhibit the C3b inactivator system of complement (Hong *et al.*, J. Immunol. 127: 104-108, 1981). Other suitable agents for practicing methods of the present invention include griseofulvin (Weinberg, in Principles of Medicinal Chemistry, 2d Ed., Foye, W. O., ed., Lea & Febiger, Philadelphia, Pa., p. 813, 1981), isopannarin (Djura *et al.*, Aust. J. Chem.36: 1057, 1983), and metabolites of Siphonodictyon coralli-phagum (Sullivan *et al.*, Tetrahedron 37: 979, 1981).

A combination therapy regimen may be additive, or it may produce synergistic results (*e.g.*, reductions in complement pathway activity more than expected for the combined use of the two agents). In some embodiments, the present invention provide a combination therapy for preventing and/or treating AMD or another complement related disease as described

above with a C5-binding antibody of the invention and an anti-angiogenic, such as anti-VEGF agent.

5.5. Diagnostic Uses

In one aspect, the invntion encompasses diagnostic assays for determining C5 protein and/or nucleic acid expression as well as C5 protein function, in the context of a biological sample (*e.g.*, blood, serum, cells, tissue) or from individual is afflicted with a disease or disorder, or is at risk of developing a disorder associated with AMD.

Diagnostic assays, such as competitive assays rely on the ability of a labelled analogue (the "tracer") to compete with the test sample analyte for a limited number of binding sites on a common binding partner. The binding partner generally is insolubilized before or after the competition and then the tracer and analyte bound to the binding partner are separated from the unbound tracer and analyte. This separation is accomplished by decanting (where the binding partner was preinsolubilized) or by centrifuging (where the binding partner was precipitated after the competitive reaction). The amount of test sample analyte is inversely proportional to the amount of bound tracer as measured by the amount of marker substance. Dose-response curves with known amounts of analyte are prepared and compared with the test results in order to quantitatively determine the amount of analyte present in the test sample. These assays are called ELISA systems when enzymes are used as the detectable markers. In an assay of this form, competitive binding between antibodies and C5-binding antibodies results in the bound C5 protein, preferably the C5 epitopes of the invention, being a measure of antibodies in the serum sample, most particularly, neutralising antibodies in the serum sample.

A significant advantage of the assay is that measurement is made of neutralising antibodies directly (*i.e.*, those which interfere with binding of C5 protein, specifically, epitopes). Such an assay, particularly in the form of an ELISA test has considerable applications in the clinical environment and in routine blood screening.

Immunologic techniques employ polyclonal or monoclonal antibodies against the different epitopes of the various complement components (*e.g.*, C3, C4, C5) to detect, *e.g.*, the split products of complement components (see, *e.g.*, Hugli *et al.*, Immunoassays Clinical Laboratory Techniques 443-460, 1980; Gorski *et al.*, J Immunol Meth 47: 61-73, 1981; Linder *et al.*, J Immunol Meth 47: 49-59, 1981; and Burger *et al.*, J Immunol 141: 553-558, 1988). Binding of the antibody with the split product in competition with a known concentration of labeled split product could then be measured. Various assays such as radio-immunoassays, ELISA's, and radial diffusion assays are available to detect complement split products.

The immunologic techniques provide high sensitivity to detect complement activation, since they allow measurement of split-product formation in blood from a test subject and

control subjects with or without macular degeneration-related disorders. Accordingly, in some methods of the present invention, diagnosis of a disorder associated with ocular disorders is obtained by measurement of abnormal complement activation through quantification of the soluble split products of complement components in blood plasma from a test subject. The measurements can be performed as described, *e.g.*, in Chenoweth *et al.*, N Engl J Med 304: 497-502, 1981; and Bhakdi *et al.*, Biochim Biophys Acta 737: 343-372, 1983. Preferably, only the complement activation formed *in vivo* is measured. This can be accomplished by collecting a biological sample from the subject (*e.g.*, serum) in medium containing inhibitors of the complement system, and subsequently measuring complement activation (*e.g.*, quantification of the split products) in the sample.

In the clinical diagnosis or monitoring of patients with disorders associated with ocular diseases or disorders, the detection of complement proteins in comparison to the levels in a corresponding biological sample from a normal subject is indicative of a patient with disorders associated with macular degeneration.

In vivo diagnostic or imaging is described in US2006/0067935. Briefly, these methods generally comprise administering or introducing to a patient a diagnostically effective amount of a C5 binding molecule that is operatively attached to a marker or label that is detectable by non-invasive methods. The antibody-marker conjugate is allowed sufficient time to localize and bind to complement proteins within the eye. The patient is then exposed to a detection device to identify the detectable marker, thus forming an image of the location of the C5 binding molecules in the eye of a patient. The presence of C5 binding antbody or an antigen-binding fragment thereof is detected by determining whether an antibody-marker binds to a component of the eye. Detection of an increased level in selected complement proteins or a combination of protein in comparison to a normal individual without AMD disease is indicative of a predisposition for and/or on set of disorders associated with macular degeneration. These aspects of the invention are also preferred for use in eye imaging methods and combined angiogenic diagnostic and treatment methods.

The invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically.

The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with dysregulation of complement pathway activity. For example, mutations in a C5 gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a disorder characterized by or associated with C5 protein, nucleic acid expression or activity.

Another aspect of the invention provides methods for determining C5 nucleic acid expression or C5 protein activity in an individual to thereby select appropriate therapeutic or prophylactic agents for that individual (referred to herein as "pharmacogenomics"). Pharmacogenomics allows for the selection of agents (*e.g.*, drugs) for therapeutic or prophylactic treatment of an individual based on the genotype of the individual (*e.g.*, the genotype of the individual examined to determine the ability of the individual to respond to a particular agent.)

Yet another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs) on the expression or activity of C5 protein in clinical trials.

5.6. Pharmaceutical Compositions

The invention provides pharmaceutical compositions comprising the C5-binding antibodies (intact or binding fragments) formulated together with a pharmaceutically acceptable carrier. The compositions can additionally contain one or more other therapeutica agents that are suitable for treating or preventing a complement-associated disease (*e.g.*, AMD). Pharmaceutically carriers enhance or stabilize the composition, or to facilitate preparation of the composition. Pharmaceutically acceptable carriers include solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible.

A pharmaceutical composition of the present invention can be administered by a variety of methods known in the art. The route and/or mode of administration vary depending upon the desired results. It is preferred that administration be intravenous, intramuscular, intraperitoneal, or subcutaneous, or administered proximal to the site of the target. In a specific embodiment, the antibodies of the invention are formulated so that they can be administered intravitreally into the eye. The pharmaceutically acceptable carrier should be suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (*e.g.*, by injection or infusion). Depending on the route of administration, the active compound, *i.e.*, antibody, bispecific and multispecific molecule, may be coated in a material to protect the compound from the action of acids and other natural conditions that may inactivate the compound.

The composition should be sterile and fluid. Proper fluidity can be maintained, for example, by use of coating such as lecithin, by maintenance of required particle size in the case of dispersion and by use of surfactants. In many cases, it is preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol or sorbitol, and sodium chloride in the composition. Long-term absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

Pharmaceutical compositions of the invention can be prepared in accordance with methods well known and routinely practiced in the art. See, *e.g.*, Remington: The Science and Practice of Pharmacy, Mack Publishing Co., 20th ed., 2000; and Sustained and Controlled Release Drug Delivery Systems, J.R. Robinson, ed., Marcel Dekker, Inc., New York, 1978. Pharmaceutical compositions are preferably manufactured under GMP conditions. Typically, a therapeutically effective dose or efficacious dose of the C5-binding antibody is employed in the pharmaceutical compositions of the invention. The C5-binding antibodies are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art. Dosage regimens are adjusted to provide the optimum desired response (*e.g.*, a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level depends upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors.

A physician or veterinarian can start doses of the antibodies of the invention employed in the pharmaceutical composition at levels lower than that required to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. In general, effective doses of the compositions of the present invention, for the treatment of an allergic inflammatory disorder described herein vary depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. Treatment dosages need to be titrated to optimize safety and efficacy. For systemic administration with an antibody, the dosage

ranges from about 0.0001 to 100 mg/kg, and more usually 0.01 to 15 mg/kg, of the host body weight. An exemplary treatment regime entails systemic administration once per every two weeks or once a month or once every 3 to 6 months. For intravitreal administration with an antibody, the dosage ranges from about 0.0001 to about 10 mg. An exemplary treatment regime entails systemic administration once per every two weeks or once a month or once every 3 to 6 months.

Antibody is usually administered on multiple occasions. Intervals between single dosages can be weekly, monthly or yearly. Intervals can also be irregular as indicated by measuring blood levels of C5-binding antibody in the patient. In some methods of systemic administration, dosage is adjusted to achieve a plasma antibody concentration of 1–1000 µg/ml and in some methods 25–500 µg/ml. Alternatively, antibody can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the antibody in the patient. In general, humanized antibodies show longer half life than that of chimeric antibodies and nonhuman antibodies. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and preferably until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

6. EXAMPLES

The following examples are provided to further illustrate the invention but not to limit its scope. Other variants of the invention will be readily apparent to one of ordinary skill in the art and are encompassed by the appended claims.

Example 1 : Generation of Cynomolgus C5 and Human C5

1. Generation of Cynomolgus C5

Cynomolgus C5 was purified successfully from cynomolgus serum by affinity chromatography using MOR07086 hu IgG1. Cynomolgus C5 was quality tested by SDS-PAGE, Western blot, mass spectrometry and hemolytic assays. Quality of purified cynomolgus C5 was shown to be high by SDS-PAGE and Western blot. Lack of C3 contamination was confirmed by SDS and Western blot. In addition, the identity of cynomolgus C5 sequence was determined by mass spectrometric analysis and the activity of purified cynomolgus C5 was tested in hemolytic assays. In hemolytic assays the new preparation was equipotent to human C5 (*e.g.*, Sample 6, which was used in affinity

maturation pannings, reconstituted complement activity of 20% human C5-depleted serum with similar activity to purified human C5).

2. Quality Control of Human and Cynomolgus Biotinylated and Non-Biotinylated C5 Proteins

Bioactivity of purified human C5 was characterized and confirmed by the alternative pathway hemolytic activity. C5 was spiked into C5-depleted human serum at varying concentrations to obtain an EC50. EC50 values ranging between 0.02-0.1nM were considered acceptable.

Before using, the bioactivity of every purified human C5 protein lot was tested in the hemolytic assay. The same quality control was done for cynomolgus C5 after purification from cynomolgus serum. After biotinylation of human and cynomolgus C5, the bioactivity of the material was also tested in hemolytic assays, in order to analyze if there was a loss of activity caused by biotinylation.

Example 2: Generation of C5-specific antibodies from the HuCAL GOLD® Library

C5 antibodies were generated by selection of clones having high binding affinities, using as the source of antibody variant proteins a commercially available phage display library, the MorphoSys HuCAL GOLD® library.

HuCAL GOLD® library is a Fab library (Knappik *et al.*, 2000) in which all six CDRs are diversified by appropriate mutation, and which employs the CysDisplayTM technology for linking the Fab to the phage surface (WO01/05950, Löhning *et al.*, 2001).

1. Selection by panning of C5 specific antibodies from the library

For the selection of antibodies against C5, two different panning strategies were applied. The six different pools were individually subjected to three rounds of: (a) a solid phase panning where the antigens (human and cynomolgus C5) were directly coated on Maxisorp 96 well microtiter plates (Nunc, Wiesbaden, Germany); or (b) a solution panning with biotinylated human and cyno C5 where the phage-antigen complex was captured by Streptavidin magnetic beads (Dynabeads M-280; Dynal) for each panning pool.

The HuCAL GOLD® library was amplified in 2xYT medium containing 34µg/ml chloramphenicol and 1% glucose (2xYT-CG). After infection with VCSM13 helper phage at an OD600nm of 0.5 (30 min at 37°C without shaking; 30 min at 37°C shaking at 250 rpm), cells were spun down (4120 g; 5 min; 4°C), resuspended in 2xYT/ 34µg/ml chloramphenicol/ 50 µg/ml kanamycin/ 0.25mM IPTG and grown overnight at 22°C. Phage were PEG-precipitated from the supernatant, resuspended in PBS/ 20% glycerol and stored at -80°C. Phage amplification between two panning rounds was conducted as follows: mid-log phase E. coli TG1 cells were infected with eluted phage and plated onto LB-agar supplemented with

1% of glucose and 34µg/ml of chloramphenicol (LB-CG plates). After overnight incubation at 30°C, the TG1 colonies were scraped off the agar plates and used to inoculate 2xYT-CG until an OD600nm of 0.5 was reached. VCSM13 helper phage were added for infection as described above.

Taken together 354 clones derived from all panning strategies were sequenced, resulting in 64 unique clones with the desired profile: binding to human and cynomolgus C5 and no binding to the counter targets C3 and C4.

45 clones derived from solid phase pannings and 19 clones from solution pannings were selected for protein expression and purification. Four Fabs from solid phase pannings (MOR06525, MOR06756, MOR06757 and MOR06763) and 6 Fabs from solution pannings (MOR07086, MOR07087, MOR07091, MOR07092, MOR07093 and MOR07094) entered affinity maturation.

Solid Phase Panning Against C5 on Directly Coated Protein

The first panning variant was solid phase panning alternating human C5 (first and third round of selection) and cynomolgus C5 (second round of selection).

Three wells of a Maxisorp plate (F96 Nunc-Immunoplate) were coated with 200 µl of 50nM C5 each o/n at 4°C. The coated wells were washed 2x with 400µl PBS and blocked with 350µl 5% MPBS for 2h at RT on a microtiter plate shaker. For each panning about 10^{13} HuCAL GOLD® phage-antibodies were blocked with equal volume of PBST/5% milk powder for 2h at room temperature. The coated wells were washed 2x with 400µl PBS after the blocking procedure. 200µl of pre-blocked HuCAL GOLD® phage-antibodies were added to each coated well and incubated for 2h at RT on a shaker. Washing was performed by adding five times 350µl PBS/0.05% Tween, followed by washing another five times with PBS. For some panning conditions a more stringent wash procedure was applied.

Elution of phage from the plate was performed with 200 µl 20mM DTT in 10mM Tris/HCl pH8 per well for 10 min. The DTT phage eluate was added to 15ml of E.coli TG1, which were grown to an OD600 of 0.6-0.8 at 37°C in 2YT medium and incubated in 50ml plastic tubes for 45min at 37°C without shaking for phage infection. After centrifugation for 5 min at 4120 x g, the bacterial pellets were each resuspended in 600µl 2xYT medium, plated on 3xYT-CG agar plates and incubated overnight at 37°C. Colonies were scraped off the plates and phages were rescued and amplified as described above.

The second and third rounds of solid phase panning were performed according to the protocol of the first round. In the second selection round for some panning conditions the output of the first round was used for selections on cynomolgus C5 in order to enrich for cynomolgus cross-reactive antibodies.

For some panning conditions washing stringency was increased and antigen concentration was decreased within the three round of selection in order to generate high affinity antibodies.

The HuCAL GOLD® phagemid library was used to select specific Fab antibody fragments against human C5. First strategy was a solid phase panning on directly coated human C5 protein (panning procedure described above).

After the the 3rd panning round, the enriched phage pools were subcloned from the pMORPH®23 library vector (allowing efficient antibody display on the phage surface) into the pMORPH®x9_Fab_MH expression vector which mediates periplasmic expression of soluble Fabs. Single clones were picked and soluble Fabs were expressed from these single clones.

In total, 6624 clones were analyzed in primary screening which was performed by binding of the Fabs directly from the bacterial lysates to human C5 immobilized on Maxisorp microtiter plates. 1660 hits were obtained from the primary screening on human C5 with signals >5-fold over background. 384 hits were further analyzed in a secondary screening to confirm binding on human C5 and to screen for binding to the counter targets human C3 and C4.

Many primary hits could be confirmed on human C5 and showed no cross-reactivity to human C3 and C4, but only 6 Fabs had weak cross-reactivity to cynomolgus C5.

As a first consequence new solid phase pannings were performed alternating on human and cynomolgus C5. In parallel, quality controls of the purified cynomolgus C5 batch revealed a high amount of cynomolgus C3 within the cynomolgus C5 batch. Considering this results, a new method to screen for cynomolgus cross-reactive antibodies was applied. Cynomolgus C5 was captured from cynomolgus serum using an C5-binding polyclonal antibody (see Example 3, section 3). Using this method the initial primary hits were screened again on cynomolgus C5 and 56 clones were confirmed for binding to cynomolgus C5.

For the alternating solid phase pannings, the 1st round output of the most successful 12 human solid phase pannings was used for selections on cynomolgus C5 (protein batch contaminated with cynomolgus C3; not known during pannings). 376 clones were confirmed in a secondary screening for binding to human C5 and 361 clones for binding to cynomolgus C5 captured from cynomolgus serum.

Solution Panning on Biotinylated C5 Protein

The second panning variant was solution panning against biologically active (in hemolytic assays) biotinylated human C5 and biotinylated cynomolgus C5.

For this panning 200µl of Streptavidin magnetic beads (Dynabeads M-280; Dynal) were washed once with PBS and blocked with Chemiblocker for 2h at RT. 300µl of the PBS diluted phage were blocked also with Chemiblocker for 1-2h at RT on a rotator. The blocked phages were twice pre-adsorbed against 50µl blocked Streptavidin magnetic beads for 30min. The phage supernatant was transferred to a new blocked 2ml reaction tube and human biotinylated C5 was added and incubated for 1h at RT on a rotator. 100µl of the blocked Streptavidin magnetic beads were added to each panning pool an incubated for 10min on a rotator. The beads were collected with a particle separator (Dynal MPC-E) for approx. 2.5min and the solution was removed carefully.

Beads were then washed 7x in PBS/0.05% Tween using a rotator, followed by washing another three times with PBS. Elution of phage from the Dynabeads was performed by adding 200µl 20mM DTT in 10mM Tris/HCl pH 8 to each tube and incubation for 10min. Dynabeads were removed by the magnetic particle separator and the supernatant was added to 15ml of an E.coli TG-1 culture grown to OD600nm of 0.6-0.8. Beads were then washed once with 200µl PBS and together with additionally removed phages the PBS was added to the 15ml E.coli TG-1 culture. For phage infection, the culture was incubated in 50ml plastic tubes for 45min at 37°C without shaking. After centrifugation for 5min at 4120 x g, the bacterial pellets were resuspended each in 600µl 2xYT medium, plated on 3xYT-CG agar plates and incubated overnight at 37 °C. Colonies were scraped off the plates and phages were rescued and amplified as described above. The second and third rounds of selection were performed in an identical way to the first round of selection.

A further panning strategy was solution panning using human C5 and alternating human and cynomolgus C5 (protein batch contaminated with cynomolgus C3, not known during pannings). Therefore the proteins were biotinylated and the retained bio-functionality after the biotinylation procedure was confirmed in hemolytic bioassays.

The phage-antigen complex was captured on Streptavidin magnetic beads via the biotin moiety of the antigen. After washing only specific bound phage were eluted (panning procedure described above).

First screening was done on directly coated proteins (see Example 3, section 1) and only 80 clones could be confirmed on human C5. Due to the fact that during the pannings the antigen was kept in solution, a new screening method was developed. In a solution ELISA the Fabs were incubated with biotinylated antigen on a NeutrAvidin plate. Using this solution screening procedure, a significantly higher amount of human and cynomolgus C5 specific clones could be selected. These results confirmed that many Fabs derived from solution pannings recognize C5 only in solution or when captured (e.g. via a polyclonal C5-binding antibody).

2. Subcloning and Expression of Selected Fab Fragments

To facilitate rapid expression of soluble Fabs, the Fab-encoding inserts of the selected HuCAL GOLD® phages were subcloned via XbaI and EcoRI into the E. coli expression vector pMORPH®x9_MH. Fab fragments carry a C-terminal Myc tag and as a second C-terminal tag the 6x His-tag (Chen *et al.*, Gene 139:73-75 (1994)). After transformation of the expression plasmids into E. coli TG1 F- cells chloramphenicol-resistant single clones were picked into the wells of a sterile 384-well microtiter plate pre-filled with 60µl 2xYT-CG medium and grown o/n at 30°C. 5µl of each E.coli TG-1 o/n culture were transferred to a fresh, sterile 96-well microtiter plate pre-filled with 40µl 2xYT medium supplemented with 34µg/ml chloramphenicol per well. The microtiter plates were incubated at 30°C shaking at 400rpm on a microplate shaker until the cultures were slightly turbid (~2-4 h) with an OD600nm of ~0.5. To these expression plates, 10µl 2xYT medium supplemented with 34µg/ml chloramphenicol and 3mM IPTG (isopropyl-ß-D-thiogalactopyranoside) was added per well (end concentration 0.5mM IPTG). The microtiter plates were sealed with a gas-permeable tape, and incubated o/n at 30°C shaking at 400rpm. To each well of the expression plates, 15µl BEL buffer was added containing 2.5mg/ml lysozyme, 4mM EDTA and 10U/µl Benzonase and incubated for1h at 22°C on a microtiter plate shaker (400rpm) followed by an optional freezing step for at least 2h at -80°C. The BEL extracts were used for binding analysis by ELISA or Fab SET screening after affinity maturation.

Expression of Fab fragments encoded by pMORPH®x9_Fab_MH in TG-1 cells was carried out in shaker flask cultures using 750ml of 2xYT medium supplemented with 34µg/ml chloramphenicol. Cultures were shaken at 30°C until the OD600nm reached 0.5. Expression was induced by addition of 0.75mM IPTG for 20h at 30°C. Cells were disrupted using lysozyme and Fab fragments isolated by Ni-NTA chromatography (Qiagen, Hilden, Germany). Buffer exchange to 1 x Dulbecco's PBS (pH 7.2) was performed using PD10 columns. Samples were filtered sterile (0.2µm, Millipore). Purity of samples was determined in denatured, reduced state by SDS-PAGE (15% Criterion Gels, BioRad) and in native state by size exclusion chromatography (HP-SEC). Protein concentrations were determined by UV-spectrophotometry (Krebs *et al.*, J. Immunol. Methods 254:67-84 (2001)).

On Fab level, the overall expression rates and the percentage of monomeric fraction in SEC (Size Exclusion Chromatography) ranged from acceptable to good for most of the identified antibody fragments. 64 parental Fabs were expressed and 61 Fabs could be purified. 60 affinity matured Fabs were purified in the mg scale. Most of the Fabs were good expressors and had no aggregation tendency.

Example 3: Identification of C5-specific antibodies from the HuCAL GOLD® Library

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Below four different Enzyme Linked Immunosorbent Assay (ELISA) methods describe the screening of C5-binding antibodies (as bacterial BEL lysates or purified Fabs) on specific and counter antigens.

1. Screening on Directly Coated protein

Maxisorp (Nunc, Rochester, NY, USA) 384 well plates were coated with 20µl per well of 2.5µg/ml antigen (human C5 and the counter proteins human C3 and C4) in PBS, pH 7.4 o/n at 4°C. In parallel, plates were coated with 20µl per well of 5µg/ml sheep anti-human IgG, Fd fragment specific (The Binding Site, Birmingham, UK), diluted in PBS, pH 7.4 to check for Fab expression level.

The plates were blocked with PBS/ 0.05% Tween 20 (PBST) containing 5% milk powder for 1-2h at RT. After washing the wells with PBST, BEL-extracts, purified HuCAL GOLD® Fabs or control Fabs diluted in PBS were added and incubated for 1 h at RT. To detect Fab binding, anti-HIS6 antibody coupled to peroxidase was applied (Roche).

For detection of POD-conjugates fluorogenic substrate QuantaBlu (Pierce) was used according to manufacturer's instructions. Between all incubation steps, the wells of the microtiter plates were washed three times and five times with PBST after the final incubation with the secondary antibody. Fluorescence was measured in a Tecan GENios Pro plate reader.

2. Solution Screening with Biotinylated Proteins

The ELISA method decribed below was used for screening of HuCAL GOLD® Fabs after solution pannings using biotinylated complement proteins.

NeutrAvidin plates were blocked with 1x Chemiblocker (Chemicon) diluted in PBS o/n at 4°C. These plates were used to screen for binding to human C5 and to the counter targets C3 and C4. In parallel, Maxisorp 384 well plates (Nunc, Rochester, NY, USA) were coated with 20µl per well of 5 µg/ml sheep anti-human IgG, Fd fragment specific (The Binding Site, Birmingham, UK), diluted in PBS, pH 7.4. These plates were used to check for Fab expression levels and for non-specific biotin binding. On the next day, coated Maxisorp plates were washed 2x with PBST and blocked with 3% BSA in TBS for 1-2h at RT. Periplasmic BEL extracts containing Fabs or purified HuCAL GOLD® Fabs were added to both blocked NeutrAvidin and Maxisorp plates.

Subsequently, 20µl per well of biotinylated human C5 (to detect specific binding) and in parallel, biotinylated human C3 and C4 (to detect unwanted binding) were added to wells of the NeutrAvidin plates. The biotinylated antigens were incubated with the HuCAL GOLD® Fabs for 1-2h at RT. Biotinylated unrelated antigen Transferrin was then added to the

Maxisorp plates to check for biotin binding Fabs (in this case the HuCAL®-Fab fragments were previously captured via anti-Fd antibody).

Following secondary antibodies were applied for detection: Alkaline phosphatase (AP)-conjugated Streptavidin-AP AffiniPure F(ab')2 fragment, goat anti-human, was added to the Maxisorp expression plates; anti-HIS6 Peroxidase conjugated mouse antibody, Roche, was added to the NeutrAvidin plates and Streptavidin-Alkaline Phosphatase, ZYMED, was added to the Maxisorp plates with the biotinylated Transferrin.

For detection of AP-conjugates, fluorogenic substrate AttoPhos (Roche Diagnostics, Mannheim, Germany) and for detection of POD-conjugates, fluorogenic substrate QuantaBlu (Pierce) were used according to manufacturer's instructions. Fluorescence was measured in a Tecan GENios Pro plate reader.

Using this method it was possible to screen for anti-human C5 Fabs which recognize human C5 in solution and to exclude antibodies binding to the biotin moiety of the target antigens.

3. Determination of Cross-reactivity to Cynomolgus C5

A polyclonal C5-binding antibody (US Biological Cat#C7850-24) was used to capture cynomolgus C5 from cynomolgus serum.

384 well Maxisorp plates were coated with 20µl/well of 5µg/ml polyclonal C5-binding in PBS and incubated o/n at 4°C. On the next day the plates were washed 3x with PBST and blocked with 100µl/well of diluent (4% BSA/ 0.1% Tween20/ 0.1% Triton-X 100/ PBS) for 2 hours at RT. Cynomolgus serum was diluted 1:20 in diluent (4% BSA/ 0.1% Tween20/ 0.1% Triton-X 100/ PBS) (~approx. concentration of cynomolgus C5 4µg/ml) and 20µl/well was added to the 2x PBST washed Maxisorp plates. After 1h incubation at RT the plates were washed 3x PBST and BEL lysates containing Fab fragments or purified Fabs were added and incubated for 1h at RT. The plates were washed again and detection antibody anti-HIS6-POD (Roche #1965085), was added. POD substrate, BM Blue, soluble, (Roche Applied Science) was added and the reaction was stopped with 1M H_2SO_4. Absorbance was read at 450 nm using the BMG Reader device.

Example 4: Affinity Maturation

1. Construction of Affinity Maturation Libraries of Selected C5-Binding Fabs

To increase affinity and biological activity of selected antibody fragments, L-CDR3 and H-CDR2 regions were optimized in parallel by cassette mutagenesis using trinucleotide directed mutagenesis (see *e.g.*, Virnekas *et al.*, Nucleic Acids Res. 22:5600-5607 (1994)), while the framework regions were kept constant. Prior to cloning for affinity maturation, all parental Fab fragments were transferred from the corresponding expression vector

(pMORPH®x9_MH) into the CysDisplayTM vector pMORPH®25 via XbaI/EcoRI. pMORPH®25 was created from the HuCAL GOLD® display vector pMORPH®23 by removal of one BssHII site interfering with library cloning for H-CDR2 optimization. For optimizing L-CDR3 of parental Fabs, the L-CDR3, framework 4 and the constant region of the light chains (405 bp) of the binders were removed by BpiI/SphI and replaced by a repertoire of diversified L-CDR3s together with framework 4 and the constant domain.

10 parental C5-binding Fabs were divided in 7 pools according to different selection criteria and only Fabs with same framework were put together: (1) MOR07086; (2) MOR06525 + 6756 (same framework); (3) MOR06757; (4) MOR06763; (5) MOR07087; (6) MOR07091 + 7092 (same framework); (7) MOR07093 + 7094 (same framework).

Approximately 1.5µg of the single Fab vector fragment and of the Fab pool were ligated with a 3 to 5-fold molar excess of the insert fragment carrying the diversified L-CDR3s. In a second library set, the H-CDR2 (XhoI/BssHII) was diversified while the connecting framework regions were kept constant. In order to monitor the cloning efficiency, the parental H-CDR2 was replaced by a dummy before the diversified H-CDR2 cassette was cloned in.

Ligation mixtures of the different libraries were electroporated into E.coli TOP10 F' cells (Invitrogen) yielding from $2x10^7$ to $2x10^8$ independent colonies. The libraries were amplified. For quality control, several single clones per library were randomly picked and sequenced using primers CFR84 (VL) and OCAL_Seq_Hp (VH).

As described above, seven maturation sub pools were generated and kept separate during the subsequent selection process.

14 different affinity maturation libraries (one LCDR3 and one HCDR3 library for each lead or pool) were generated by standard cloning procedures and transformation of the diversified clones into electro-competent E. coli TOP10F' cells (Invitrogen). Library sizes were good, being in the range of $2x10^7$ – $5x10^8$. Sequencing of randomly picked clones showed a diversity of 100%. No parental binders but derivatives of all respective parental input binders were found. Finally phages of all 14 libraries were prepared separately.

Table 2. Overview of maturation libraries

MOR0	Maturation	VH/VL Type	Library Size
6757	HCDR2	VH3	3.70x10E7
6763	HCDR2	VH3	4.95x10E7
7086	HCDR2	VH1A	1.58x10E8
7087	HCDR2	VH1A	7.85x10E7
6525 + 6756	HCDR2	VH5	5.22x10E7
7091+ 7092	HCDR2	VH5	3.51x10E7
7093 + 7094	HCDR2	VH2	2.01x10E7
6757	LCDR3	Vkappa1	1.89x10E7
6763	LCDR3	Vlambda2	7.35x10E7
7086	LCDR3	Vlambda3	7.54x10E7
7087	LCDR3	Vkappa1	5.46x10E7
6525 + 6756	LCDR3	Vlambda2	8.50x10E7
7091+ 7092	LCDR3	Vlambda3	4.98x10E8
7093 + 7094	LCDR3	Vlambda2	1.33x10E8

2. Preparation of Antibody-Phages for Affinity Maturation

The HuCAL® maturation libraries were amplified in 2xYT medium containing 34µg/ml chloramphenicol and 1% glucose (2xYT-CG). After infection with VCSM13 helper phage at an OD600nm of 0.5 (30min at 37°C without shaking; 30min at 37°C shaking at 250rpm), cells were spun down (4120 x g; 5min; 4°C), resuspended in 2xYT/ 34µg/ml chloramphenicol/ 50µg/ml kanamycin/ 0.25mM IPTG and grown o/n at 22°C. Phages were PEG-precipitated twice from the supernatant, resuspended in PBS and used for the maturation pannings described below.

3. Standard Solution Maturation Panning on Biotinylated C5 Protein

About 10^{12} phages rescued from the generated affinity maturation libraries, as described above, were subjected to pannings performed under very stringent conditions to select for affinity improved C5 specific Fabs.

Solution pannings using the respective phage pools were either performed using biotinylated human C5 or alternating biotinylated human and cynomolgus C5 proteins. In order to increase panning stringency and to select for improved off-rates, antigen concentration was decreased and prolonged washing periods were applied (washing conditions are listed in Table 3).

Table 3. Increased washing conditions within the selection rounds of solution maturation pannings

Selection Rd.	Washing conditions (modified: stringent)
1st round	• 4x PBS/ 0.05% Tween 5min on rotator • 3x PBS/ 0.05% Tween 15min on rotator-> transfer magnetic beads with the captured antigen and phages to a fresh blocked tube • 4x PBS quick • 3x PBS 5min on rotator-> transfer magnetic beads with the captured antigen and phages to a fresh blocked tube

2nd round	• 3x PBS/ 0.05% Tween quick • 7x PBS/ 0.05% Tween 15min on rotator-> transfer magnetic beads with the captured antigen and phages to a fresh blocked tube • 3x PBS quick • 7x PBS 15min on rotator-> transfer magnetic beads with the captured antigen and phages to a fresh blocked tube
3rd round	• 5x PBS/ 0.05% Tween quick • 8x PBS/ 0.05% Tween 15min on rotator • 1x PBS/ 0.05% Tween **o/n** on rotator • 3x PBS/ 0.05% Tween quick • 6x PBS/ 0.05% Tween 15min on rotator -> transfer magnetic beads with the captured antigen and phages to a fresh blocked tube • 5x PBS quick • 8x PBS 15min on rotator -> transfer magnetic beads with the captured antigen and phages to a fresh blocked tube

Pre-blocked phage (1:2 mixture with 2x Chemiblocker incubated for 1h at RT) were incubated with low concentration of biotinylated C5 protein for 1-2h at RT. The panning strategy is similar to a standard solution panning described above. The phage antigen complex was captured via the biotin moiety of C5 to pre-blocked Streptavidin magnetic beads 30min at RT. Beads were then washed more stringently compared to a normal panning. Elution and amplification of phage was performed as described above.

The second and third rounds of selection were performed in an identical way to the first round, but at higher stringency washing conditions and lower antigen concentrations. For each antibody lead or pool several different pannings were performed. For each panning strategy different stringency conditions were applied. Panning strategies are summarized in Table 4.

Table 4. Overview of solution maturation pannings 1783 and 1784 on biotinylated human C5 and biotinylated cynomolgus C5

Panning #	Library	Panning mode	Antigen 1st round	Antigen 2nd round	Antigen 3rd round	Antigen Conc.	Washing
1783.1	MOR06525 + 6756 HCDR2	solution Streptavidin beads	human C5	human C5	human C5	50nM human / 5nM human / 0.25nM human	modified (more stringent)
1783.2	MOR07086 HCDR2						
1783.3	MOR06763 HCDR2						
1783.4	MOR07087 HCDR2						
1783.5	MOR06525 + 6756 LCDR3						
1783.6	MOR07086 LCDR3						
1783.7	MOR06763 LCDR3						
1783.8	MOR07087 LCDR3						
1783.9	MOR06525 + 6756 HCDR2	solution Streptavidin beads	human C5	cyno C5	human C5	25nM human / 5nM cyno / 0.25nM human	modified (more stringent)
1783.10	MOR07086 HCDR2						
1783.11	MOR06763 HCDR2						
1783.12	MOR06525 + 6756 LCDR3						
1783.13	MOR07086 LCDR3						
1783.14	MOR06763 LCDR3						
1784.1	MOR06757 HCDR2	solution Streptavidin beads	human C5	human C5	human C5	50nM human / 5nM human / 0.25nM human	modified (more stringent)
1784.2	MOR07091 + 7092 HCDR2						
1784.3	MOR07093 + 7094 HCDR2						

1784.4	MOR06757 LCDR3						
1784.5	MOR07091 + 7092 LCDR3						
1784.6	MOR07093 + 7094 LCDR3						
1784.7	MOR06757 HCDR2	solution Streptavidin beads	human C5	cyno C5	human C5	25nM human / 5nM cyno / 0.25nM human	modified (more stringent)
1784.8	MOR07091 + 7092 HCDR2						
1784.9	MOR07093 + 7094 HCDR2						
1784.10	MOR07087 HCDR2						
1784.11	MOR06757 LCDR3						
1784.12	MOR07091 + 7092 LCDR3						
1784.13	MOR07093 + 7094 LCDR3						
1784.14	MOR07087 LCDR3						

After maturation pannings, the enriched phagemid pools were sub-cloned into pMORPH®x9_MH expression vector.

4. Cross-Combination of Optimized VL (L-CDR3) with Optimized VH (H-CDR2)

For further improvement of affinity and potency, the independently optimized heavy and light chains from matured antibodies, derived from the same parental clone, were combined (see e.g., Rauchenberger *et al.*, J. Biol. Chem. 278:38194-38205 (2003); Chen *et al.*, J. Mol. Biol. 293:865-881 (1999); and Schier *et al.*, J. Mol. Biol. 263:551-567 (1996)). This procedure, called cross-cloning, was applied for binders deriving from the same parental clones.

5. Affinity Screening and Maturation Panning Outcome

A total of 2640 clones derived from all pannings were screened as bacterial lysates for improved affinities on human C5. Preliminary affinities were estimated by solution equilibrium titration (SET). Based on their estimated affinities, clones derived from each parental Fab or Fab pools were sequenced. Table 5 shows number of sequenced clones and number of obtained unique sequences for each panning condition.

Table 5. Overview of affinity improved clones selected for sequence analysis

Parental/Maturation	Antigen	Sequenced clones	Unique Sequences	Parental of unique
MOR06525 + 6756 HCDR2	hu/hu/hu	10	9	6525
MOR07086 HCDR2	hu/hu/hu	10	4	7086
MOR06763 HCDR2	hu/hu/hu	22	10	6763(8x), 7086(2x)
MOR07087 HCDR2	hu/hu/hu	10	4	7087
MOR06757 HCDR2	hu/hu/hu	10	0	
MOR07091 + 7092 HCDR2	hu/hu/hu	24	7	7092
MOR07093 + 7094 HCDR2	hu/hu/hu	10	10	7093
MOR06525 + 6756 LCDR3	hu/hu/hu	20	5	6756
MOR07086 LCDR3	hu/hu/hu	10	5	7086
MOR06763 LCDR3	hu/hu/hu	10	8	7086
MOR07087 LCDR3	hu/hu/hu	6	1	7086
MOR06757 LCDR3	hu/hu/hu	16	0	
MOR07091 + 7092 LCDR3	hu/hu/hu	6	6	7091(1x), 7092(5x)
MOR07093 + 7094 LCDR3	hu/hu/hu	10	9	7094
MOR06525 + 6756 HCDR2	hu/cyno/hu	10	8	6525
MOR07086 HCDR2	hu/cyno/hu	10	6	7086
MOR06763 HCDR2	hu/cyno/hu	22	5	6763
MOR06757 HCDR2	hu/cyno/hu	15	2	6757
MOR07091 + 7092 HCDR2	hu/cyno/hu	15	6	7091(3x), 7092(3x)
MOR07093 + 7094 HCDR2	hu/cyno/hu	10	10	7093
MOR07087 HCDR2	hu/cyno/hu	10	6	7087(5x), 7086(1x)
MOR06525 + 6756 LCDR3	hu/cyno/hu	12	0	
MOR07086 LCDR3	hu/cyno/hu	10	1	7086
MOR06763 LCDR3	hu/cyno/hu	10	0	
MOR06757 LCDR3	hu/cyno/hu	9	1	7094
MOR07091 + 7092 LCDR3	hu/cyno/hu	11	9	7091(6x), 7092(3x)
MOR07093 + 7094 LCDR3	hu/cyno/hu	10	7	7094
MOR07087 LCDR3	hu/cyno/hu	10	0	
Sum		338	139	

6. Sequence Analysis and Selection of Affinity Optimized Fabs for Protein Production

A very good diversity was maintained by recovering derivatives of all 10 parental Fabs. The nucleotide sequences of the heavy chain (VH) for 188 HCDR2 improved clones and the light chain (VL) variable regions for 150 improved LCDR3 clones were determined. 87 unique HCDR2 and 52 unique LCDR3 sequences were selected for a detailed analysis of sequence diversity within the matured CDRs. Fabs containing possible glycosylations sites in the CDRs were omitted from further characterizations.

The VH and VL sequence analysis and affinity data showed that all 10 parental Fabs yielded affinity-improved successors. Parental Fabs MOR06525, MOR06757, MOR06763, MOR07087 and MOR07094 yielded only HCDR2 improved clones and parentals MOR06756 and MOR07093 yielded only LCDR3 improved clones. MOR07086, MOR07091 and MOR07092 had matured clones for both VH and VL. This later allowed cross-cloning of VH and VL matured chains. From all data, 60 clones with best affinity and highest diversity in the matured CDRs were selected for Fab expression. Selected VH and VL amino acid, as well as nucleotide sequences, are listed in Table 1.

Example 5: IgG Conversion

1. Conversion into Human IgG2 Format

In order to express full length immunoglobulin (Ig), variable domain fragments of heavy (VH) and light chains (VL) were subcloned from the pMORPH®x9_MH Fab expression vectors into pMORPH®2_h_Ig vector series for human IgG2. Restriction enzymes MfeI, and BlpI were used for subcloning of the VH domain fragment into pMORPH®2_h_IgG2. Subcloning of the VL domain fragment into pMORPH®2_h_Igκ was performed via the EcoRV and BsiWI sites, whereas subcloning into pMORPH®2_h_Igλ2 was done using EcoRV and HpaI.

All ten parental Fabs (MOR06525, 6756, 6757, 6763, 7086, 7087, MOR07091, 7092, 7093 and 7094) were converted into human IgG2. The IgGs were also expressed.

2. Conversion into Human IgG1AA Format

In order to express full length immunoglobulin, variable domain fragments of Fab heavy (VH) and light chains (VL) were subcloned from the Fab expression vectors into IgG1 expression vectors. Restriction enzymes MfeI, and BlpI were used for subcloning of the VH domain fragment into pMORPH®2_h_IgG1AA, in which leucines at positions 234 and 235 were mutated to alanines to abrogate FcRγ binding and attenuate effector functions. The restrictions enzymes EcoRV and HpaI were used to subclone of the VL domain fragment into pMORPH®2_h_Igλ2.

Following matured Fabs with desired profile were subcloned into human IgG1AA format: MOR07832, 7834, 7872, 7876, 7829, 7871, 7865, 7873, 7830, 7878, 7910. Cross-cloning on IgG level was achieved by transfecting cells with combinations of light and heavy chain constructs. For example, MOR08114 was the product of the germlined heavy chain from MOR07829 and the germlined light chain from MOR07871. Table 6 summarizes the most relevant cross-cloned germlined IgGs.

Table 6. Overview of most relevant cross-cloned germlined IgGs

MOR0 Nr.	VH/VL germlined	VH/VL		matured CDRs		format
		VH	VL	matured VH	matured VL	
8114	yes	7829	7871	7091/HCDR2	7091/LCDR3	hulg1AA
8125	yes	7091	7873	-	7091/LCDR3	hulg1AA
8126	yes	7829	7873	7091/HCDR2	7091/LCDR3	hulg1AA
8127	yes	7830	7873	7091/HCDR2	7091/LCDR3	hulg1AA
8128	yes	7092	7878	-	7092/LCDR3	hulg1AA
8129	yes	7909	7092	7092/HCDR2	-	hulg1AA
8130	yes	7909	7878	7092/HCDR2	7092/LCDR3	hulg1AA
8131	yes	7910	7092	7092/HCDR2	-	hulg1AA
8132	yes	7910	7878	7092/HCDR2	7092/LCDR3	hulg1AA

3. Transient Expression and Purification of Human IgG

Eukaryotic HKB11 and HEK293 cells were transfected with an equimolar ratio of IgG heavy and light chain expression vector DNA. Cell culture supernatant was harvested at 3 or

7 days post transfection and subjected to standard protein A affinity chromatography (rProteinA FF or MabSelect SURE, GE Healthcare). As not otherwise stated, buffer exchange was performed to 1 x Dulbecco's PBS (pH 7.2, Invitrogen) and samples were sterile filtered (0.2µm). Purity of IgG was analyzed under denaturing, reducing and non-reducing conditions in SDS-PAGE or by using Agilent BioAnalyzer and in native state by HP-SEC.

Example 6: Germlining

IgG constructs were germlined via site-directed mutagenesis using QuickChange® Site-Directed Mutagenesis kit (Stratagene). The N-terminal DI of MOR08111 Vλ2 were changed to ES to match human germline sequence as well as to avoid a terminal Q (N-terminal Q can form pyroglutamine). N-terminal DI of MOR08110 Vλ3, MOR08113 Vλ3, and MOR08114 Vλ3 were germlined to SY, the most commonly found sequence in human λ3 genes. N-terminal QVQ of MOR08111 VH2 was germlined to EVT to match a λ2 gene and avoid terminal Q. N-terminal Q in MOR08109 VH5, MOR08110 VH5, MOR08113 VH5 and MOR08114 VH5 was also mutated to E.

Framework sequences for MOR08109 Vλ3 were synthesized to match the human λ3j gene and cloned into the expression vector using NheI and HpaI restriction sites. Sequence alignments of the antibodies variable domains with their respective closest related human germline sequences are shown in FIG. 1.

Example 7: Affinity Determination

1. Kon/Koff and K_D Determination of anti-human C5 antibodies using Surface Plasmon Resonance (Biacore)

It was determined that anti-Fab antibodies used to immobilize Fabs to the Biacore chip were influencing differently the binding affinity of each Fab for human C5, thus making the comparison of the Fabs to each other difficult. Biacore analysis was performed on IgG antibodies.

A CM4 chip was coated with 50µg/ml goat anti-human Fc antibody (500-2000 RU) in 10mM acetate buffer, pH 4.5, using standard EDC-NHS amine coupling chemistry. Each anti-human C5 IgG was captured on the chip in HBS-EP buffer at constant flow rate of 10µl/min for a contact time leading to a ligand density around 20 RU. After capturing the anti-hu C5 IgG, different concentrations of human or cynomolgus C5, in the range between 0.156nM to 2.5nM, were injected. Each cycle was completed with two regeneration steps with phosphoric acid. All running conditions were carried out at 25°C in 1x HBS-EP buffer. The resulting signals were adjusted by double referencing, substracting the refraction index values from the reference flow cell and the binding step with no analyte. Data were collected

at 10Hz and analyzed using the Biacore T100 Evaluation Software Version 1.1 (GE). This program uses a global fitting analysis method for the determination of rate and affinity constants for each interaction.

The specificity of the antibodies were measured. Preferably, the Kon and Koff values for binding to human and cynomolgus C5 are as follows: Kon > 1 x 10^5, Koff < 1 x 10^{-4}). These measurements were performed in Biacore for the germlined IgGs and resulting data are listed in Table 7.

Table 7. K_D, Kon and Koff values of the germlined IgGs determined in Biacore

antiC5 final IgG	C5 sample	ka [1/Ms]	kd [1/s]	KD [pM]
MOR08109	huC5	2.13E+06	2.56E-05	12
	cynoC5	1.23E+06	4.49E-05	37
MOR08110	huC5	4.15E+06	4.69E-05	12
	cynoC5	1.81E+06	9.24E-05	60
MOR08111	huC5	1.00E+06	3.07E-05	31
	cynoC5	8.91E+05	1.28E-04	144
MOR08113	huC5	2.51E+06	6.77E-05	28
	cynoC5	1.53E+06	1.27E-04	83
MOR08114	huC5	2.09E+06	3.12E-05	15
	cynoC5	1.06E+06	3.13E-05	31
5G1.1	huC5	1.29E+06	7.22E-05	56

2. Determination of Picomolar Affinities Using Solution Equilibrium Titration (SET) for Purified Fabs or Fabs Bacterial Lysates (Meso Scale Discovery (MSD))

For K_D determination by solution equilibrium titration (SET), monomer fractions (at least 90% monomer content, analyzed by analytical SEC; Superdex75, Amersham Pharmacia) of Fab protein were used. Affinity determination in solution was basically performed as described in the literature (Friguet *et al.*, J. Immunol Methods 77:305-319 (1985)). In order to improve the sensitivity and accuracy of the SET method, it was transferred from classical ELISA to ECL based technology (Haenel *et al.*, Anal Biochem 339:182-184 (2005).

1mg/ml goat-anti-human $(Fab)_2$ fragment specific antibodies (Dianova) were labelled with ECL Sulfo-TAGTM NHS-Ester (Meso Scale Discovery, Gaithersburg, MD, USA) according to manufacturer's instructions. Experiments were carried out in polypropylene microtiter plates and PBS pH 7.4 with 0.5% BSA and 0.02% Tween 20 as assay buffer. Unlabelled antigen was diluted in 2^n series, starting with a concentration at least 10 times

higher than the K_D. Wells without antigen were used to determine Bmax values; wells with neither antigen nor Fab were used to determine background. After addition of *e.g.* 10pM Fab (final concentration in 60µl final volume), the mixture was incubated over night at RT. The applied Fab concentration was similar to or below the expected K_D.

Streptavidin MSD plates were coated with 0.2µg/ml biotinylated human C5 (30µl/well) and blocked with 5% BSA in PBS. Subsequently the equilibrated samples were transferred to those plates (30µl per well) and incubated for 20min. After washing, 30µl/well of the ECL Sulfo-tag labeled detection antibody (goat anti-human (Fab)2) in a final dilution of 1:1500 was added to the MSD plate and incubated for 30min on an Eppendorf shaker (700rpm).

After washing and adding 30µl/well MSD Read Buffer T with surfactant Electrochemiluminescence signals were detected using a Sector Imager 6000 (Meso Scale Discovery, Gaithersburg, MD, USA).

Data were evaluated with XLfit (IDBS) software applying customized fitting models. For data evaluation *i.e.* K_D determination of Fab molecules the following fit model was used (model of Abraham et al16, modified according to *et al.*, 200515): y=Bmax-(Bmax/(2*cFab)*(x +cFab+KD-sqrt((x+cFab+ KD)*(x+cFab+ KD)-4*x*cFab))); cFab: applied Fab concentration; x: applied total soluble antigen concentration (binding sites); sqrt: square root. Using the assay conditions described above (monomeric) affinities for the affinity-optimized C5-binding Fabs were determined in solution.

Parental Fabs

In order to further characterize the C5-binding antibodies, affinity of the parental Fabs to human C5 was determined. Because characterization focus was on efficacy in hemolytic assays, affinity measurements were done only for the most relevant Fabs. For a reliable determination of monovalent affinities only Fab batches were used for measurements which showed ≥ 90% monomeric fraction in a qualitative size exclusion chromatography.

Affinities of the 10 parental Fabs which entered affinity maturation are summarized in Table 8. Affinities ranged from 72 pM to 3.7 nM.

Table 8. Affinities of the 10 parental Fabs determined in SET

	SET	
MOR0 Number	KD [pM]	(n = 1)
6525	72	
6756	1521	
6757	1186	
6763	820	
7086	108	
7087	3793	
7091	324	
7092	229	
7093	576	
7094	1364	
3207 (negative control)	no binding	

Matured Fabs

Monovalent affinities of the purified Fabs to human C5 were measured in SET. Affinities were in the low pM range and best affinities were obtained for derivatives of MOR07086, 7091, 7092 and 7093. Subsequently affinity measurements of these derivatives to cynomolgus C5 showed affinities in the mid to low pM range.

The affinity maturation process was very successful resulting in a repertoire of binders with markedly improved affinity. Table 9 summarizes affinities to human and cynomolgus C5 of the best improved binders. Certain Fabs have K_D to human C5 ≤ 30pM and to cynomolgus C5 ≤ 150pM.

Table 9. Overview of affinities to human and cynomolgus C5 for the best affinity improved Fabs

MOR	Matured	SET hu C5 (n=1-2) KD [pM]	SET cyno C5 (n=1) KD [pM]
6525		270 / 29	
7312	HCDR2	437	
7313	HCDR2	137	
7318	HCDR2	116	
6757		3650 / 1245	
7515	HCDR2	491	70
7507	HCDR2	179	
6763		673 / 962	
7520	HCDR2	62	
7086		12 / 65	10
7321	HCDR2	7	30
7322	HCDR2	8	14
7323	HCDR2	5	10
7324	HCDR2	55 / 130	
7364	LCDR3	22	974
7365	LCDR3	10	38
7366	LCDR3	10	191
7367	LCDR3	10	151
7368	LCDR3		384
7369	LCDR3	2	83
7370	LCDR3	12	500
7087		120	
7327	HCDR2	361	
7328	HCDR2	2477 / 1730	
7091		135 / 138	704
7328	HCDR2	429	110
7329	HCDR2	399	75
7330	HCDR2	75*	39*

MOR	Matured	SET hu C5 (n=1-2) KD [pM]	SET cyno C5 (n=1) KD [pM]
7071	LCDR3	3	4
7072	LCDR3	2	3
7073	LCDR3	13 / 13	6
7074	LCDR3	25	8
7092		96	491
7331	HCDR2	14	36
7332	HCDR2	4	13
7905	HCDR2	7	10
7910	HCDR2	27	31
7375	LCDR3	72	60
7377	LCDR3	29	141
7378	LCDR3	32	70
7379	LCDR3	25	122
7093		431 / 992	3146
7333	HCDR2	47	107
7334	HCDR2	4	15
7335	HCDR2	23	23
7336	HCDR2	11	
7390	HCDR2	46	
7094			
7380	LCDR3	15	13
7381	LCDR3	99	
7382	LCDR3	70	
7383	LCDR3	49	
7384	LCDR3	93	
7385	LCDR3	25	
7386	LCDR3	[illegible]	

*settling (no reliable measurement)

3. K_D determination of IgG molecules using Solution Equilibrium Titration (SET)

Affinities of the germlined IgGs (human IgG1AA format) to human and cynomolgus C5 were determined in SET as described below. Similar data sets between two independent measurements showed higher affinities of the lead IgGs to human C5 than reference IgG 5G1.1 (see U.S. Pat. NO. 6,355,245). Final IgGs had affinities for human C5 ranging from 1 to 14pM and affinities to cynomolgus C5 ranging from 3 to 29pM.

Table 10. K_D values determination for the final lead IgGs (human IgG1AA format) in SET

		1st measurement		2nd measurement	
		human C5 KD [pM]	cyno C5 KD [pM]	human C5 KD [pM]	cyno C5 KD [pM]
hu IgG1AA germlined	MOR08109	4	13	2	6
	MOR08110	7	18	3	8
	MOR08111	5	14	3	17
	MOR08113	14	29	8	16
	MOR08114	1	5	2	4
hu IgG2/4 (reference IgG)	5G1.1	24	no binding	19	no binding

For K_D determination by solution equilibrium titration (SET), monomer fractions of IgG protein were used (at least 90% monomer content, analyzed by analytical SEC MALS; Tosoh TSKgel G3000SWXL, Wyatt Treos miniDAWN). Affinity determination in solution was basically performed as described in the literature (Friguet *et al.*, J. Immunol Methods 77:305-

319 (1985)). In order to improve the sensitivity and accuracy of the SET method, it was transferred from classical ELISA to ECL based technology (Haenel *et al.*, Anal Biochem 339:182-184 (2005)).

1mg/ml goat-anti-human $(Fab)_2$ fragment specific antibodies (Dianova) were labelled with ECL Sulfo-TAGTM NHS-Ester (Meso Scale Discovery, Gaithersburg, MD, USA) according to the manufacturer's instructions. The experiments were carried out in polypropylene microtiter plates and PBS pH 7.4 with 0.5% BSA and 0.02% Tween 20 as assay buffer. Unlabeled antigen was diluted in 2n or 1.75n series, respectively, starting with a concentration at least 10 timer higher than the K_D. Wells without antigen were used to determine Bmax values; wells containing neither antigen nor IgG were used to determine background. After addition of *e.g.* 10pM IgG (final concentration in 60µl final volume), the mixture was incubated over night at RT. The applied IgG concentration was similar to or below the expected K_D.

Streptavidin MSD plates were coated with 0.2µg/ml biotinylated human C5 (30µl/well) and blocked with 5% BSA in PBS. Subsequently the equilibrated samples were transferred to those plates (30µl per well) and incubated for 20min. After washing, 30µl/well of the ECL Sulfo-tag labeled detection antibody (goat anti-human $(Fab)_2$) in a final dilution of 1:1500 was added to the MSD plate and incubated for 30min on an Eppendorf shaker (700 rpm).

Electrochemiluminescence signals were detected after washing and adding 30µl/well MSD Read Buffer T with surfactant using a Sector Imager 6000 (Meso Scale Discovery, Gaithersburg, MD, USA).

Data were evaluated with XLfit (IDBS) software applying customized fitting models. For data evaluation *i.e.* K_D determination of IgG molecules the following fit model for IgG was used (modified according to Piehler *et al.*, 199717): y=Bmax/(cIgG/2)*(cIgG/2-((x+cIgG+KD)/2-((x+cIgG+KD)^2/4-x*cIgG^0.5)^2/(2*IgG)); cIgG = applied IgG concentration, complete molecule (not binding sites); x = applied total soluble antigen concentration (binding sites); sqrt : square root.

Example 8: Characterization by Hemolytic Assays

The hemolytic assay is a basic functional assay that tests for complement activation and has been used to evaluate the ability of anti-human C5 mAbs and Fab molecules to block lysis of red blood cells (RBCs) by complement pathways (see *e.g.*, Evans *et al.*, Mol. Immunol 32: 1183-1195 (1995); Thomas *et al.*, Mol Immunol 33:1389-1401 (1996); Rinder *et al.*, J Clin Invest 96:1564-1572 (1995)). Briefly, for classical pathway assays, sensitized red blood cells are used as targets for lysis by complement proteins present in serum. This assay is of interest for the characterization and screening of high-affinity anti-human C5 mAbs.

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1. Classical Pathway

The desired number of chicken red blood cells was washed four times with cold gelatin veronal buffer (GVB++) and resuspended to $5x10^7$ cells/ml. To sensitize the cells rabbit anti-chRBC IgG was added to RBC cell suspension to a final concentration of 1µg/ml IgG. After 15 minutes incubation on ice, the sensitized chRBCs were centrifuged, washed twice with GVB++ and diluted to $8.33x10^7$ cells/ml.

Round-bottom 96 well plates were used for hemolytic assay. Antibodies were diluted in GVB++ buffer and added to the wells (when calculating the required concentration of C5-binding Abs, it was considered that the sample will be diluted two-fold when serum is added). 50µl of 40% human serum (diluted in GVB++) was added to 50µl antibody dilutions, resulting in a final serum assay concentration of 20%.

The control and blank wells were prepared as described here: control wells: i) 0% lysis control → 100µl GVB++, ii) 100% lysis control → 100µl 0.1% NP-40, iii) 20% serum control → 100µl of 20% serum (0% Ab control). blank wells: i) 20% serum blank → 100µl 20% serum, ii) GVB++ blank → 100µl GVB++, iii) NP-40 blank→ 100µl 0.1% NP-40.

$2.5x10^6$ (30µl) sensitized chRBCs/well were added to all sample and control wells. To the blank wells PBS was added instead of cells. Assay plate was incubated 30min at 37°C, centrifuged (2.000rpm, 5min) and 85µl supernatant was transferred to a new, flat-bottomed 96-well plate. The new plate was centrifuged (2.000rpm, 3min) to get rid of any bubbles. Hemoglobin release was measured by reading absorbance at 415nm. Percentage of hemolysis was calculated with respect to the control and blank wells using the following calculation algorithms:

$$\%Hemolysis = 100 \times \frac{ODsample - ODnegativecontrol}{ODpositivecontrol - ODnegativecontrol}$$

where

$$ODsample = \left[AverageOD_{sample}\right] - \left[AverageOD_{20\%SerumBlank}\right]$$

$$ODnegativecontrol = \left[AverageOD_{0\%Lysis}\right] - \left[AverageOD_{GVB++Blank}\right]$$

$$ODpositivecontrol = \left[AverageOD_{100\%Lysis}\right] - \left[AverageOD_{NP-40Blank}\right]$$

Using this procedure, anti human-C5 antibodies which were able to inhibit red blood cell lysis could be identified. To screen for cross-reactivity to cynomolgus C5, the classical pathway was performed using 5% cynomolgus serum.

2. Alternative Pathway

Hemolytic assays undergoing the alternative pathway were done in a similar way to the classical pathway hemolytic assays. In the alternative pathway RBCs cells from rabbit were used and there was no need to sensitize the cells. The rabbit RBCs are different from chicken RBCs in that they are sensitive to lysis caused by the complement alternative pathway.

The working buffer was GVB++ supplemented with 10mM EGTA and 5mM Mg++, since the C5 convertase of the alternative pathway is Mg++ dependent and the C5 convertase of the classical pathway is Ca++ dependent.

Hemolytic assays of the alternative pathway were run with: i) 20% human serum, ii) 100pM human C5 added to 20% human C5-depleted serum, iii) 0.025% cynomolgus serum added to 20% human C5-depleted serum, iv) 100pM cynomolgus C5 added to 20% human C5-depleted serum, v) 10% cynomolgus serum. These settings were used to screen for antibodies with high affinity to the human and cynomolgus C5 proteins which were able to inhibit very effectively the red blood cell lysis induced by the alternative complement pathway.

3. Hemolytic Assays with Parental Fabs

Hemolytic assays were used as a basic bio-functional assay to evaluate the ability of anti-human C5 mAbs to block complement mediated lysis of red blood cells. C5 convertase cleaves C5 into C5a peptide and C5b fragment, that is subsequently incorporated into the membrane-attack complex (MAC), which leads to cell lysis. C5 convertase of the classical pathway, formed by a C3bC4bC2a complex has a different structure than the C5 convertase of the alternative pathway which is formed by a C3bC3bBb complex. HuCAL GOLD® generated antibodies should be inhibitory in both classical and alternative pathway, but with focus on the alternative pathway because mainly the alternative pathway (factor H, factor B and factor H-related genes) is implicated in AMD.

The classical and alternative pathway assays were performed with 20% human serum (~60nM C5). To increase sensitivity of alternative pathway assays, new assay formats were developed. 10-100pM purified human C5 or 0.025% cynomolgus serum (~100pM cynomolgus C5) were added to human C5-depleted serum (but containing all other serum and complement components).

FIG. 2 shows that considerable hemolysis could be observed between 10 and 100 pM purified human C5 added to human C5-depleted serum. Cynomolgus serum was added to human C5-depleted serum to test for cross-reactivity. FIG. 3 shows that 0.025% of cynomolgus serum (~100pM C5) added to human C5 depleted serum restores hemolytic activity.

Classical Pathway

First Fab selection was done in the classical pathway (20% human serum). Approximately half of the 61 purified parental Fabs were weak to strong inhibitors of the classical pathway. IC50 values of the best inhibitory Fabs were between 35 and 900nM.

Assays were done showing congruent results (as shown in FIG. 4). % hemolysis was calculated with respect to the control and blank wells. Fab inhibition of cell lysis was compared to a maximum lysis caused by 20% human serum (=100%). An irrelevant human Fab (hen egg white lysozyme binder MOR03207) was used as negative control and anti-human C5 IgG monoclonal antibody (Quidel) as positive control. FIG. 4 show an example with the best inhibitory Fabs.

Alternative Pathway

Fabs which showed inhibitory activity in the classical pathway were further evaluated in the alternative pathway. Hemolytic assays were run with 100pM purified human C5 or 0.025% cynomolgus serum added to human C5-depleted serum. IC_{50} values for the human alternative assays were between 0.1 and 90nM (examples of assays with the most relevant Fabs are shown in FIG. 5.

The positive control of the classical pathway (anti-human C5 antibody, Quidel) was not inhibitory in the alternative pathway. Therefore an anti-complement factor P antibody (Quidel) was used as positive control. As shown in FIG. 5, MOR07086 had best inhibitory activity and NVS data revealed a better potency than for the reference antibody 5G1.1.

To test for cynomolgus cross-reactivity, hemolytic assays of the alternative pathway were performed with 0.025% cynomolgus serum added to human C5-depleted serum. A comparison to 5G1.1 was not possible, since 5G1.1 does not recognize cynomolgus C5. The anti-Factor P antibody was used as positive control. Results of assays revealed IC_{50} values between 0.1 and 400nM for the best inhibitory Fabs. Again, MOR07086 showed best potency (shown in FIG. 6).

A consistent inhibitory activity of the Fabs was noticed in both classical and alternative pathway. Table 11 below summarizes the results of hemolytic assays for the most relevant 22 Fabs. To have a reliable comparison between different experiments, lysis caused by 20% human serum was normalized to 100%.

Table 11. Summary of hemolytic assays with the most relevant Fabs

	MOR IC50 [nM]			NVS IC50 [nM]		
MOR-Nr	CP [human] normalized	AP (0.1nM C5) [human] normalized	AP (0.025% cyno serum) [cyno] normalized	CP [human] normalized	AP (0.1nM C5) [human] normalized	AP (0.025% cyno serum) [cyno] normalized
6525	190	15	11	185	7	5
6758	320	80	400	225	70	2500
6757	500	90	30	305	130	25
6763	250	45	110	195	20	360
6764	n.t.	50	n.t.	n.t	25	30% inh
6776	>4000	40		n.t.	20*	50% inh
6952	90	20	>1000	110	15	200
6961	100	25	600	85	15	30
7081	180	5	40% inh	170	3	10
7082	70	2.5	1	90	1	1
7083	100	30	300	140	10	5
7084	120	10	1.2	160	5	1.5
7086	35	0.2 / 0.2	0.2 / 0.4	85	0.1	0.1
7087	>4000	50	100	775	10	1
7088	110	15	230	130	5	15
7089	150	75	900	250	20	50
7090	105	20	10	120	10	1
7091	82	7	40	110	3	4
7092	100	1	1.5	90	0.5	1.5
7093	>4000	7	190	230	5	15
7094				770	40	190
7095*	120*	0.5**	1.3**	n.t.		

*not pure as MH

**as pMx9_FS

4. Hemolytic Assays with Matured Fabs

Classical Pathway

(1) Classical Pathway Using 20% Human Serum

Matured Fabs were tested in the classical pathway with 20% human serum. Derivatives of MOR07086, 7091, 7092 and 7093 showed highest potency (IC50 values in the low nM range). Descendants of MOR07091, 7092 and 7093 showed strongly improved potency. FIG. 7 shows examples of hemolytic assays with derivatives of MOR07086, 7091, 7092 and 7093.

(2) Classical Pathway Using 5% Cynomolgus Serum

Assays of the complement pathway were also run in the presence of 5% cynomolgus serum in order to test for cross-reactivity. Derivatives of MOR07086, 7091, 7092 and 7093 could very effectively inhibit red blood cell lysis. The negative control, MOR03207 (anti-lysozyme Fab), had no impact on the complement pathway. Results of these assays are shown in FIG. 8.

Alternative Pathway

(1) Alternative Pathway Using 100pM Human C5

Matured Fabs were tested in the alternative pathway hemolytic assay with 100pM human C5. Some derivatives of MOR06525, 6757, 6763, and 7087 showed potency improvement compared to their parentals. MOR07086-, 7091-, 7092-, 7093-, and 7094-derived Fabs showed highest potency (IC50 values in the low nM range). Descendants of MOR07091, 7092, 7093, and 7094 showed highly improved potency, many of which are more potent than reference antibody 5G1.1. FIG. 9 shows examples of hemolytic assay results for the affinity matured Fabs and 5G1.1.

(2) Alternative Pathway Using 20% Human Serum

Matured Fabs were tested in the alternative pathway hemolytic assay with 20% human serum. MOR07086-, 7091-, 7092- and 7093-derived Fabs showed best inhibitory activity. Many of these Fabs had better inhibitory activity than 5G1.1. FIG. 10 shows examples of hemolytic assay results for the affinity matured Fabs and reference antibody 5G1.1.

(3) Alternative Pathway Using 100pM Cynomolgus C5

Matured Fabs were tested in the alternative pathway hemolytic assay using 100pM cynomolgus C5 added to 20% human C5-depleted serum. MOR07091-, 7092- and 7093-derived Fabs showed best inhibitory activity; 5G1.1 does not crossreact with cynomolgus C5. FIG. 11 shows examples of hemolytic assay results for the affinity matured Fabs.

5. Hemolytic Assays with Germlined IgGs (Human IgG1AA Format)

Classical Pathway

(1) Classical Pathway Using 20% Human Serum

Classical pathway assays using 20% human serum were run at MOR. IC50 values of the final germlined hu IgGAA - MOR08109, 8110, 8113, 8114 - were better or similar to reference IgG 5G1.1 (see FIG. 12).

(2) Classical Pathway Using 5% Cynomolgus Serum

A comparision to 5G1.1 in the classical pathway using 5% cynomolgus serum was not applicable, since this reference antibody does not recognize cynomolgus C5. The final germlined IgGs could completely inhibit lysis of the red blood cells induced by cynomolgus serum except MOR08111. Data are shown in FIG. 13.

Alternative Pathway

(1) Alternative Pathway Using 100pM Human C5

The germlined IgGs were tested in the alternative pathway hemolytic assay using 100pM human C5. All antibodies showed potent inhibitory activity with IC50 values between

28 and 128pM (with the exception of MOR08111, see FIG. 14), all were equal to or better than 5G1.1. FIG. 14 shows examples of hemolytic assay results for the IgGs.

(2) Alternative pathway Using 20% Human Serum and C5a Generation ELISA

The germlined IgGs were also tested in the alternative pathway hemolytic assay with 20% human serum. The majority of the antibodies tested achieve complete inhibition with IC50 values lower than 80nM. Reference antibody 5G1.1 does not fully inhibit hemolysis in this assay. FIG. 15 shows examples of hemolytic assay results for the IgGs. Inhibition of C5a generation by the final IgGs was similar to 5G1.1 (IC50 values in the low nM range).

(3) Alternative Pathway Using 100pM Cynomolgus C5

Hemolytic assays of the alternative pathway in 20% human C5-depleted serum were reconstituted with 100 pM cynomolgus C5. Potency of the germlined final candidates against cynomolgus C5 was within 5-fold of that for human C5 (IC50 values in the low pM range).

(4) Alternative Pathway Using 10% Cynomolgus Serum

In hemolytic assays of the alternative pathway using 10% cynomolgus serum ([C5] ~ 40 nM) the potency of the germlined candidates was similar to the potency in human serum (success criterion was to have a potency not more than 5-fold weaker than for the fuctional assay using human C5).

Example 9: C5a Generation ELISA

C5a-des-Arg ELISA was developed to measure C5a generation during hemolysis to confirm that antibodies that were inhibitory in the hemolytic assay also inhibited cleavage of C5 into C5a and C5b.

A Maxisorp plate was coated with 100µl/well mouse anti-human C5a-des-Arg (US Biologics) at 1µg/ml in coating buffer (bicarbonate pH 9.5-9.8) and was incubated overnight at 4°C. After washing 3x with PBST, the plate was blocked with 300µl/well diluent (Synblock, AbD Serotec) for 2 hours at room temperature. After aspirating the blocking solution, 100µl samples or standards diluted with diluent were incubated for 1 hour at room temperature. Standards were prepared as follows: start was at 20ng/ml standard (rC5a-des-Arg) and 1:4 serial dilutions were prepared for a 7-point curve. Samples of hemolytic assays were diluted 1:5 in diluent (hemolytic assay supernatants should be stored at -80°C until used in C5a ELISA). In between the plate was washed 3x with PBST. 100µl/well of 0.4µg/ml detection antibody (biotin-goat anti-human c5a, R&D Systems) diluted in diluent was added and after 1 hour incubation at room temperature, 100µl/well Strep-HRP (poly-HRP streptavidin) diluted 1:5000 in HRP diluent (poly-HRP diluent) was added for 30 minutes. After washing 4x with PBST, 100µl/well TMB Substrate (Ultra TMB substrate solution) was added for 5-10 minutes.

Reaction was stopped with 50µl/well stop solution (2N H_2SO_4). Absorbance was read (A450-A570) and data were analyzed using SoftMax Pro.

Matured Fabs were tested for C5a generation during hemolysis to confirm that inhibitory activity was due to blocking C5 cleavage into C5a and C5b. The supernatants from hemolytic assays in 20% human serum were used for quantifying the C5a formation.

All Fabs tested brought C5a levels down to baseline. FIG.16 shows examples of C5a ELISA results.

Example 10: Specificity ELISA on Human C3, C4, C5 and Cynomolgus C5

All purified Fabs were analyzed in a solution ELISA (method described above) for binding to human C3, C4 and C5. Fabs were incubated with biotinylated antigen on a Neutravidin plate and detected via the histidin tag.

Improved binding was seen for almost all matured Fabs compared to their respective parental. No binding to the counter targets human C4 and C3 was detected up to 100nM Fab. These results hit the success criteria for specificity: binding to human and cynomolgus C5 and no binding to human complement proteins C3 and C4. Examples for derivatives of parental Fab MOR07091 are shown in FIG. 17.

Example 11: Serum Stability Assays

Retained binding activity to human C5 in a binding assay at 50% human serum of C5-binding antibodies was determined as described below.

Antibodies (Fab format) were incubated up to 8h at 37°C with 100% human C5-depleted serum or with PBST/0.5% BSA (positive control). Wells of a blocked polypropylene plate were used for incubation to ensure no binding of the antibodies to the surface over the long incubation time. Samples were collected at different time points and stored at -20°C.

Samples were tested in a solution ELISA on NeutrAvidin plates to check binding ability to human C5. To the NeutrAvidin plates, which were blocked o/n with 1x ChemiBlocker-PBST. 20µl of serial dilutions of the different collected samples were added. First dilution of the samples was 1:2 (final serum concentration 50%), followed by 1:3 dilutions steps. After 1h incubation the plate was washed 3x with PBST and 20µl biotinylated human C5 was applied to a concentration of 2.5 µg/ml. After 1h plate was washed again 5x with PBST (0.05% Tween) and anti-HIS6-POD detection antibody for Fabs was added.

Fluorescence of the substrate (Quanta Blue or AttoPhos) was measured after 5-10 min and retained binding activity was calculated compared with the respective maximum signal (antibody incubated with PBST/0.5% BSA).

One of the "must" criteria for the C5-binding antibodies is to retain 75-80% of binding activity in human serum i) in a functional assay at 10% serum and ii) in a binding assay at 50% serum. Because hemolytic assays were run in the presence of 20% serum it was only necessary to show retained binding in a binding assay at 50% serum.

Therefore matured final Fabs were incubated with 100% human C5-depleted serum at 37°C for 8h. Samples were collected at different time points and tested for binding to human C5 in a solution ELISA. Fab + serum samples used for ELISA were diluted to a concentration of 50% serum + 10nM Fab.

FIG. 18 illustrates the results of the final C5-binding final antibodies in the Fab format. 70-93% of the binding activity was retained after an 8 hour incubation time at 37°C in 50% serum compared to incubation in PBS.

Example 12: Characterization by Epitope Binning

This procedure was used to group anti-human C5 Fabs into different epitope bins binding to the same or an overlapping epitope of the C5 protein.

Competition of each biotinylated anti-human C5 antibody with each unlabelled anti-human C5 antibody in 100-fold excess was tested in an ELISA (capture mode). It was compared with the highest signal of each antibody (biotinylated Fab without competition).

Human C5 was captured via a polyclonal anti-human C5 IgG (US Biological), which was coated previously o/n at 4°C on a 384 well black Maxisorp plates. Next day the plate was washed twice with PBST and blocked for 2h with 3% BSA-PBST. After washing 3x with PBST, 20µl human C5 was added and incubated 2h ar RT. The plate was washed 3x with PBST before adding the Fabs.

20µl unlabelled Fab (200µg/ml or 400µg/ml) (100-fold excess) was added to the wells of a Maxisorp plate and subsequently 20ng/ml or 40ng/ml of biotinylated Fab. The biotinylated and unlabelled Fabs were incubated for 1h at RT. The plate was washed 3x with PBST and Strep-AP Zymax Streptavidin-Alkaline Phosphatase, ZYMED, Code: 43-8322, Lot: 50799648 was added for detection of the biotinylated Fab binding via C5 to the plates. AttoPhos substrate (Roche) was added to the plates and Fluorescence was read after 5-10min.

Parental Fabs

C5 was captured (via a polyclonal antibody) and unlabelled FabY was applied in excess to biotinylated FabX. Binding of biotinylated FabX to human C5 was detected. Six groups of Fabs could be defined: Group 1: MOR06952, 6961; Group 2: MOR06525, 6756, 6757, 6763; Group 3: MOR07087; Group 4: MOR06764, 6776, 7081; Group 5: MOR07089; Group 6: MOR07082, 7083, 7084, 7086, 7088, 7090, 7091, 7092, 7093, 7095.

The Fabs were also divided into different epitope binding groups using a different method: FabX was immobilized, then FabY pre-incubated with biotinylated C5 was added. Following groups of Fabs could be defined: Group 1: MOR06952, 6961; Group 2: MOR06525,6757, 7083; Group 3: MOR07087 ; Group 4: MOR06763; Group 5: MOR07081; Group 6: MOR07082,7083,7084,7086,7085,7091,7092, 7093 (7089 competes with 7084). The conclusion was drawn that using two different methods, similar results could be obtained.

Matured Fabs

In order to complete Fab characterization competition of biotinylated Fab with unlabelled Fab (applied in 100-fold excess) was measured in solution ELISA. Results were compared with the highest signal (biotinylated Fab without competition).

As shown in FIG. 19, biotinylated Fabs compete with identical unlabelled Fabs and all Fabs compete for binding to the same or overlapping epitope. These results correlate with epitope binning data for the parental Fabs.

Example 13: Screening of C5 Alpha versus Beta Chain Binders and Competition Assays

Two ELISA experiments and hemolytic assays were performed to test if a Fab was an alpha or beta chain binder as described below.

In the first experiment, Fab was coated on a plate and purified C5 or supernatant from chimeric C5 preparation (human alpha, mouse beta chain) was added. As a next step 5G1.1 was applied and detection was done via an anti-human IgG.

In a second experiment, 5G1.1 was coated on a plate, purified C5 or supernatant from chimeric C5 preparation (human alpha, mouse beta chain) was added, then Fab, which was detected with an anti-Myc antibody.

Reference IgG 5G1.1 recognizes the alpha chain and was used to determine if the MorhpSys generated Fabs compete with 5G1.1 for binding. In the hemolytic assays supernatant from chimeric C5 preparation was added to human C5-depleted serum and Fabs were tested for inhibition of hemolysis.

Parental Fabs

FIG. 20 shows the results of an ELISA experiment where the Fabs were coated on a plate, C5 or supernatant of a chimeric C5 preparation (human alpha chain and mouse beta chain) was added, then 5G1.1. FIG. 21 shows the results of an ELISA experiment where purified C5 and supernatant from chimeric C5 were captured via 5G1.1.

MOR06525, 6756, 6763 were beta chain binders (bind to C5 but not chimeric C5). Most MOR070XX Fabs (derived from solution pannings) are alpha chain binders (bind to C5 and chimeric C5). MOR06952 and 6961 compete with 5G1.1 so they are negative for both C5 and chimeric C5 and, thus, are most likely alpha chain binders as 5G1.1. MOR06757 behaves like MOR06952 and 6961, *i.e.* it likely is an alpha chain binder. However, MOR06757 does not inhibit hemolysis of chimeric C5 supernatant spiked into C5-depleted serum, while all the other alpha chain binders do (see FIG. 22).

In the hemolytic assay supernatant from chimeric C5 prep was added to human C5-depleted serum and Fabs were tested for inhibition of hemolysis. MOR06525, 6756, 6757 and 6763 did not inhibit hemolysis with chimeric C5 and thus, could be beta chain binders. MOR06952, 6961, 7081, 7082, 7083, 7084, 7086, 7087, 7088, 7089, 7090, 7091, 7092, 7093, 7094, 7095 inhibited hemolysis and thus could be alpha chain binders.

Example 14: Resistance to Proteolysis

To investigate the structural rigidity of Fabs, resistance of Fabs to proteolysis by thermolysin was performed (thermolysin bacterial protease, Calbiochem). Fab was incubated with thermolysin (Fab : thermolysin = 3 : 1 (w/w), reaction volume of 8µL) either at 37°C or at 55°C (thermolysin activity is optimal at 55°C). The reaction was stopped by adding 4µL of 0.5 M EDTA and 4µL of 4x LDS sample buffer (Invitrogen) and the stopped samples were run on 4-12% SDS-PAGE at non-reducing condition. Proteolysis of Fabs was analyzed by monitoring the disappearance of Fab bands that were visualized by Coomassie staining.

Parental Fabs

Parental Fabs were tested for resistance to thermolysin proteolysis at 37°C and 55°C. Fab from a humanized IL-1β antibody was used as control. Most tested Fabs were resistant to degradation by thermolysis at 37°C up to 90 min. To further differentiate the structural rigidity of Fabs, proteolysis was performed at higher temperature of 55°C. Many of the Fabs tested were quickly degraded at 55°C (>90% Fab was degraded within 30 min), while some Fabs were still resistant to proteolysis after 90 min (*e.g.*, 7094). The resistant Fabs were suggested to have a more rigid structure such that they might show better *in vivo* pharmacokinetic properties. Results of these experiments are shown in the FIG. 23 and FIG. 24.

Matured Fabs

Fabs with the highest potency in hemolytic assays were tested for sensitivity to thermolysin at 37°C and 55°C. In FIG. 25 and FIG. 26, experiments with derivatives of MOR07086, 7091, 7092 and 7093 are shown.

Results of these tests revealed that derivatives of parentals MOR07091, 7092 and 7093 were less sensitive to proteolysis, while MOR07086 derivatives were more sensitive to proteolysis.

Example 15: MAC Deposition Assay

As the terminal complement cascade ends up with formation of the MAC, inhibition of MAC formation was a further hint for the antibody ability to block the complement cascade. The rational was to have an additional set-up independent of cells and cell behaviour

Zymosan (Sigma), which is an insoluble carbohydrate from the cell wall of yeast, used especially in the immunoassay of the alternative pathway, was coated to activate the Alternative Pathway and IgM (Sigma) was coated to activate the Classical Pathway for determination of MAC (membrane attack complex) deposition. Fabs were pre-incubated with human serum (6% for AP, 2% for CP) and added to plate. Percentage (%) inhibition of MAC deposition was calculated for each sample relative to baseline (EDTA treated human serum) and positive control (human serum), and used to generate the IC_{50} curve with XLFit.

Parental Fabs

Parental Fabs were used in different concentrations and the maximal inhibition (if applicable also IC50 values) were determined (example shown in FIG. 27). Most Fabs completely inhibited MAC deposition indicating blocking of C5 cleavage. Potency and ranking of Fabs were similar to data from hemolytic assays.

What is claimed is:

1. An isolated antibody or an antigen binding fragment thereof that specifically binds to a complement C5 protein, wherein said antibody has an affinity constant (K_A) of at least 1×10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, or 10^{11} M^{-1}.

2. The antibody of claim 1 which inhibits the alternative complete pathway as measured by in vitro hemolytic assay with an IC_{50} of 20-200 pM.

3. An antibody, or antigen binding fragment thereof, that specifically binds to complement C5 protein, and cross competes with an antibody described in Table 1.

4. An antibody, or antigen binding fragment thereof, that binds to the same epitope as an antibody described in Table 1.

5. The antibody of claim 1, 3 or 4, wherein said antibody is a monoclonal antibody.

6. The antibody of claim 5, wherein said antibody is a human or humanized antibody.

7. The antibody of claim 5, wherein said antibody is a chimeric antibody.

8. The antibody of claim 5, wherein said antibody comprises a human heavy chain constant region and a human light chain constant region.

9. The antibody of claim 5, wherein said antibody is a single chain antibody.

10. The antibody of claim 5, wherein said antibody is a Fab fragment.

11. The antibody of claim 5, wherein said antibody is a scFv.

12. The antibody of claim 5 binds to both human C5 and cynomolgus C5.

13. The antibody of claim 5 is an IgG isotype.

14. The antibody of claim 5, wherein said antibody comprises a framework in which amino acids have been substituted into the antibody framework from the respective human VH or VL germline sequences.

15. An isolated monoclonal antibody, or an antigen binding fragment thereof, comprising at least one complementarity determining (CDR) sequence having at least 95% sequence identity to SEQ ID NO: 1, 2, 3, 4, 5, 6, 17, 18, 19, 20, 21, 22, 33, 34, 35, 36, 37, 38, 49, 50,

61, 62, 63, 64, 65, 66, 77, 78, 89, 95, 101, 107, 113, 119, 120, 131, 132, 133, 134, 135, 136, 145, 146, 147, 148, 149, 150, 159, 160, 161, 162, 163, 164, 173, 174, 175, 176, 177, 178, 195, 196, 197, 198, 199, 200, 209, 226, 235, 236, 237, 238, 239, or 240, wherein said antibody binds to human C5 protein.

16. An isolated monoclonal antibody, or an antigen binding fragment thereof, comprising at least one heavy chain CDR sequence that is identical to SEQ ID NO: 1, 2, 3, 17, 18, 19, 33, 34, 35, 49, 61, 62, 63, 77, 77, 95, 107, 113, 119, 132, 131, 133, 145, 146, 147, 159, 160, 161, 173, 174, 175, 195, 196, 197, 226, 235, 236, or 237, wherein said antibody binds to human C5 protein.

17. An isolated monoclonal antibody, or an antigen binding fragment thereof, comprising at least one light chain CDR sequence that is identical to SEQ ID NO: 4, 5, 6, 20, 21, 22, 36, 37, 38, 50, 64, 65, 66, 78, 89, 101, 120, 134, 135, 136, 148, 149, 150, 162, 163, 164, 176, 177, 178, 198, 199, 200, 209, 238, 239, or 240, wherein said antibody binds to human C5 protein.

18. An isolated monoclonal antibody, or an antigen binding fragment thereof, comprising a heavy chain CDR 1 selected from the group consisting SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235; a heavy chain CDR2 selected from the group consisting SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236; and a heavy chain CDR3 selected from the group consisting SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237, wherein said antibody binds to human C5 protein.

19. An isolated monoclonal antibody, or an antigen binding fragment thereof, comprising a light chain CDR 1 selected from the group consisting SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238; a light chain CDR2 selected from the group consisting SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239; and a light chain CDR3 selected from the group consisting SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240, wherein said antibody binds to human C5 protein.

20. The antibody of claim 18, or an antigen binding fragment thereof, further comprising a light chain CDR1 selected from the group consisting SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238; a light chain CDR2 selected from the group consisting SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239; and a light chain CDR3 selected from the group consisting SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240.

21. An isolated monoclonal antibody, or an antigen binding fragment thereof, comprising a heavy chain variable region having at least 95% sequence identity to SEQ ID NO: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281, wherein said antibody binds to human C5 protein.

22. An isolated monoclonal antibody, or an antigen binding fragment thereof, comprising a light chain variable region having at leat 95% sequence identity to SEQ ID NO: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, and 289, wherein said antibody binds to human C5 protein.

23. The antibody of claim 21, or an antigen binding fragment thereof, further comprising a light chain variable region having at leat 95% sequence identity to SEQ ID NO: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, and 289.

24. An isolated monoclonal antibody, or an antigen binding fragment thereof, comprising a heavy chain having at least 95% sequence identity to SEQ ID NO: 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, or 282, wherein said antibody binds to human C5 protein.

25. An isolated monoclonal antibody, or an antigen binding fragment thereof, comprising a light chain having at least 95% sequence identity to SEQ ID NO: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, or 290, wherein said antibody binds to human C5 protein.

26. The antibody of claim 24, or an antigen binding fragment thereof, further comprising a light chain having at least 95% sequence identity to SEQ ID NO: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, or 290.

27. A pharmaceutical composition comprising an antibody selected from claims 1-26 and a pharmaceutically acceptable carrier.

28. A nucleic acid comprising a nucleotide sequence encoding a polypeptide comprising a heavy chain variable region having at least 95% sequence identity to SEQ ID NO: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281.

29. A nucleic acid comprising a nucleotide sequence encoding a polypeptide comprising a light chain variable region having at least 95% sequence identity to SEQ ID NO: 8, 24, 40,

52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, and 289.

30. A vector comprising the nucleic acid of claim 28 or 29.

31. An isolated host cell comprising (1) a recombinant DNA segment encoding a heavy chain of the antibody of claim 18, and (2) a second recombinant DNA segment encoding a light chain of the antibody; wherein said DNA segments are operably linked to a promoter, and are capable of being expressed in said host cell.

32. The host cell of claim 31, wherein the antibody is a human monoclonal antibody.

33. The host cell of claim 31 that is a non-human mammalian cell line.

34. A method of treating age related macular degeneration comprising administering to a subject in need thereof an effective amount of a composition comprising an antibody selected from claims 1-26.

35. The method of claim 34, wherein the subject is a human.

36. A method of treating a disease comprising administering to a subject in need thereof an effective amount of a composition comprising an antibody selected from claims 1-26, wherein said disease is asthma, arthritis, autoimmune heart disease, multiple sclerosis, inflammatory bowel disease, ischemia-reperfusion injuries, Barraquer-Simons Syndrome, hemodialysis, systemic lupus, lupus erythematosus, psoriasis, multiple sclerosis, transplantation, Alzheimer's disease, glomerulonephritis, or MPGN II.

37. The method of claim 36, wherein said disease is glomerulonephritis.

38. A method of treating paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to a subject in need thereof an effective amount of a composition comprising an antibody selected from claims 1-26.

39. A method of ameliorating a symptom associated with extracorporeal circulation comprising administering to a subject in need thereof an effective amount of a composition comprising an antibody of claims 1-26.

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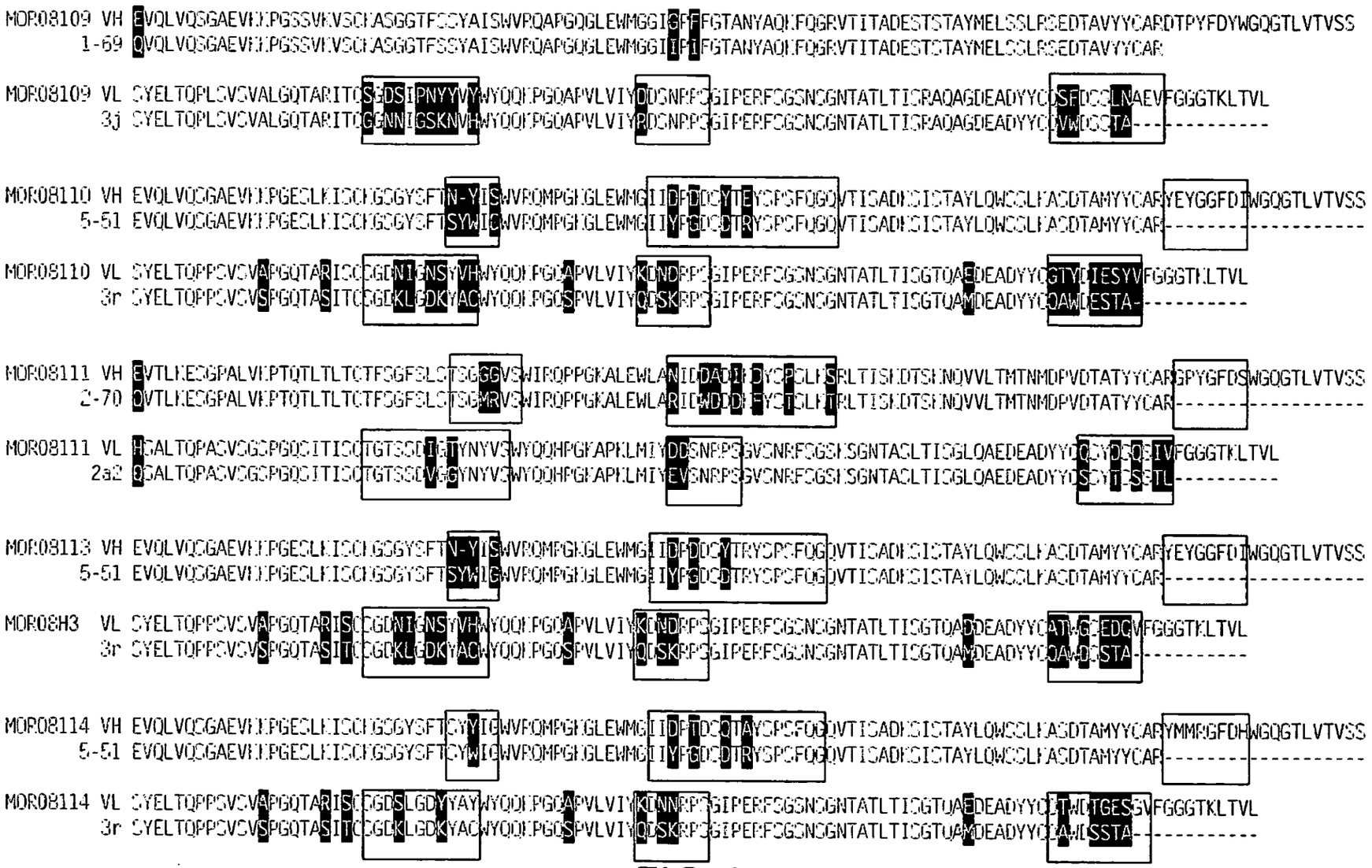


FIG.1

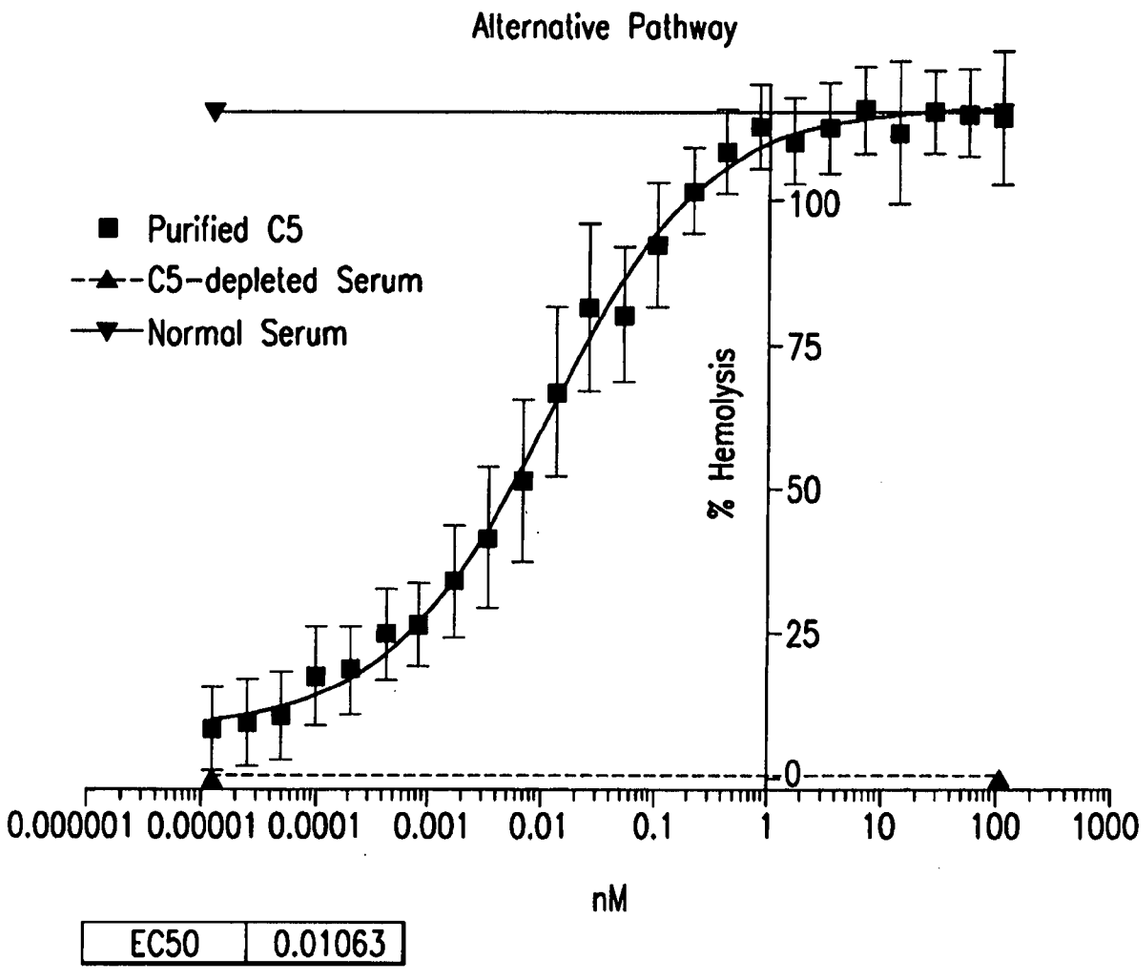

Alternative Pathway
Purified C5
C5-depleted Serum
Normal Serum
% Hemolysis
100
75
50
25
0
0.000001 0.00001 0.0001 0.001 0.01 0.1 1 10 100 1000
nM
EC50 0.01063

FIG.2

151

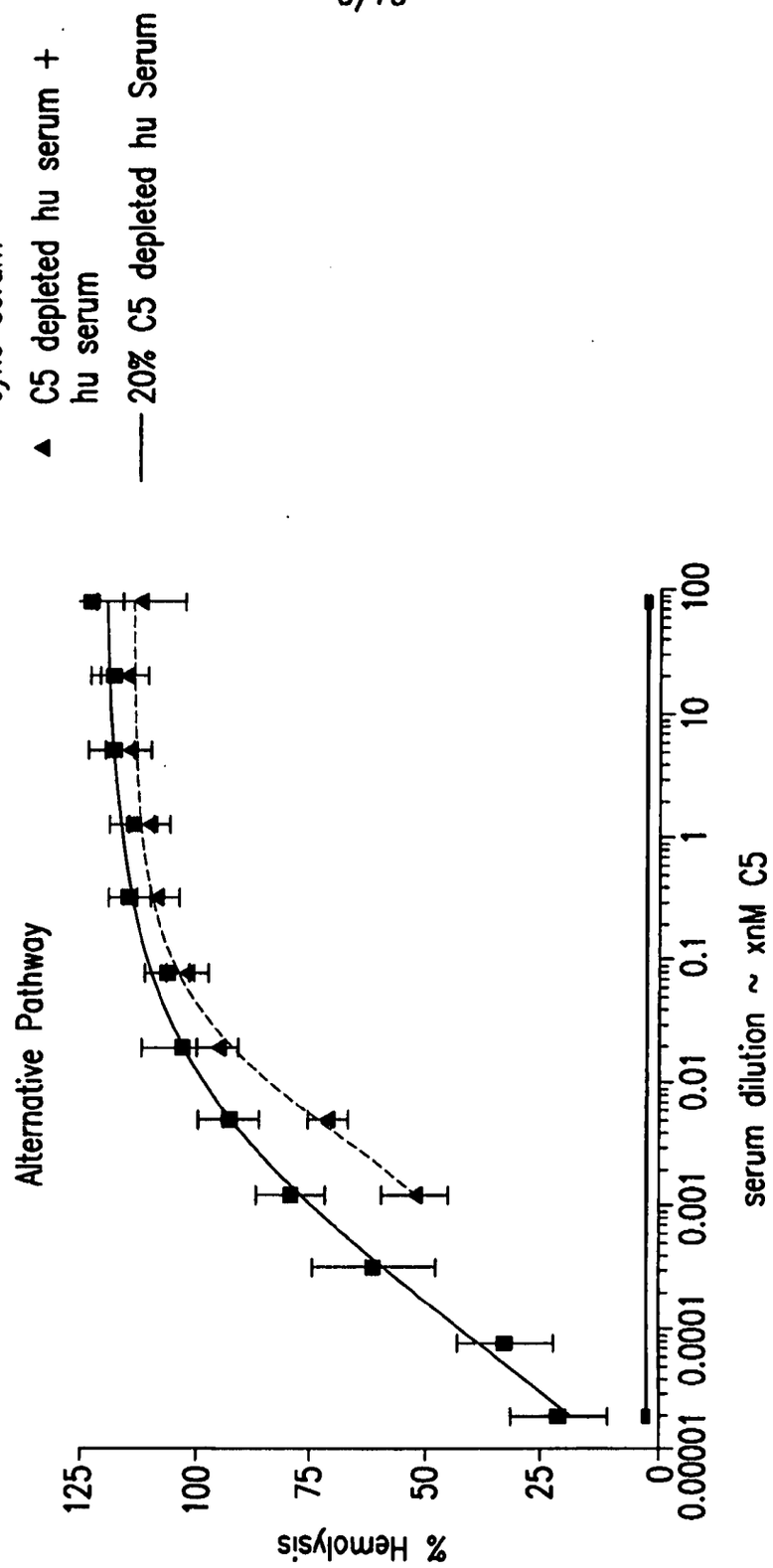

C5 depleted hu serum + cyno serum
C5 depleted hu serum + hu serum
20% C5 depleted hu Serum
Alternative Pathway
% Hemolysis
125
100
75
50
25
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
serum dilution ~ xnM C5

FIG.3

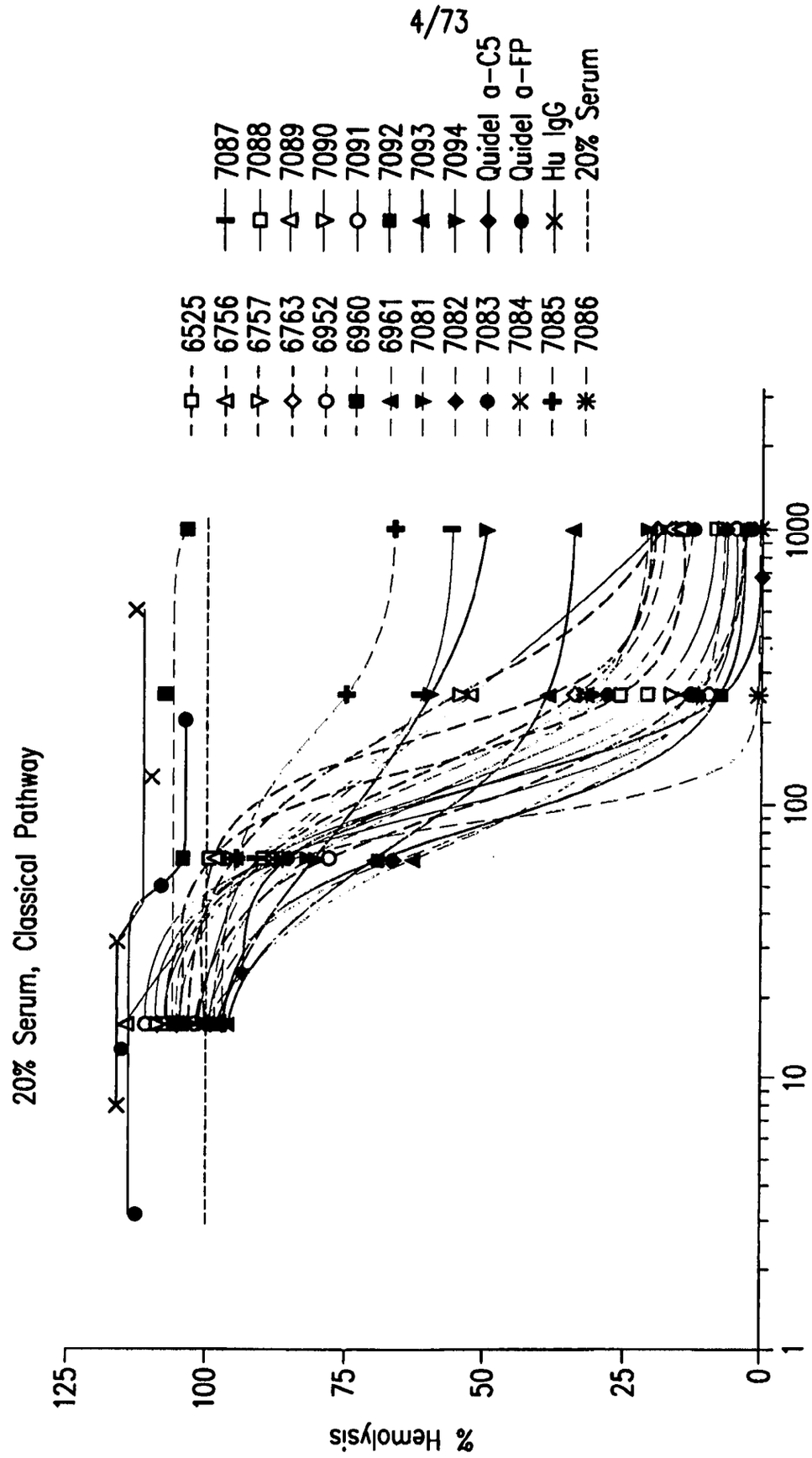

6525
6756
6757
6763
6952
6960
6961
7081
7082
7083
7084
7085
7086
7087
7088
7089
7090
7091
7092
7093
7094
Quidel α-C5
Quidel α-FP
Hu IgG
20% Serum
20% Serum, Classical Pathway
% Hemolysis
125
100
75
50
25
0
1
10
100
1000
nM Fab or Ab

FIG.4

153

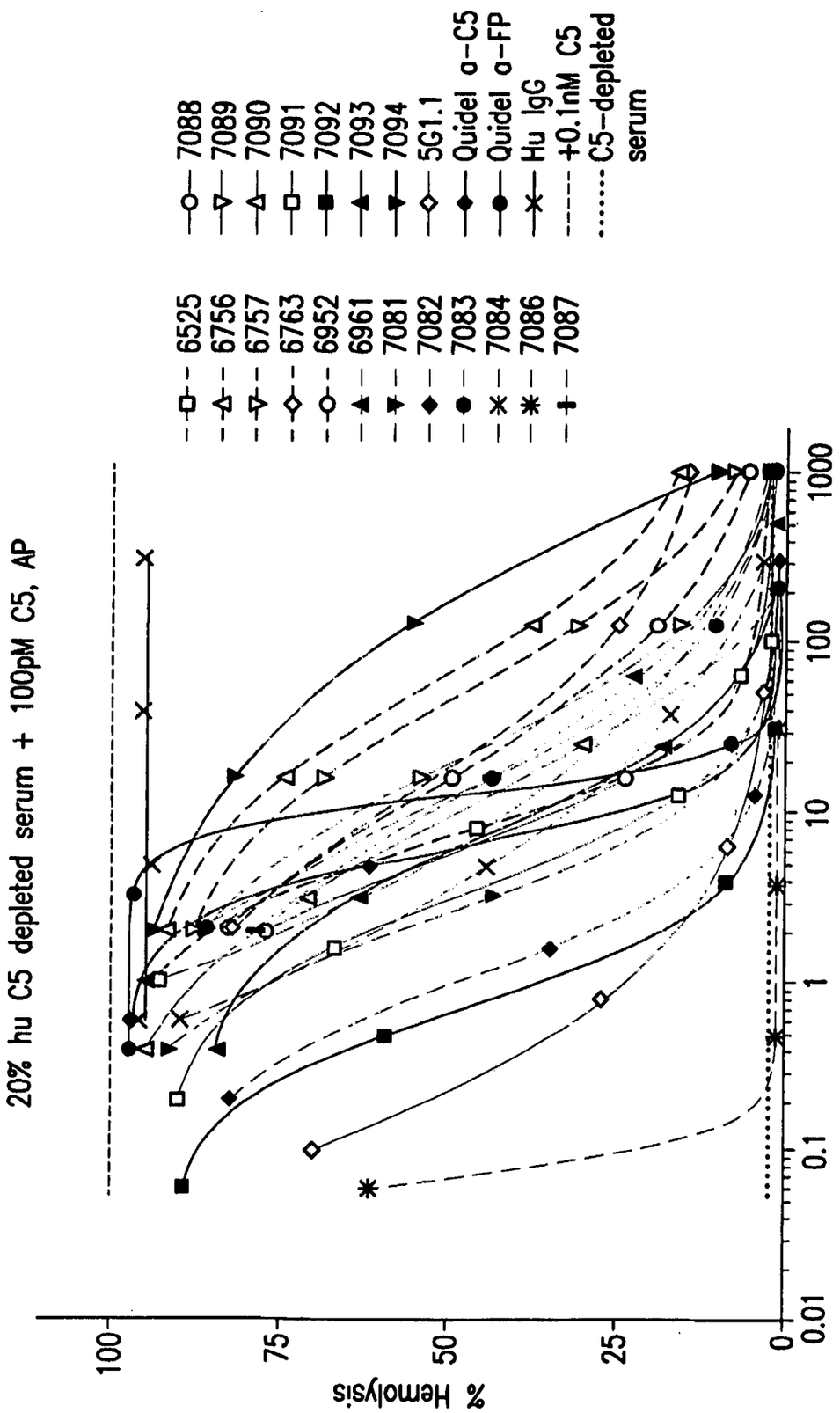

20% hu C5 depleted serum + 100pM C5, AP
% Hemolysis
nM Fab or Ab
0
25
50
75
100
0.01
0.1
1
10
100
1000
6525
6756
6757
6763
6952
6961
7081
7082
7083
7084
7086
7087
7088
7089
7090
7091
7092
7093
7094
5G1.1
Quidel α-C5
Quidel α-FP
Hu IgG
+0.1nM C5
C5-depleted serum

FIG.5

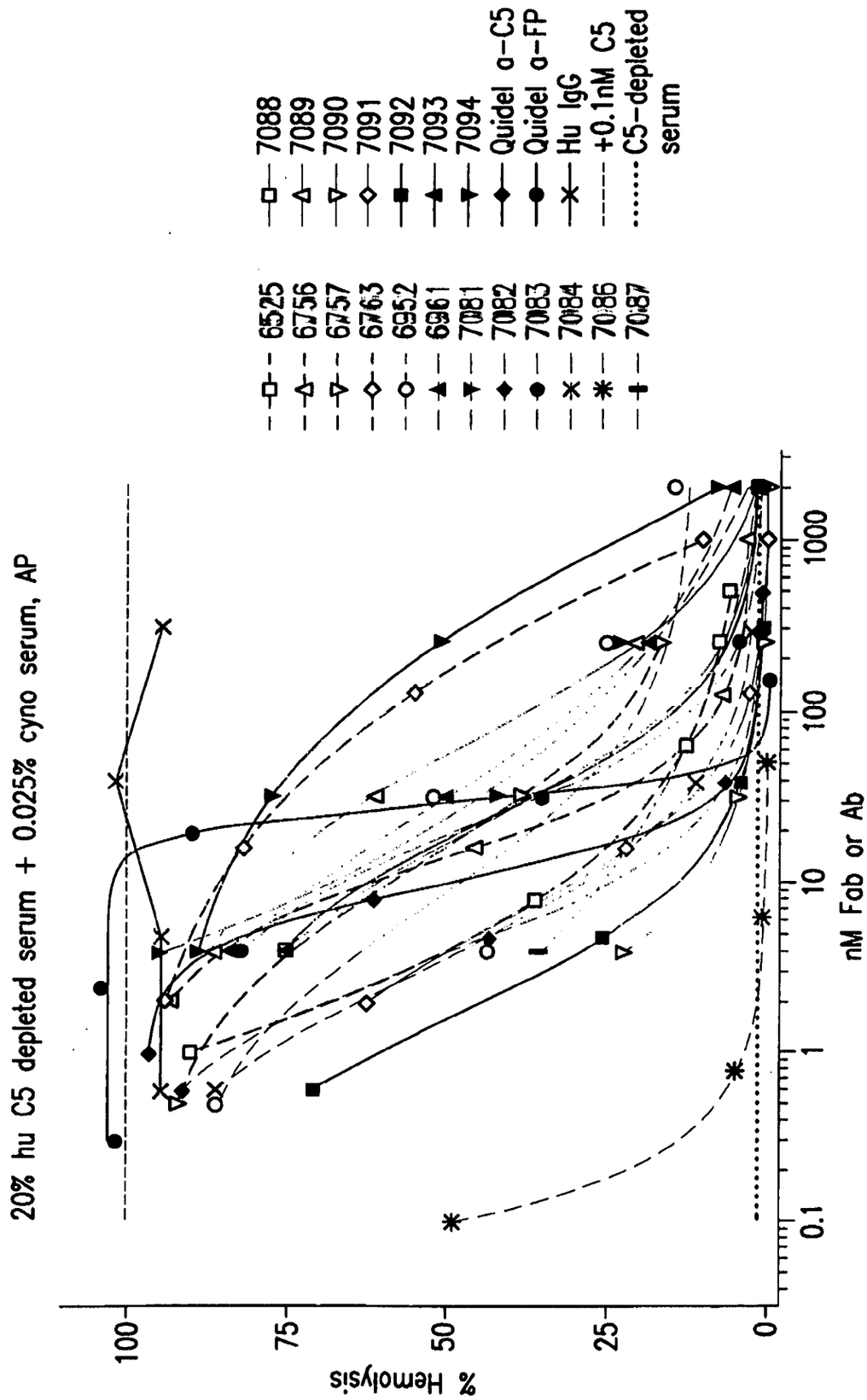
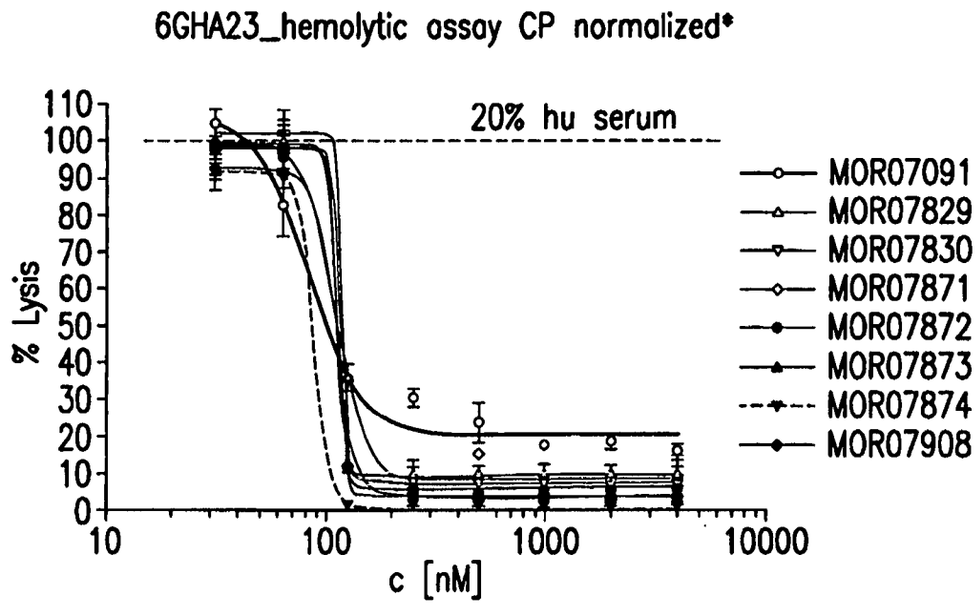

20% hu C5 depleted serum + 0.025% cyno serum, AP
% Hemolysis
nM Fab or Ab
0
25
50
75
100
0.1
1
10
100
1000
6525
6756
6757
6763
6952
6961
7081
7082
7083
7084
7086
7087
7088
7089
7090
7091
7092
7093
7094
Quidel α-C5
Quidel α-FP
Hu IgG
+0.1nM C5
C5-depleted serum

FIG.6

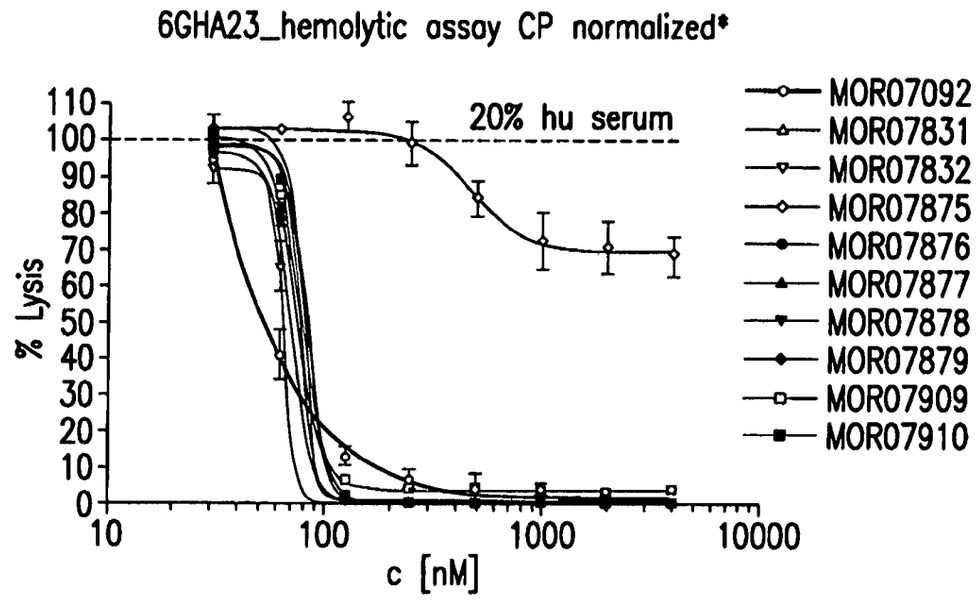


*100% lysis = 20% serum lysis

Max. inhibition (%):

MOR07091: 80
MOR07829: 95
MOR07830: 90
MOR07871: 90
MOR07872: 95
MOR07873: 97
MOR07874: 100
MOR07908: 97

FIG.7-1

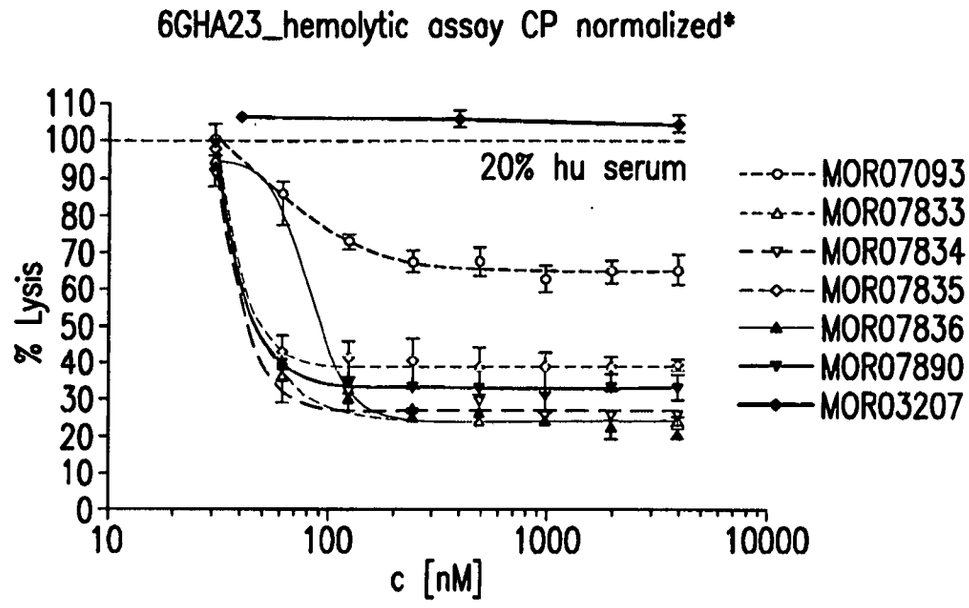


*100% lysis = 20% serum lysis

Max. inhibition (%):

MOR07092: 100
MOR07831: 100
MOR07832: 100
MOR07875: 30
MOR07876: 100
MOR07877: 100
MOR07878: 100
MOR07879: 95
MOR07909: 100
MOR07910: 100

FIG.7-2

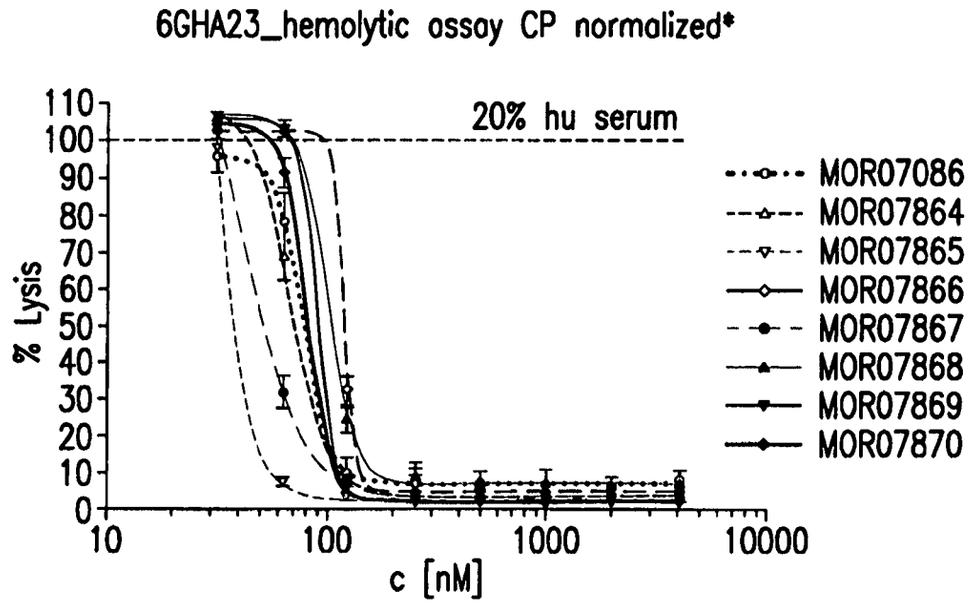


*100% lysis = 20% serum lysis

Max. inhibition (%):

MOR07093: 30
MOR07833: 75
MOR07834: 70
MOR07835: 60
MOR07836: 75
MOR07890: 65

FIG.7-3



*100% lysis = 20% serum lysis

Max. inhibition (%):
MOR07086: 95
MOR07864: 100
MOR07865: 100
MOR07866: 100
MOR07867: 100
MOR07868: 95
MOR07869: 100
MOR07870: 97

FIG.7-4

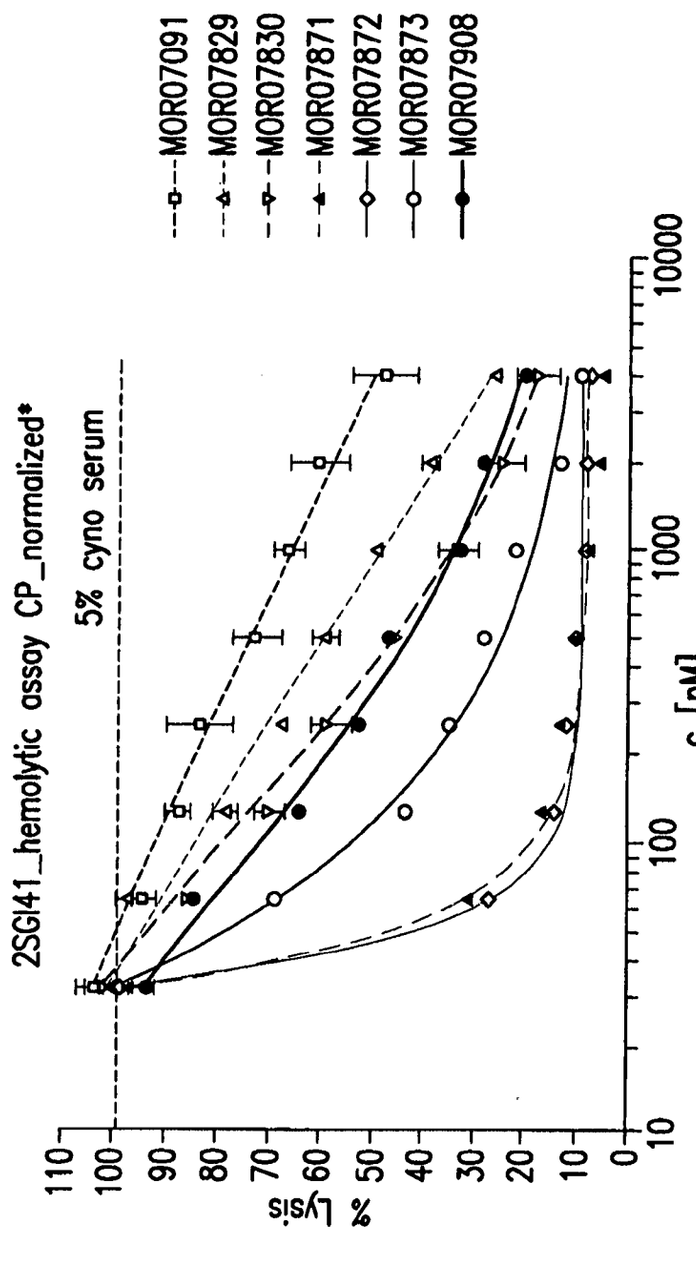

2SGI41_hemolytic assay CP_normalized*
5% cyno serum
MOR07091
MOR07829
MOR07830
MOR07871
MOR07872
MOR07873
MOR07908
% Lysis
c [nM]
*100% lysis = 5% cyno serum lysis

FIG.8-1

160

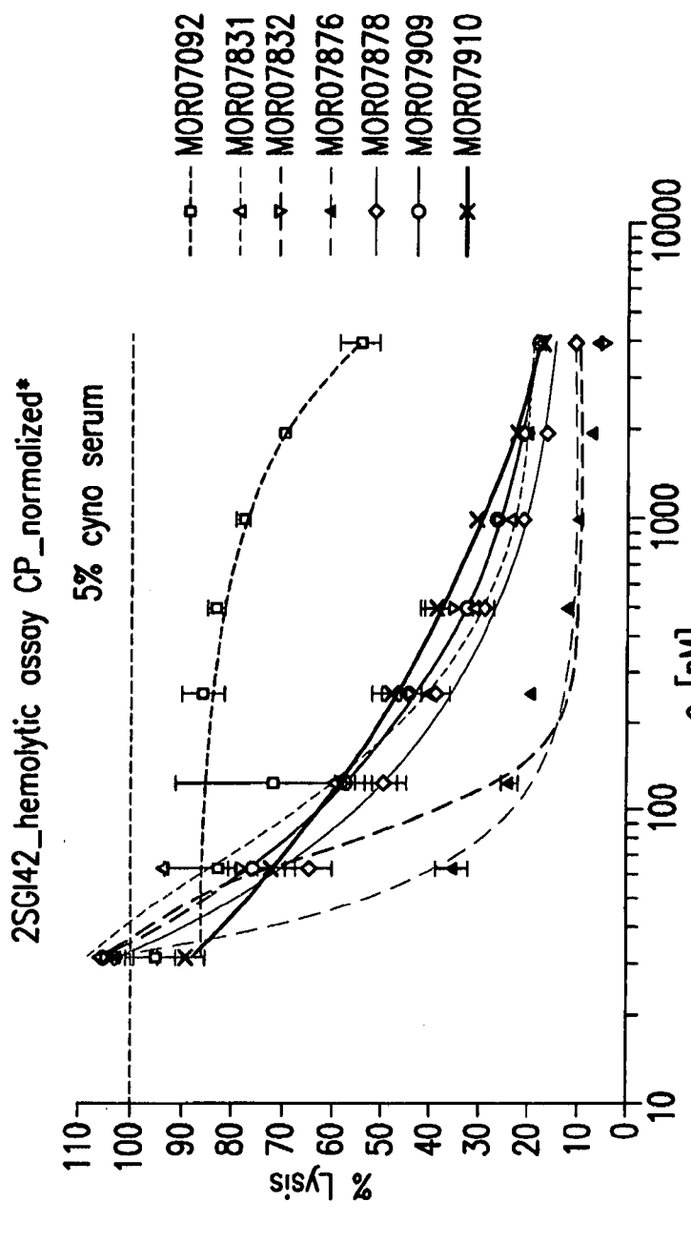

2SGI42_hemolytic assay CP_normalized*
5% cyno serum
MOR07092
MOR07831
MOR07832
MOR07876
MOR07878
MOR07909
MOR07910
% Lysis
c [nM]
*100% lysis = 5% cyno serum lysis

FIG.8-2

161

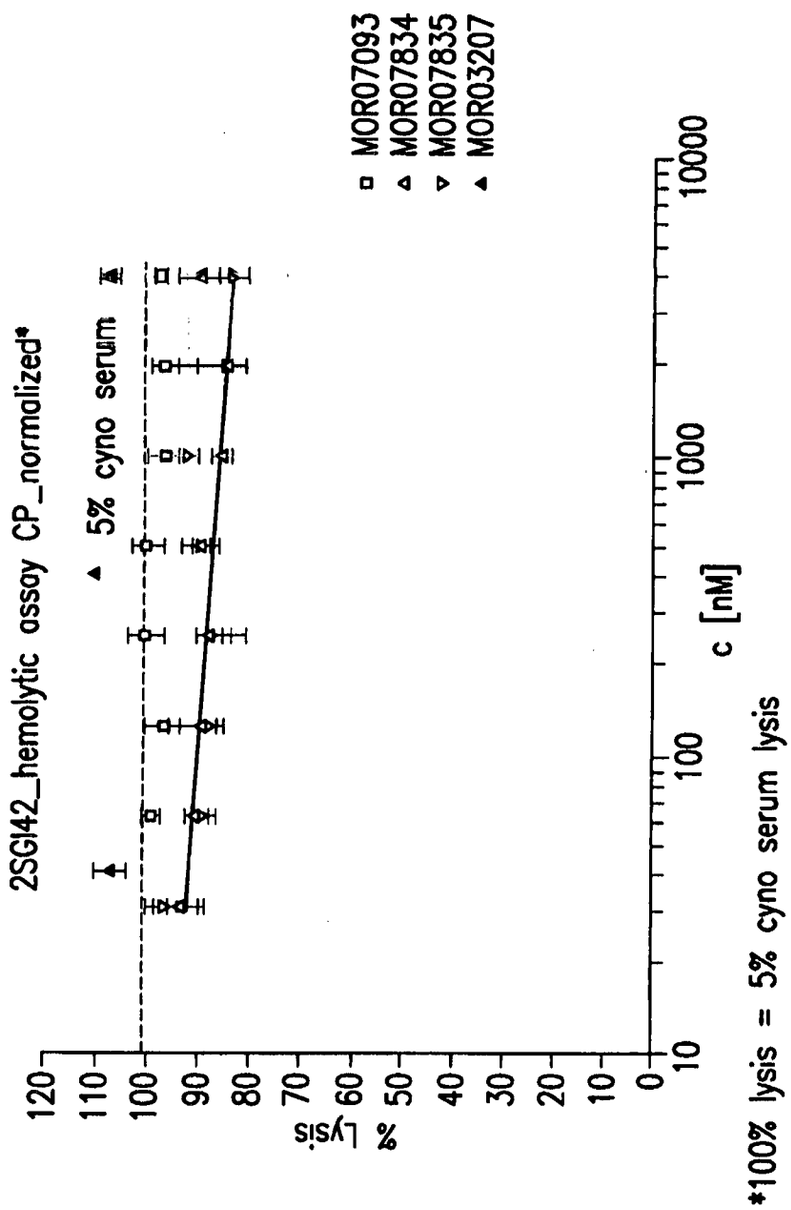

2SG142_hemolytic assay CP_normalized*
5% cyno serum
MOR07093
MOR07834
MOR07835
MOR03207
% Lysis
120
110
100
90
80
70
60
50
40
30
20
10
0
10
100
1000
10000
c [nM]
*100% lysis = 5% cyno serum lysis

FIG.8-3

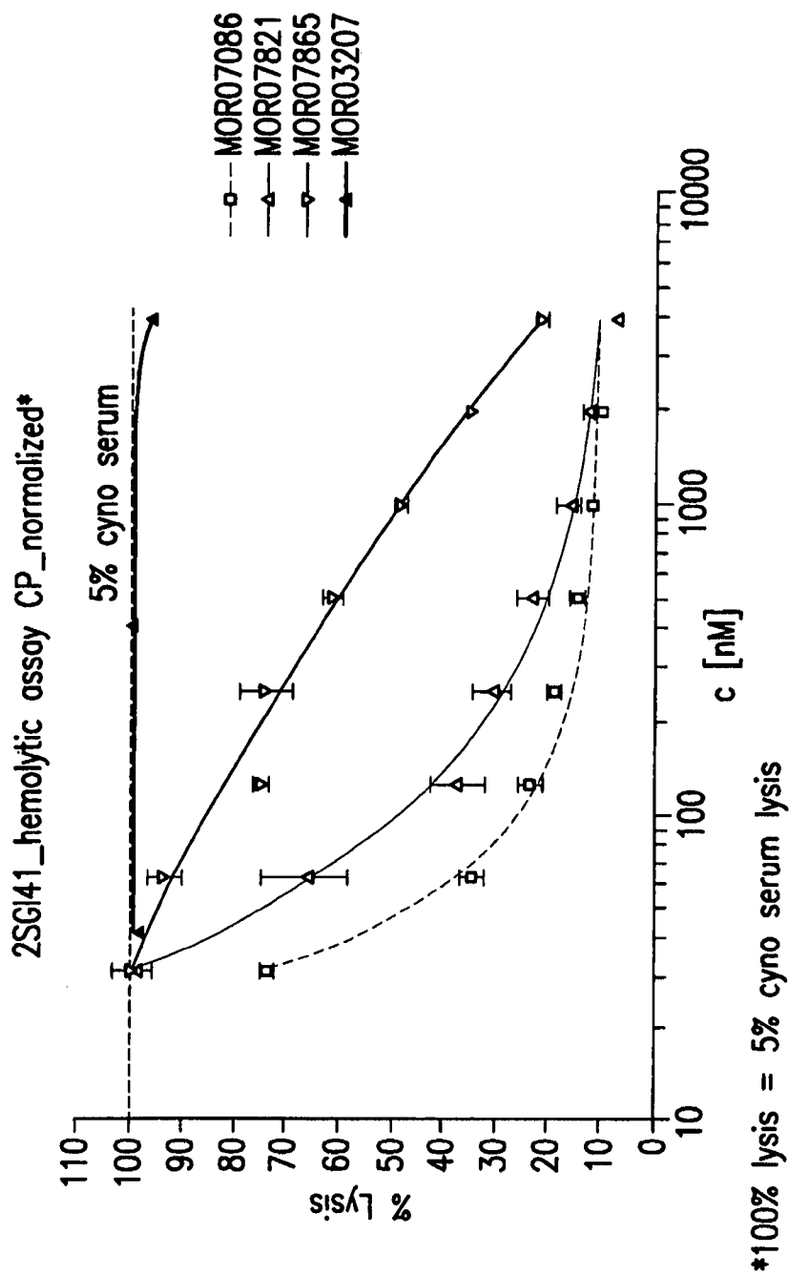

2SGI41_hemolytic assay CP_normalized*
5% cyno serum
MOR07086
MOR07821
MOR07865
MOR03207
% Lysis
c [nM]
*100% lysis = 5% cyno serum lysis

FIG.8-4

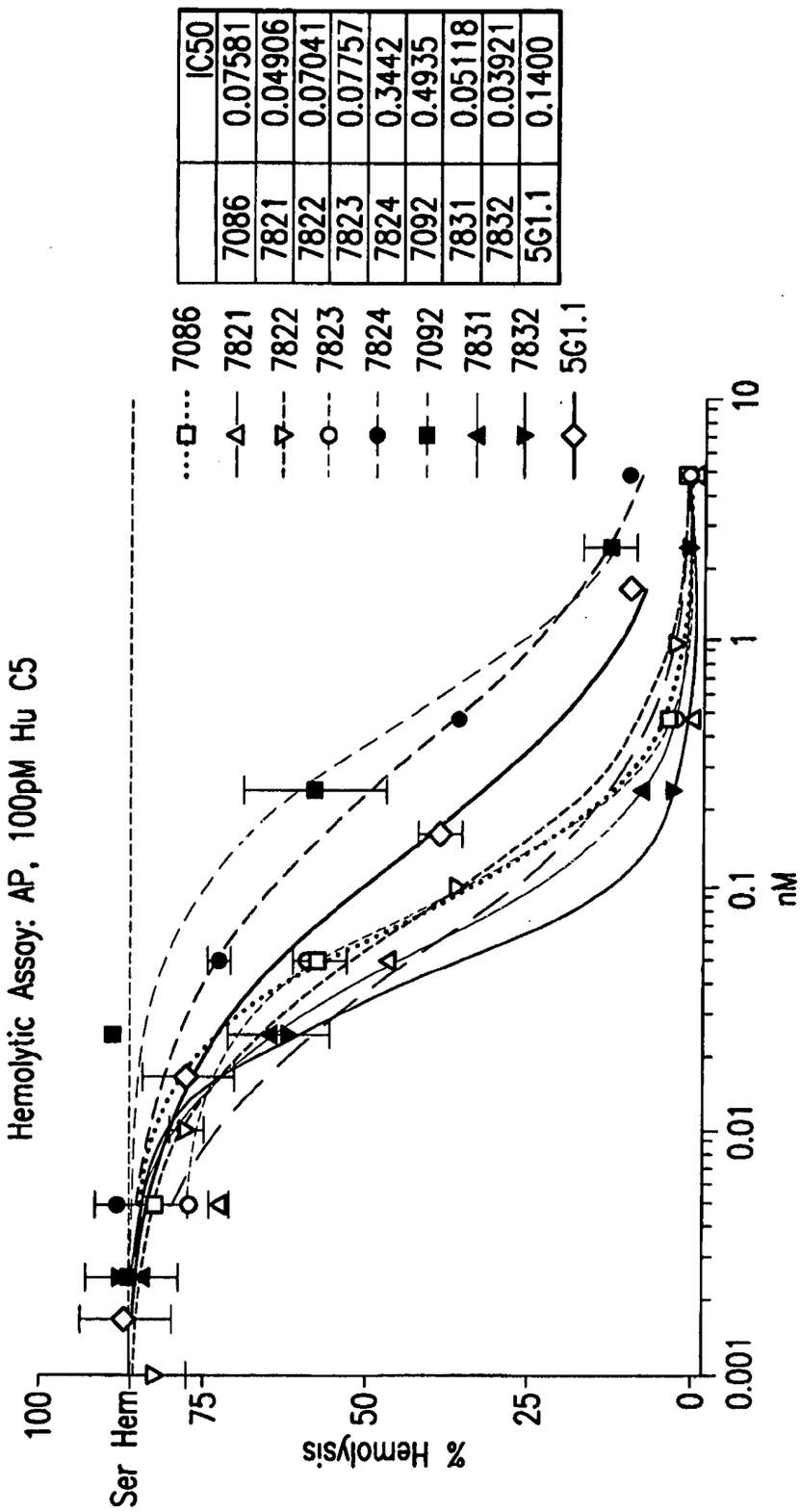

IC50
7086 0.07581
7821 0.04906
7822 0.07041
7823 0.07757
7824 0.3442
7092 0.4935
7831 0.05118
7832 0.03921
5G1.1 0.1400
7086
7821
7822
7823
7824
7092
7831
7832
5G1.1
Hemolytic Assay: AP, 100pM Hu C5
% Hemolysis
Ser Hem
100
75
50
25
0
0.001
0.01
0.1
1
10
nM

FIG.9a

16A

	IC50
7091	1.296
7829	0.4720
7830	0.4078
7093	2.823
7833	0.1161
7834	0.07866
7835	0.08439
7836	0.1694
7086	0.05113
5G1 1	0.1029

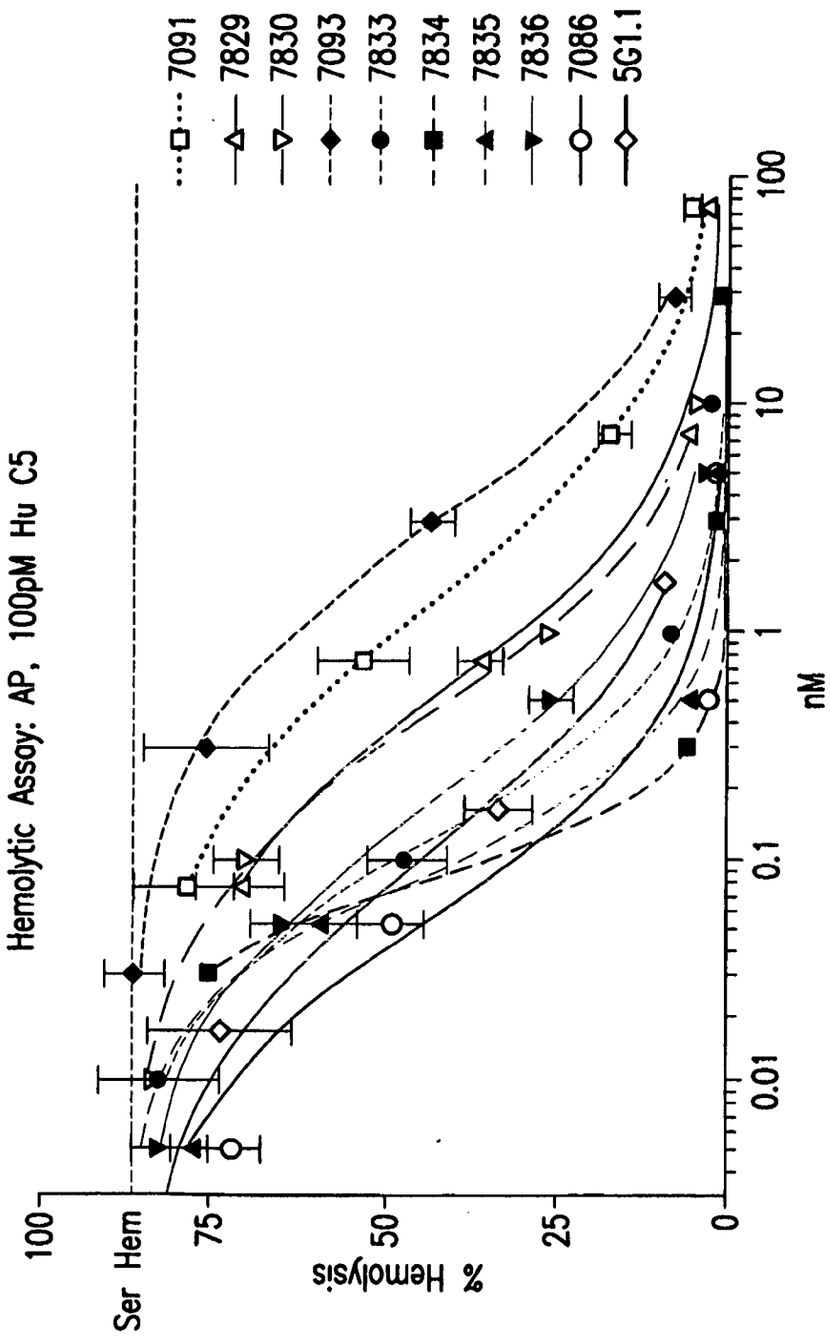
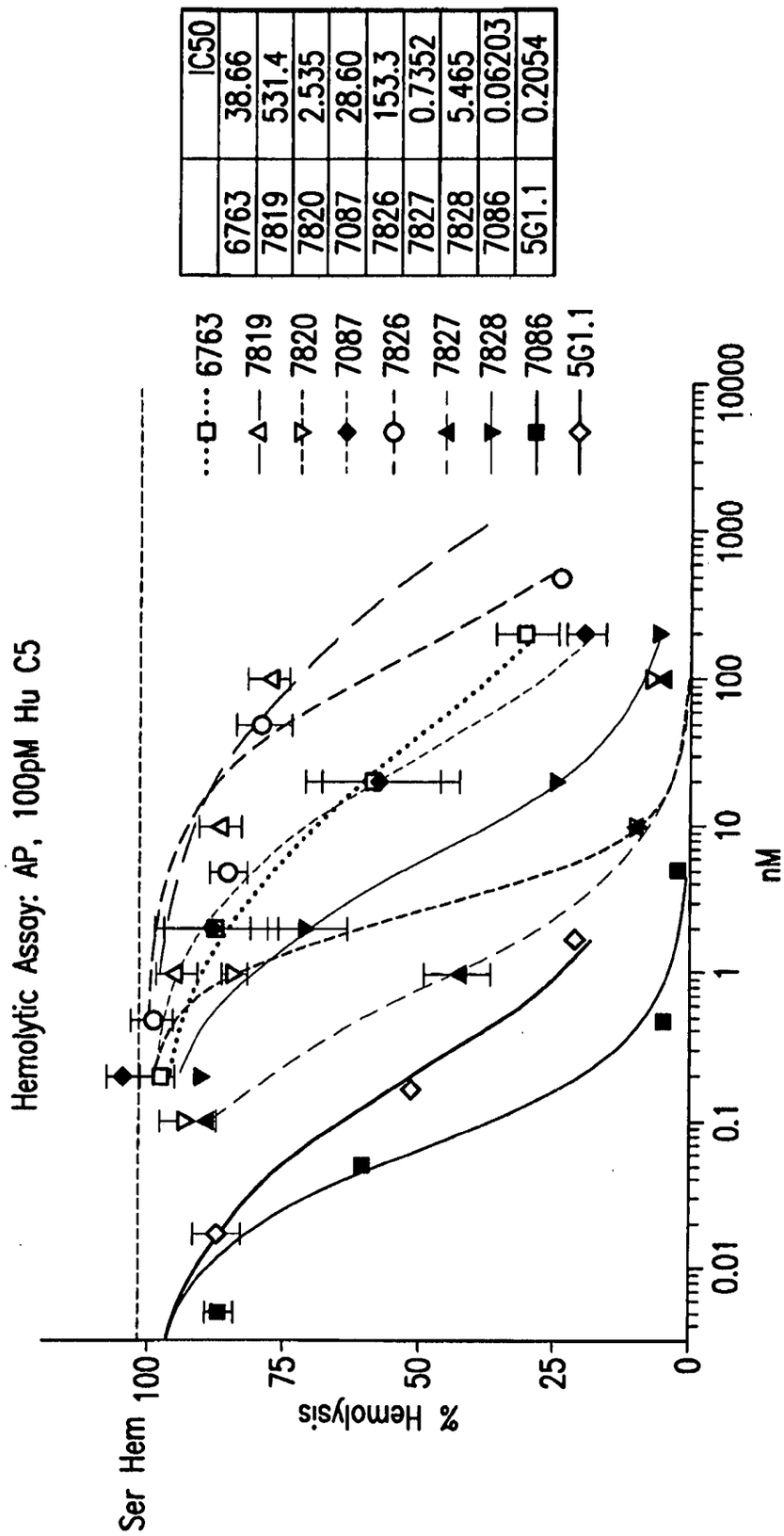


FIG.9b



	IC50
6763	38.66
7819	531.4
7820	2.535
7087	28.60
7826	153.3
7827	0.7352
7828	5.465
7086	0.06203
5G1.1	0.2054

FIG.9c

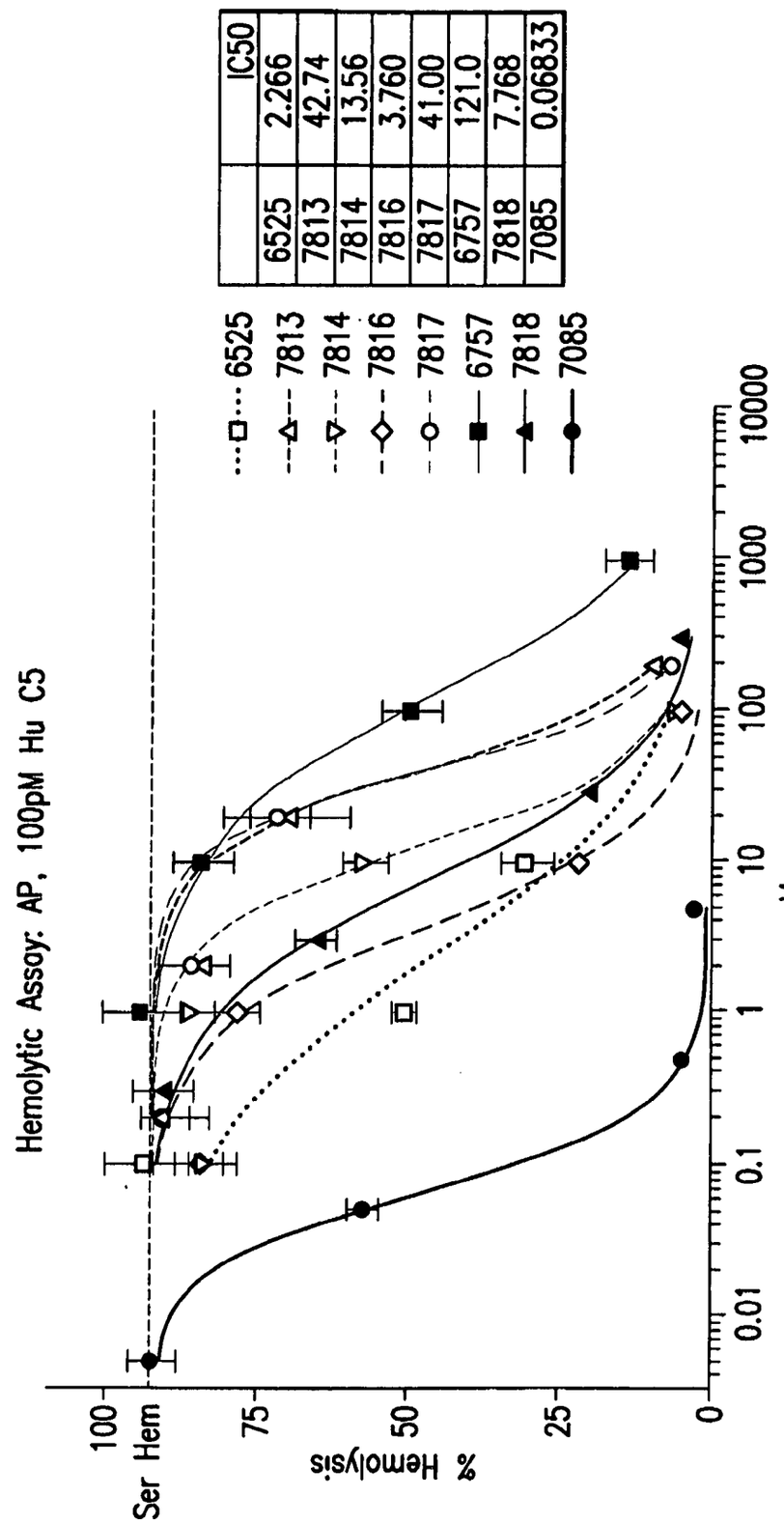
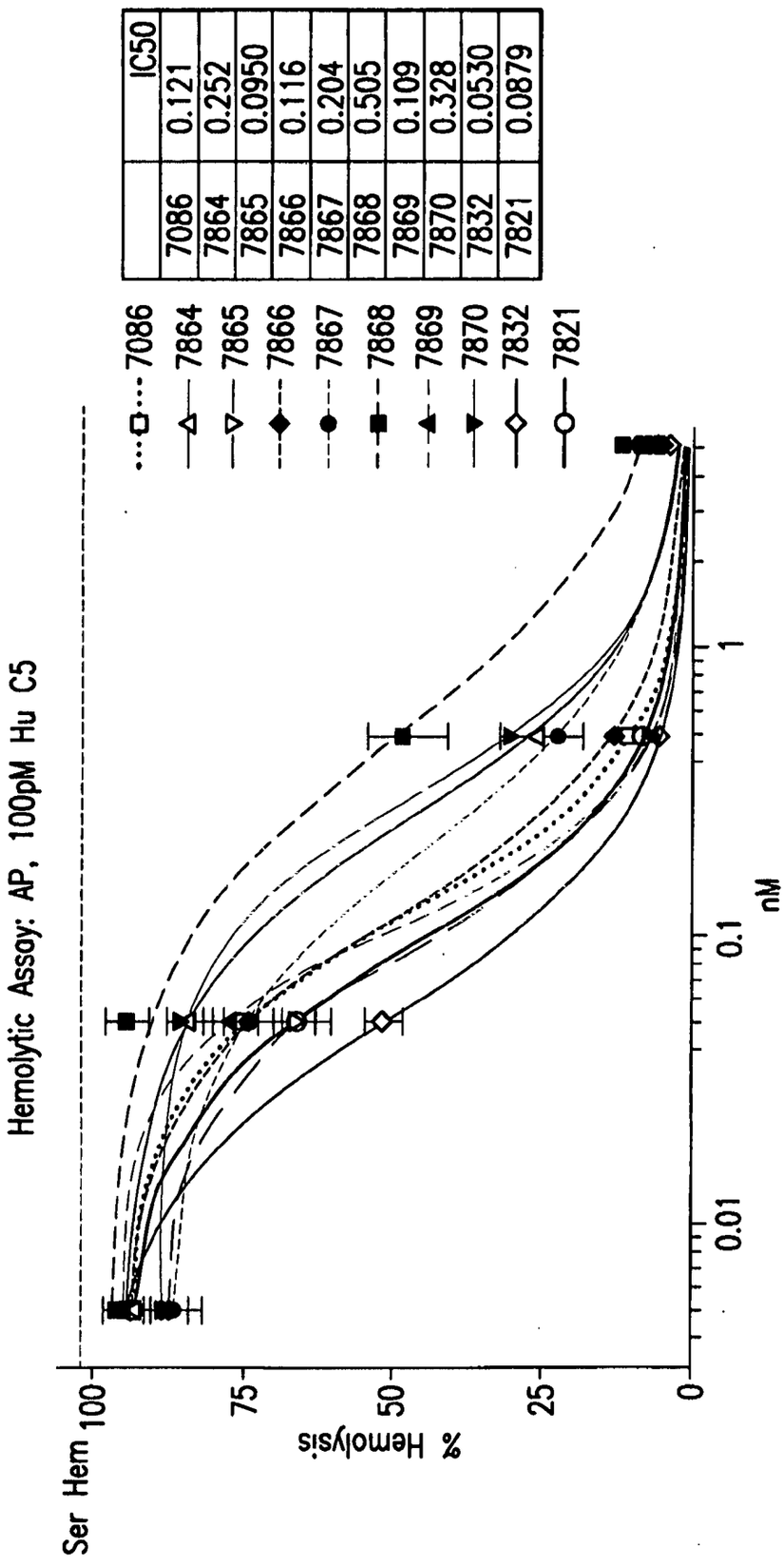

Hemolytic Assay: AP, 100pM Hu C5
% Hemolysis
Ser Hem
100
75
50
25
0
0.01
0.1
1
10
100
1000
10000
nM
6525
7813
7814
7816
7817
6757
7818
7085
IC50
6525 2.266
7813 42.74
7814 13.56
7816 3.760
7817 41.00
6757 121.0
7818 7.768
7085 0.06833

FIG.9d



	IC50
7086	0.121
7864	0.252
7865	0.0950
7866	0.116
7867	0.204
7868	0.505
7869	0.109
7870	0.328
7832	0.0530
7821	0.0879

FIG.9e

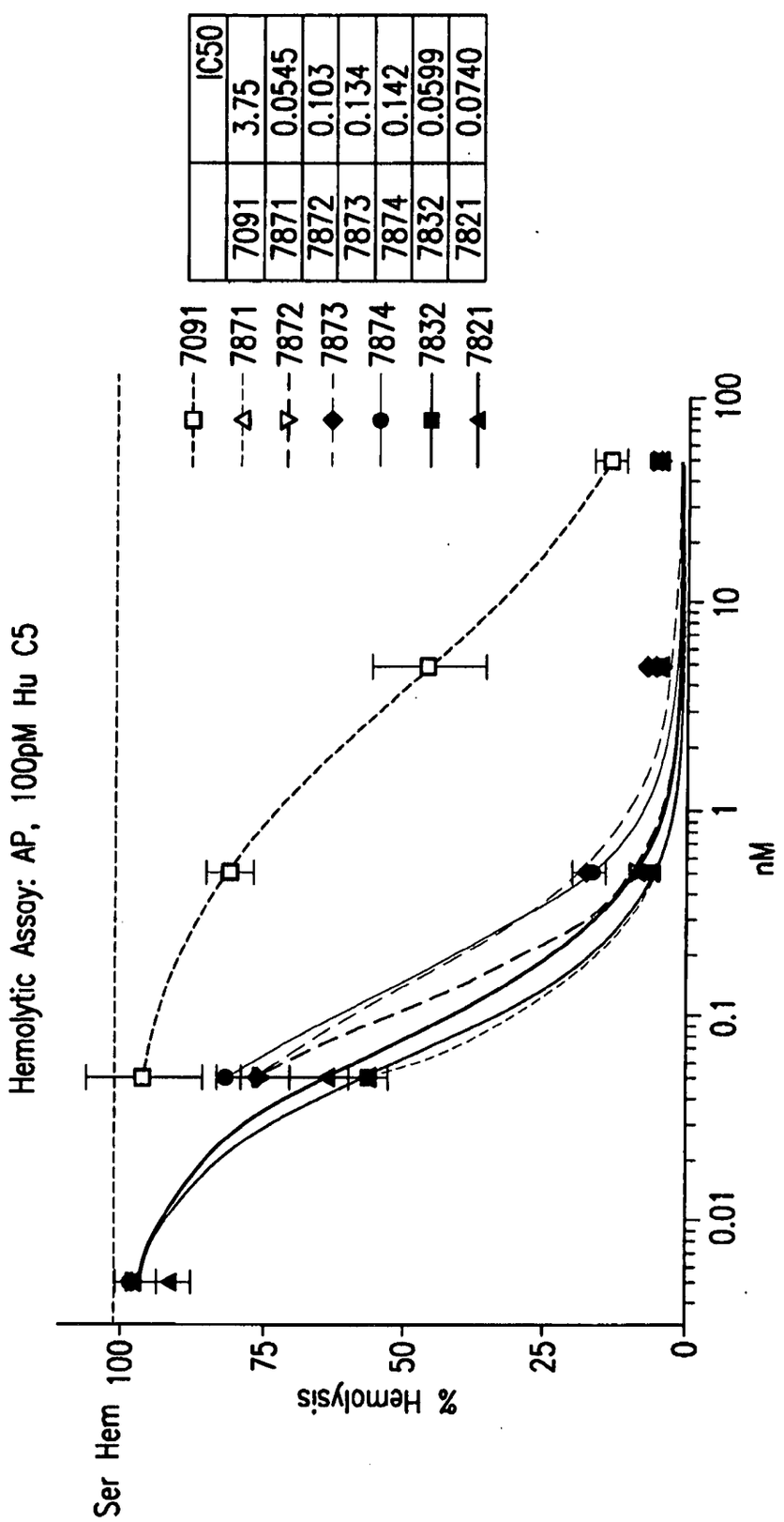

Hemolytic Assay: AP, 100pM Hu C5
Ser Hem
% Hemolysis
100
75
50
25
0
0.01
0.1
1
10
100
nM
7091
7871
7872
7873
7874
7832
7821
IC50
3.75
0.0545
0.103
0.134
0.142
0.0599
0.0740

FIG.9f

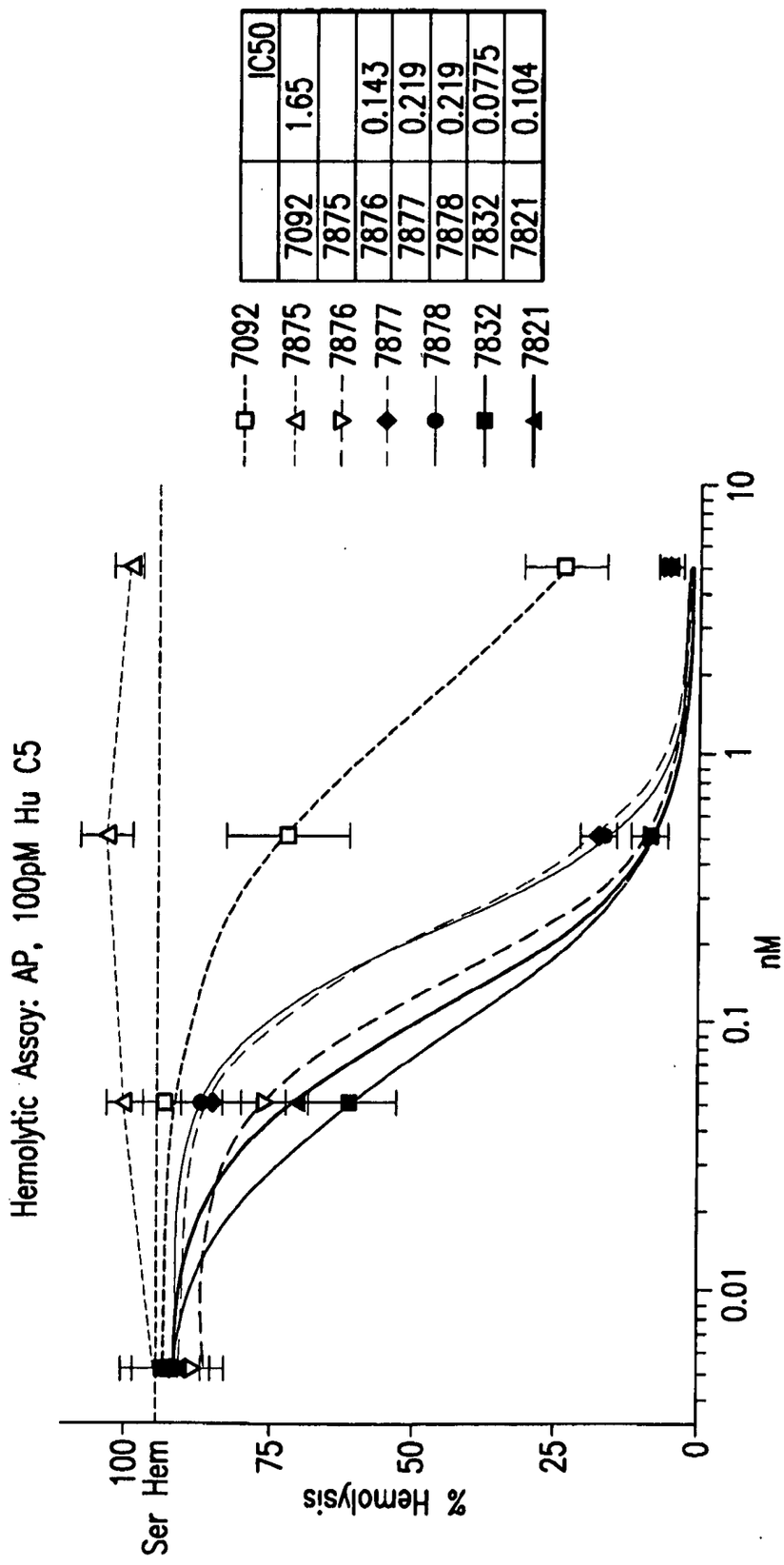

IC50
7092 1.65
7875
7876 0.143
7877 0.219
7878 0.219
7832 0.0775
7821 0.104
7092
7875
7876
7877
7878
7832
7821
Hemolytic Assay: AP, 100pM Hu C5
% Hemolysis
Ser Hem
100
75
50
25
0
0.01
0.1
1
10
nM

FIG.9g

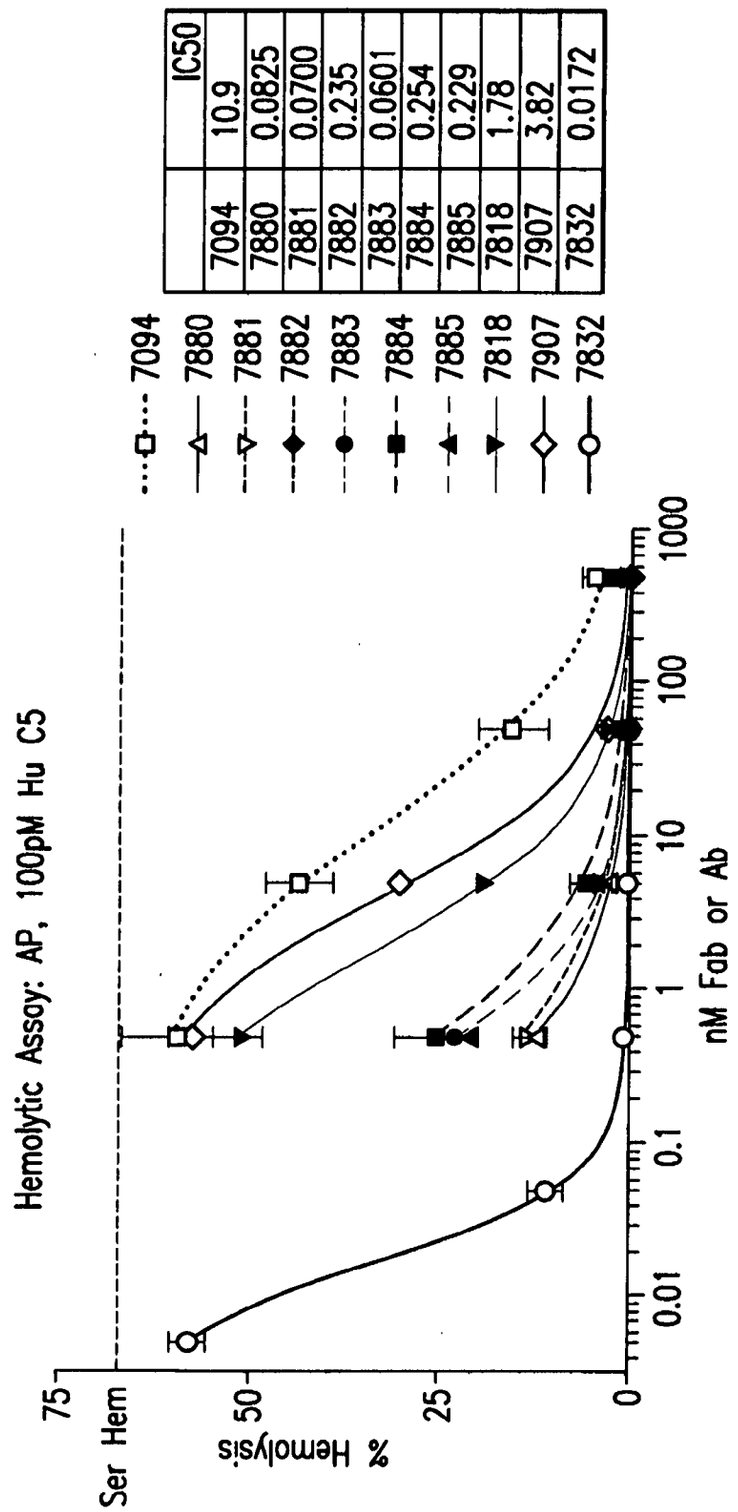
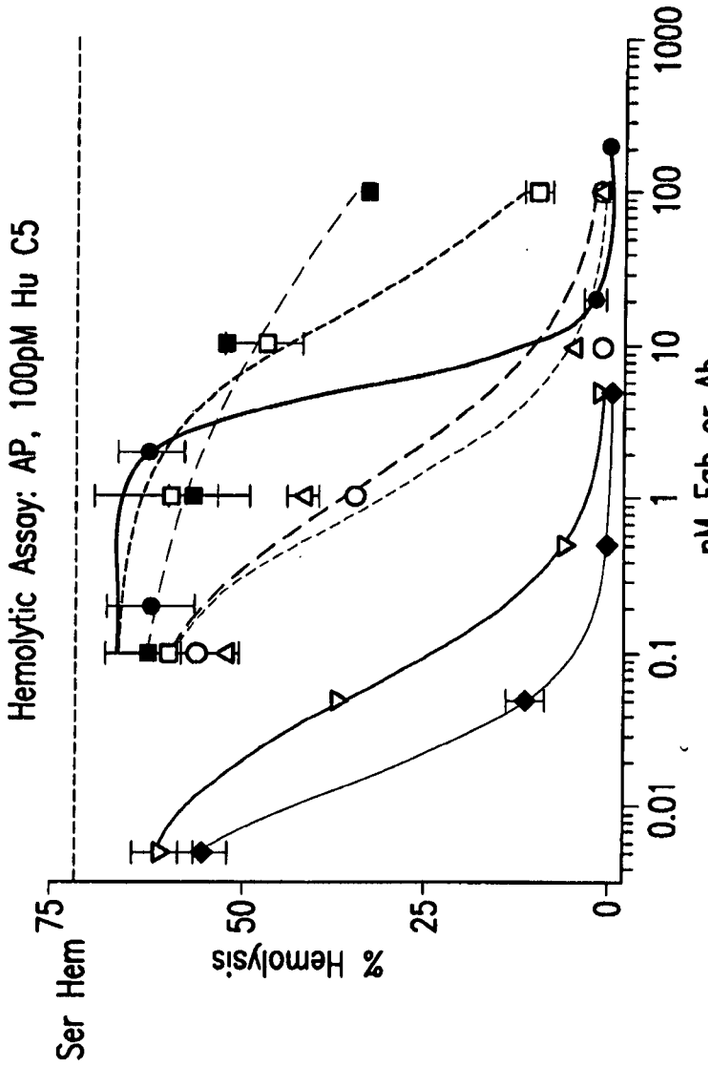
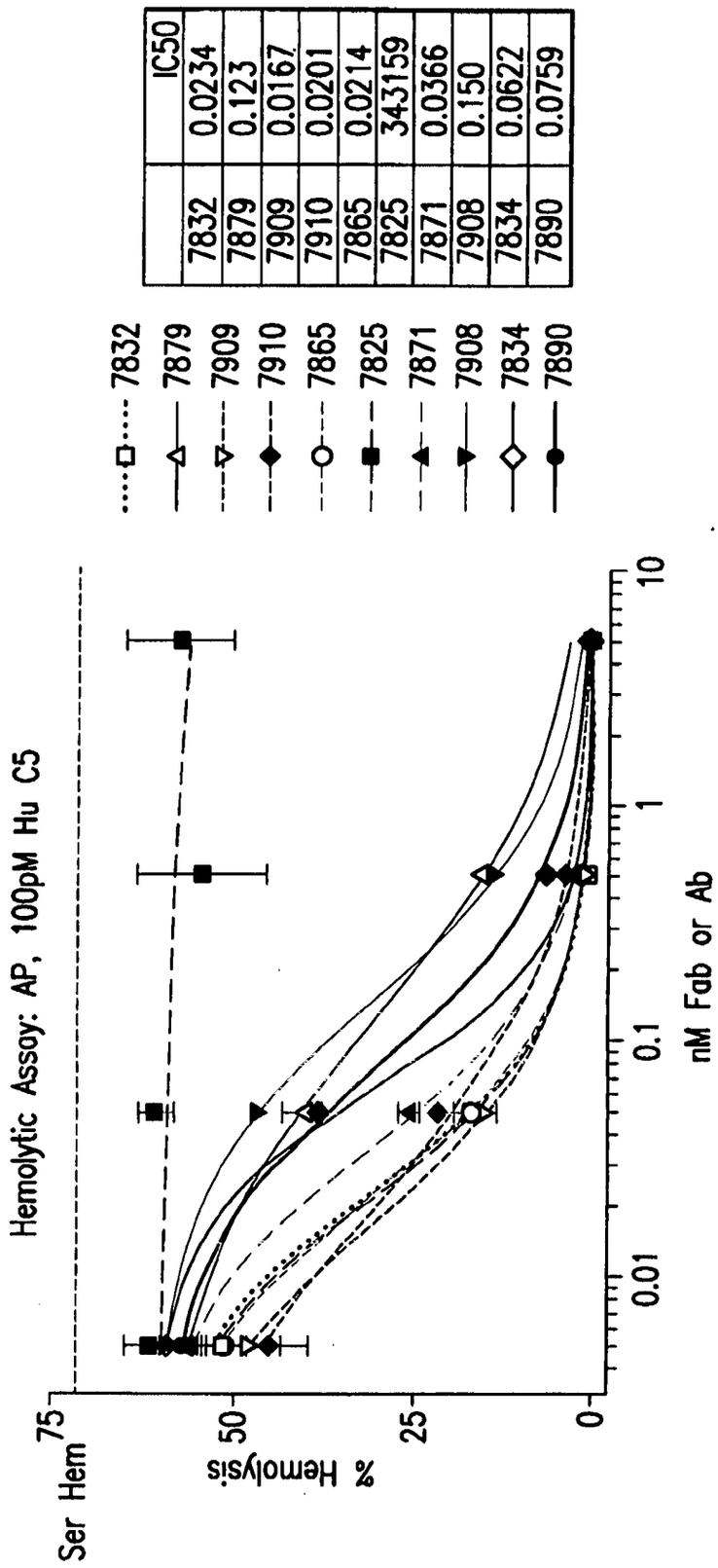

Hemolytic Assay: AP, 100pM Hu C5
% Hemolysis
Ser Hem
75
50
25
0
0.01
0.1
1
10
100
1000
nM Fab or Ab
7094
7880
7881
7882
7883
7884
7885
7818
7907
7832
IC50
7094 10.9
7880 0.0825
7881 0.0700
7882 0.235
7883 0.0601
7884 0.254
7885 0.229
7818 1.78
7907 3.82
7832 0.0172

FIG.9h



	IC50
7613	19.9
7616	1.24
7620	0.902
7689	120
7832	0.0156
5G1.1	0.0582
A233 (a-FP)	5.45

FIG.9i



	IC50
7832	0.0234
7879	0.123
7909	0.0167
7910	0.0201
7865	0.0214
7825	343159
7871	0.0366
7908	0.150
7834	0.0622
7890	0.0759

FIG.9j

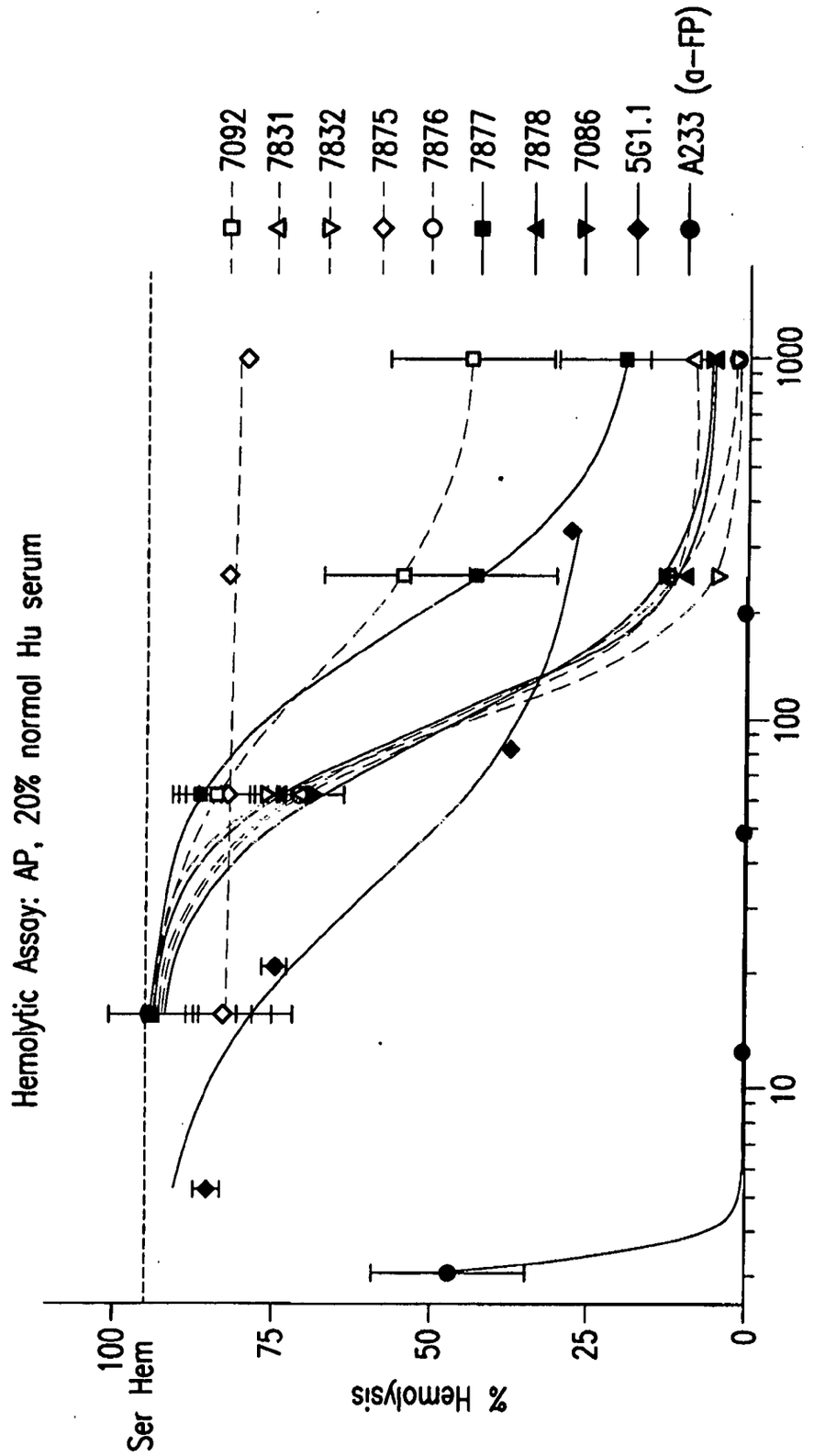

Hemolytic Assay: AP, 20% normal Hu serum
% Hemolysis
Ser Hem
100
75
50
25
0
10
100
1000
nM Fab or Ab
7092
7831
7832
7875
7876
7877
7878
7086
5G1.1
A233 (a-FP)

FIG.10a

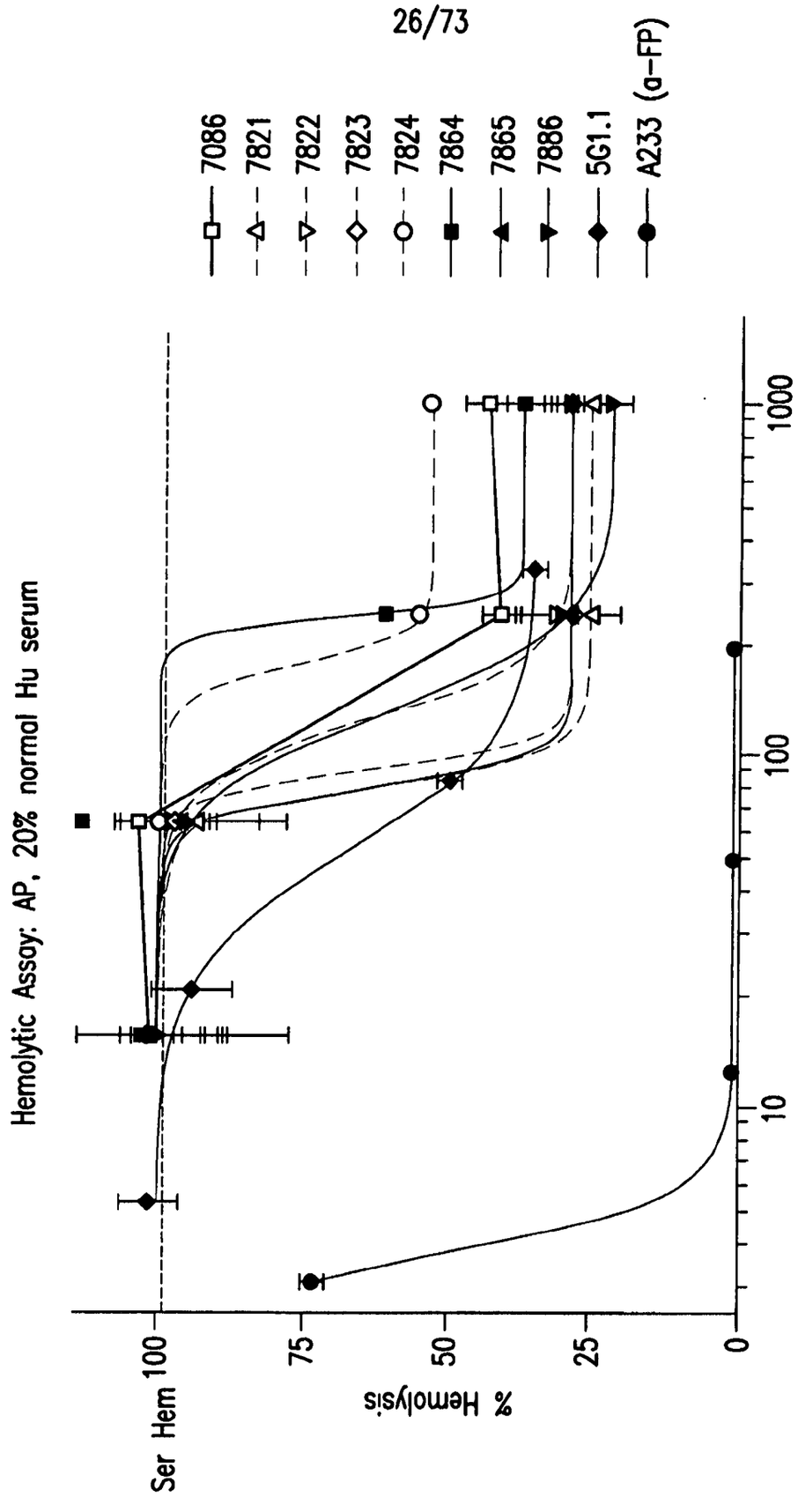

7086
7821
7822
7823
7824
7864
7865
7886
5G1.1
A233 (α-FP)
Hemolytic Assay: AP, 20% normal Hu serum
Ser Hem 100
% Hemolysis
0
25
50
75
10
100
1000
nM Fab or Ab

FIG.10b

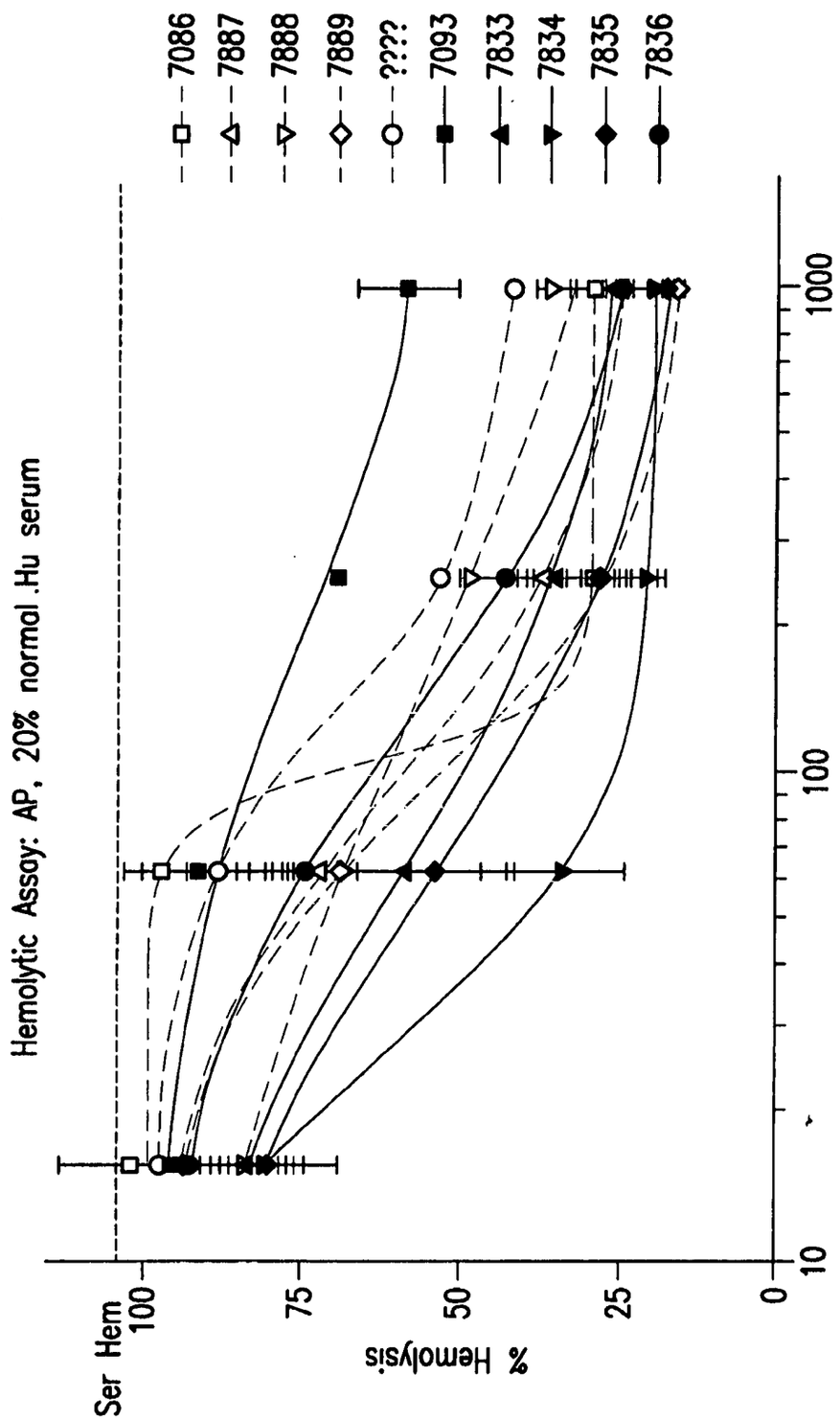

7086
7887
7888
7889
????
7093
7833
7834
7835
7836
Hemolytic Assay: AP, 20% normal .Hu serum
Ser Hem
100
75
50
25
0
% Hemolysis
10
100
1000
nM Fab or Ab

FIG.10c

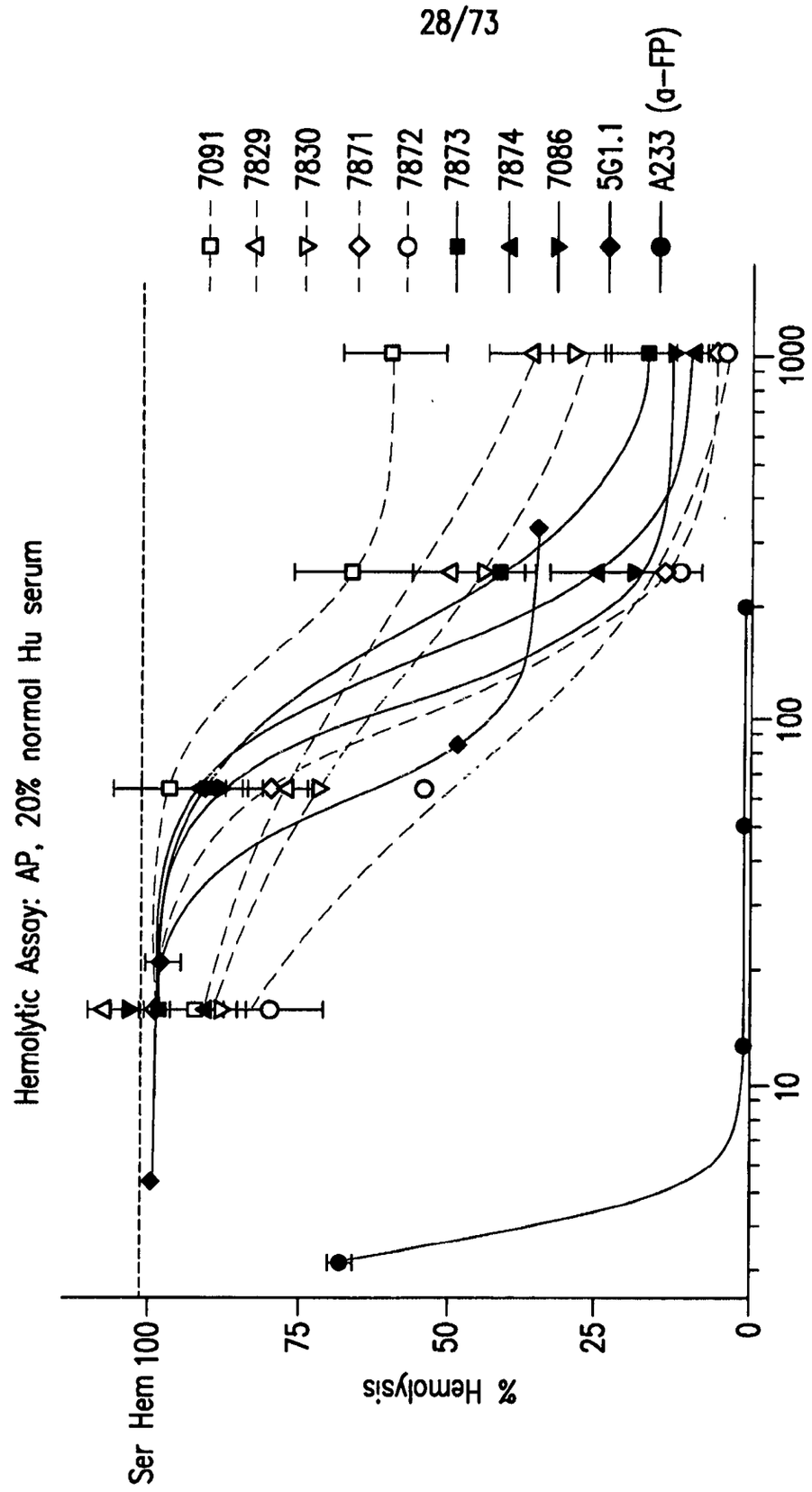

Hemolytic Assay: AP, 20% normal Hu serum
Ser Hem 100
75
50
25
0
% Hemolysis
10
100
1000
nM Fab or Ab
7091
7829
7830
7871
7872
7873
7874
7086
5G1.1
A233 (α-FP)

FIG.10d

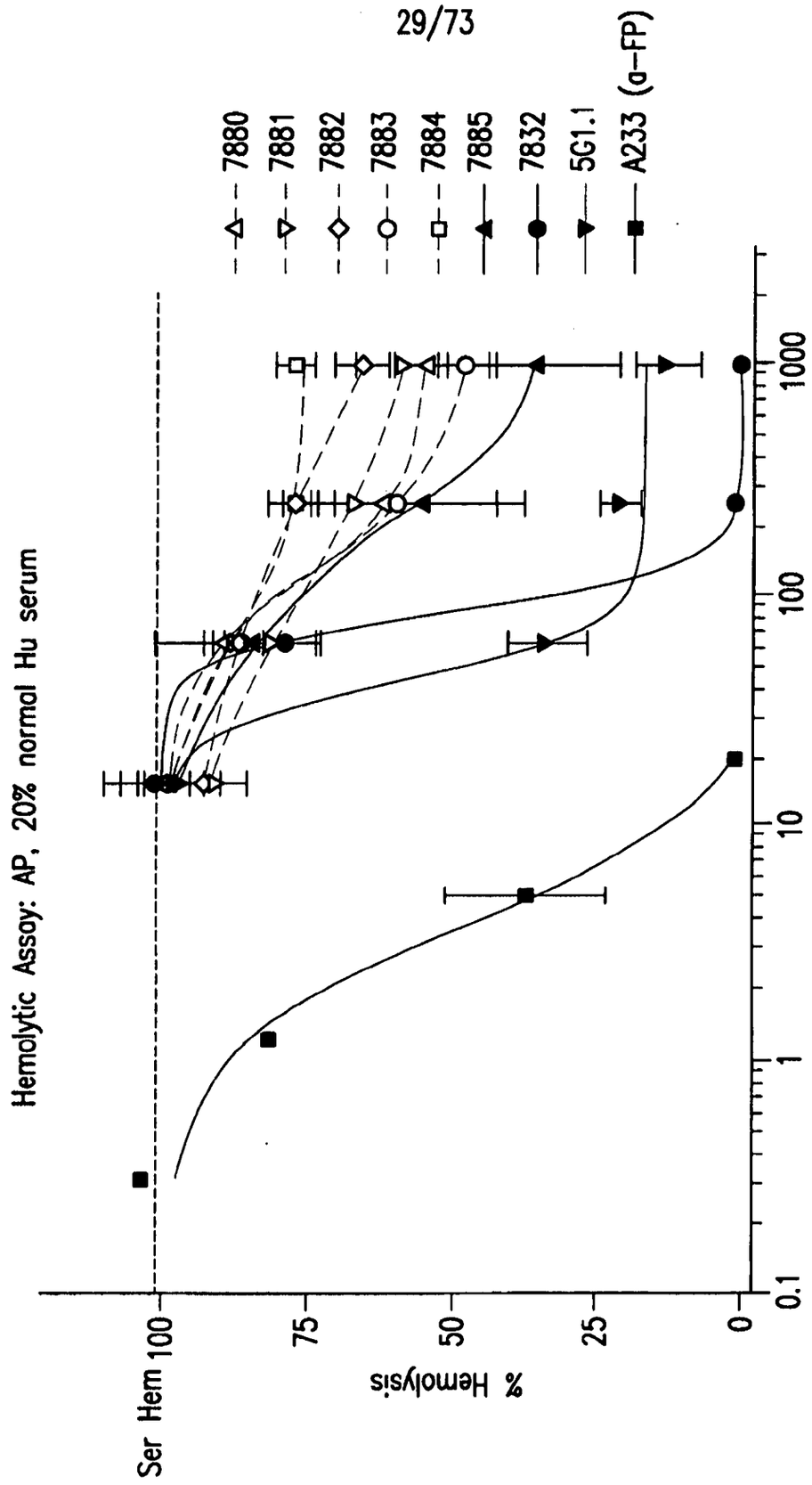

Hemolytic Assay: AP, 20% normal Hu serum
Ser Hem 100
75
50
25
0
% Hemolysis
0.1
1
10
100
1000
nM Fab or Ab
7880
7881
7882
7883
7884
7885
7832
5G1.1
A233 (a-FP)

FIG.10e

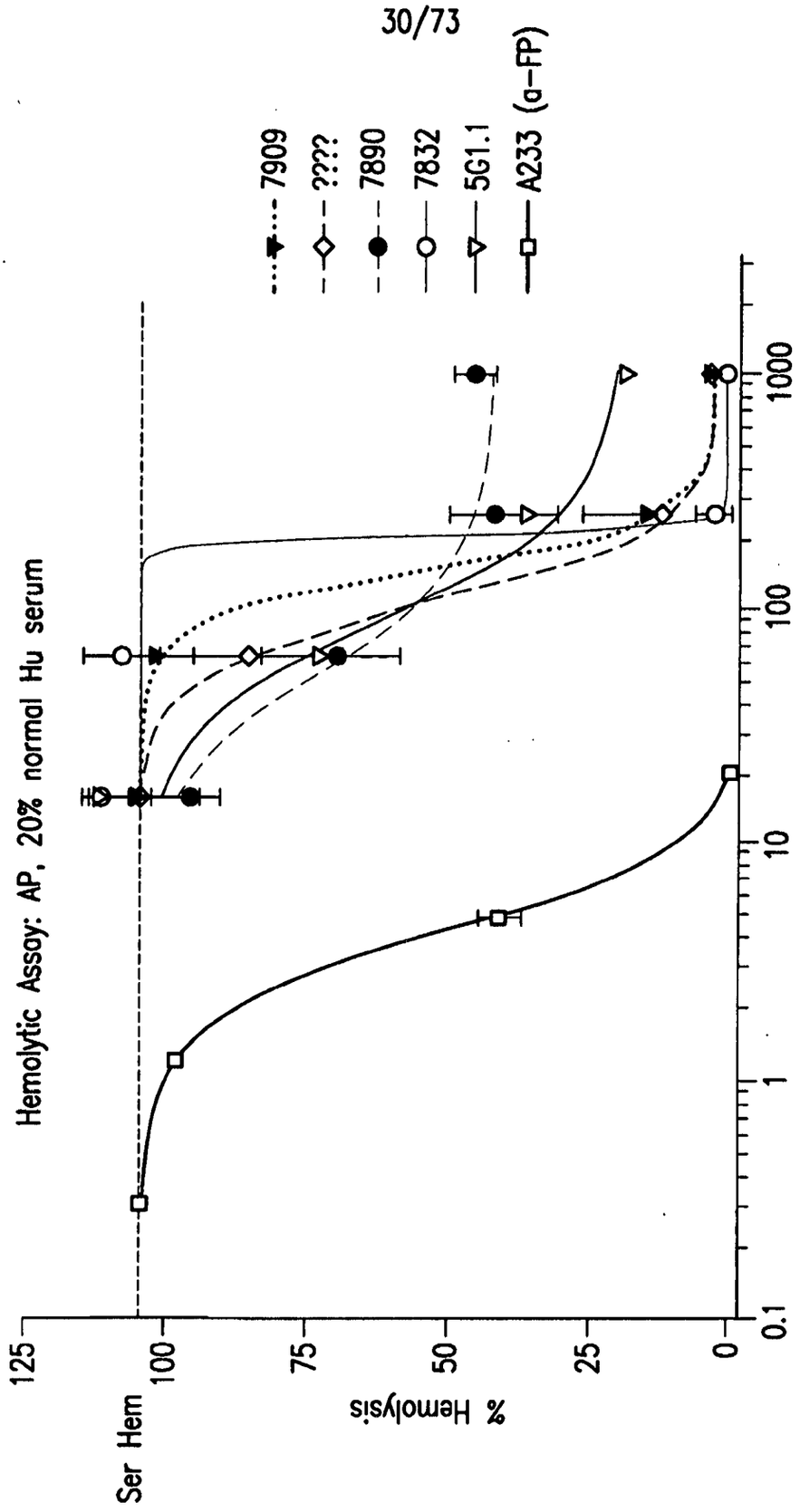

7909
????
7890
7832
5G1.1
A233 (a-FP)
Hemolytic Assay: AP, 20% normal Hu serum
% Hemolysis
Ser Hem
125
100
75
50
25
0
0.1
1
10
100
1000
nM Fab or Ab

FIG.10f

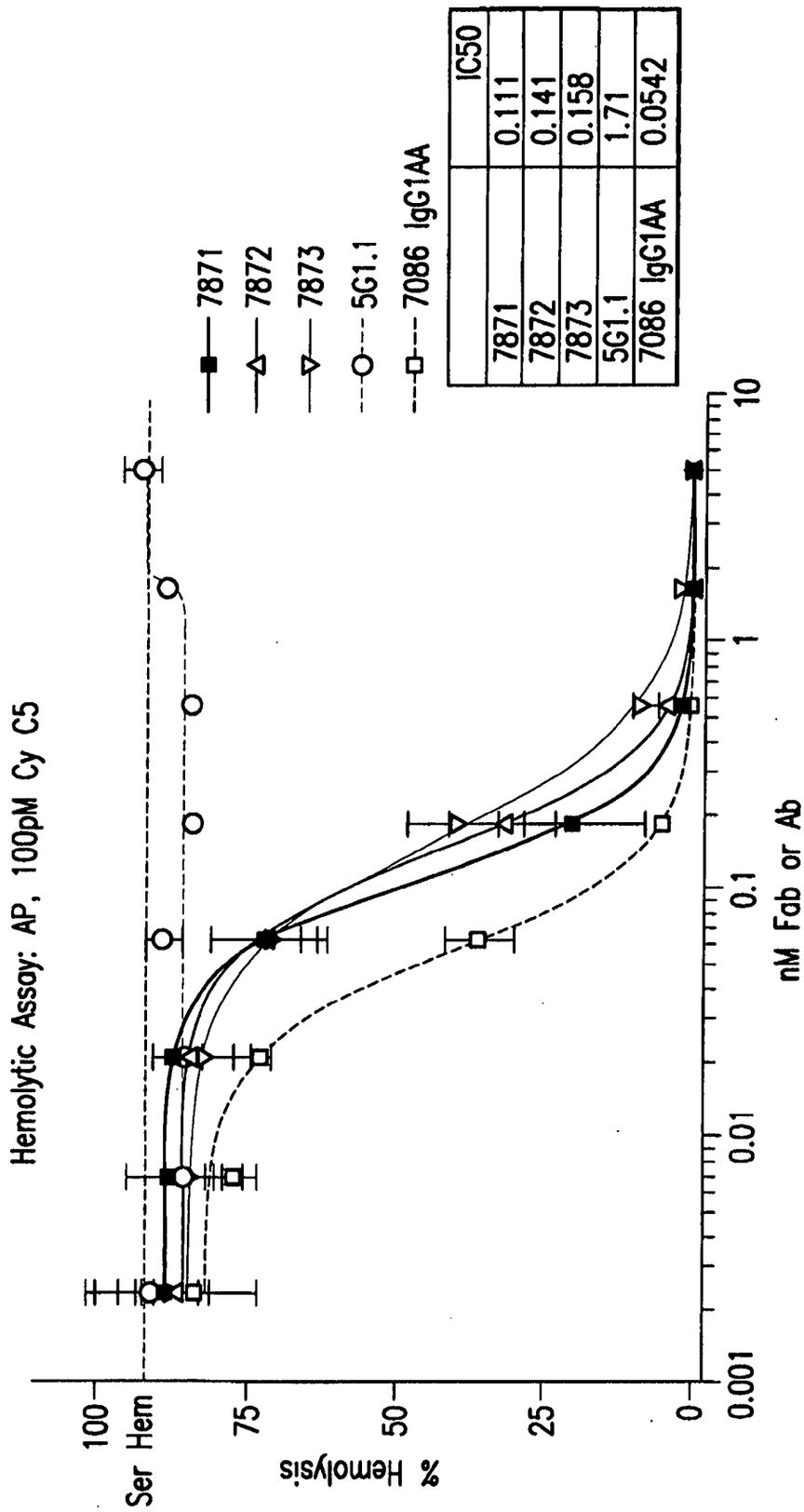

Hemolytic Assay: AP, 100pM Cy C5
7871
7872
7873
5G1.1
7086 IgG1AA
IC50
7871 0.111
7872 0.141
7873 0.158
5G1.1 1.71
7086 IgG1AA 0.0542
% Hemolysis
Ser Hem
100
75
50
25
0
0.001
0.01
0.1
1
10
nM Fab or Ab

FIG.11a

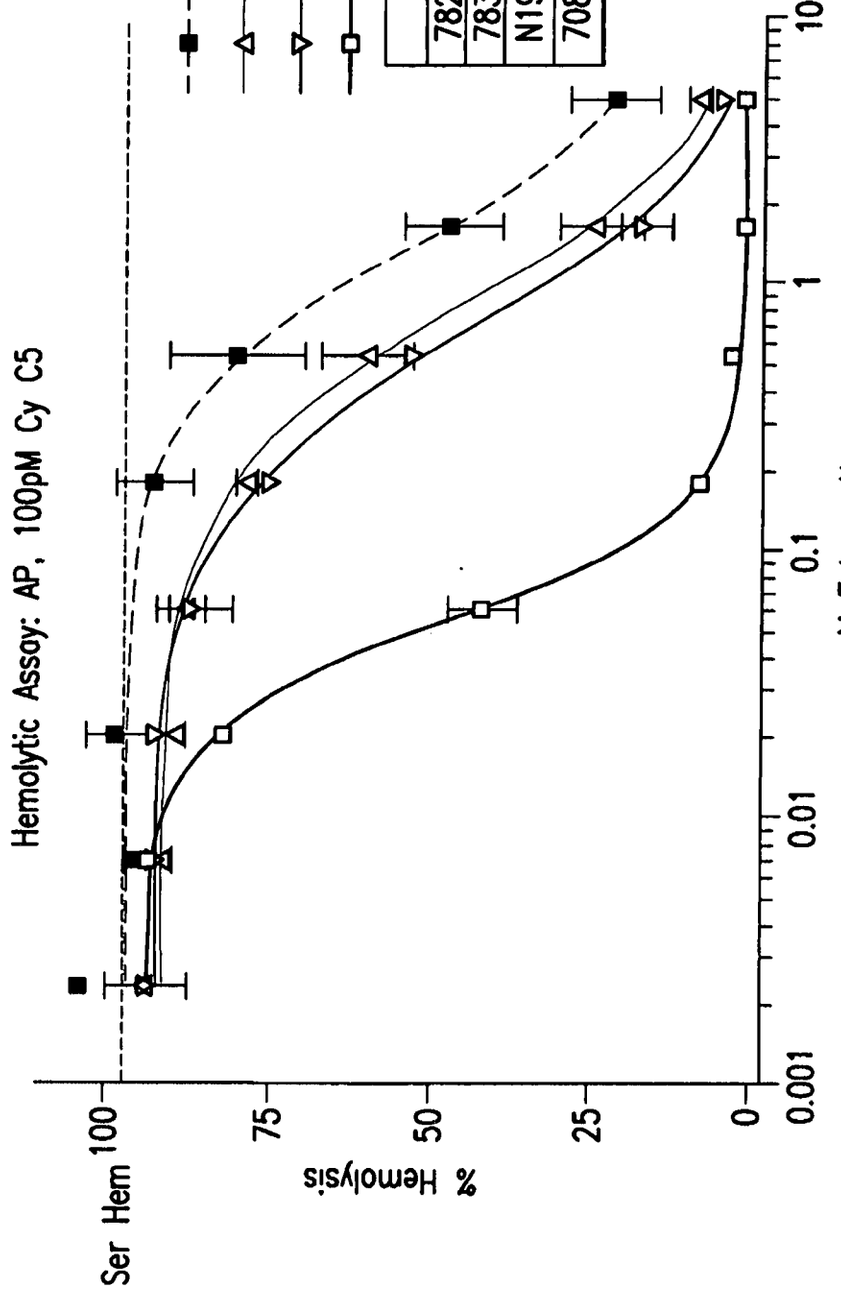

Hemolytic Assay: AP, 100pM Cy C5
7829
7830
N19/8
7086 IgG1AA
IC50
7829 1.40
7830 0.845
N19/8 0.661
7086 IgG1AA 0.0542
Ser Hem
% Hemolysis
nM Fab or Ab
100
75
50
25
0
0.001
0.01
0.1
1
10

FIG.11b

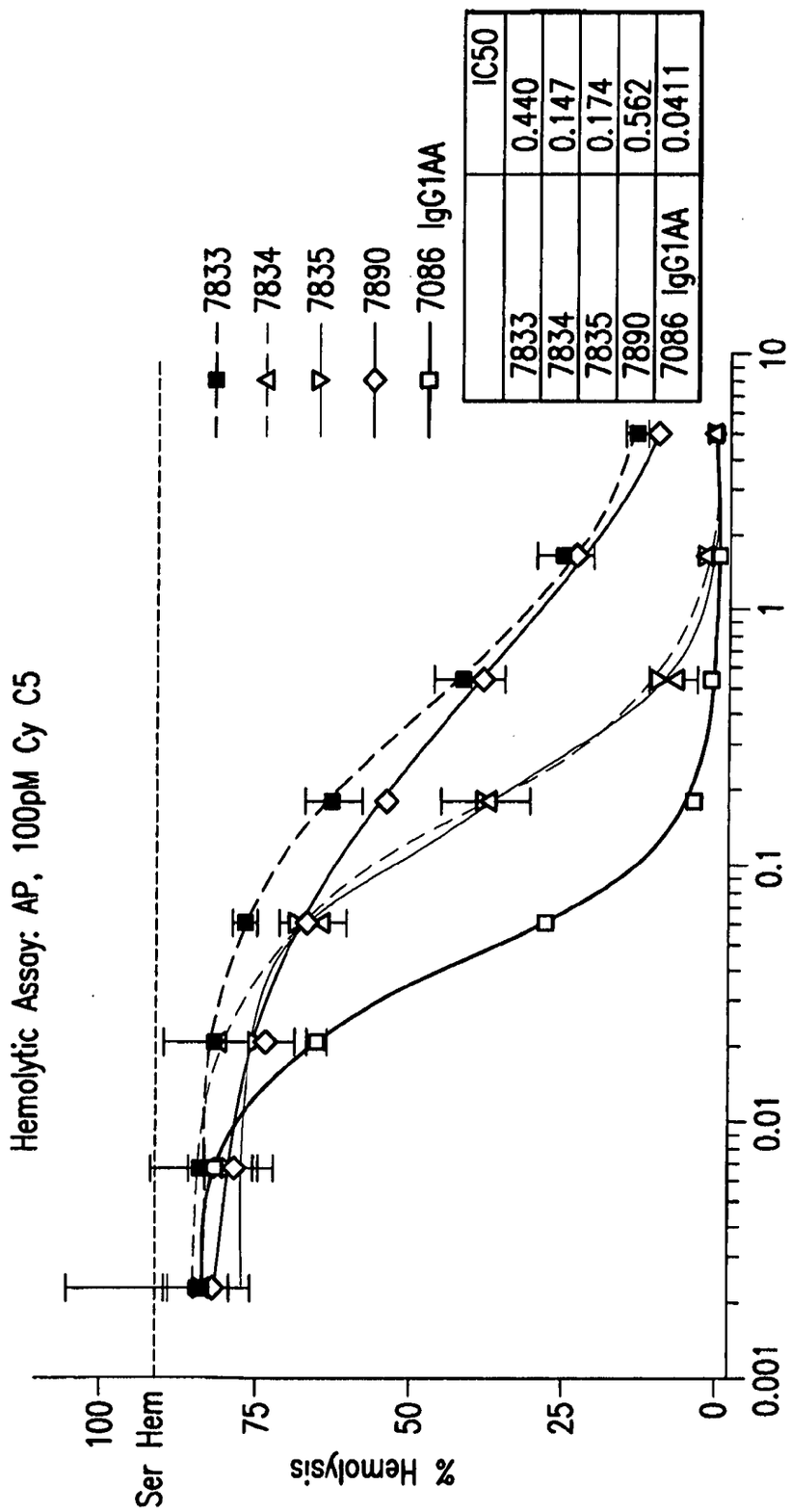

Hemolytic Assay: AP, 100pM Cy C5
% Hemolysis
Ser Hem
100
75
50
25
0
0.001
0.01
0.1
1
10
nM Fab or Ab
7833
7834
7835
7890
7086 IgG1AA
IC50
7833 0.440
7834 0.147
7835 0.174
7890 0.562
7086 IgG1AA 0.0411

FIG.11c

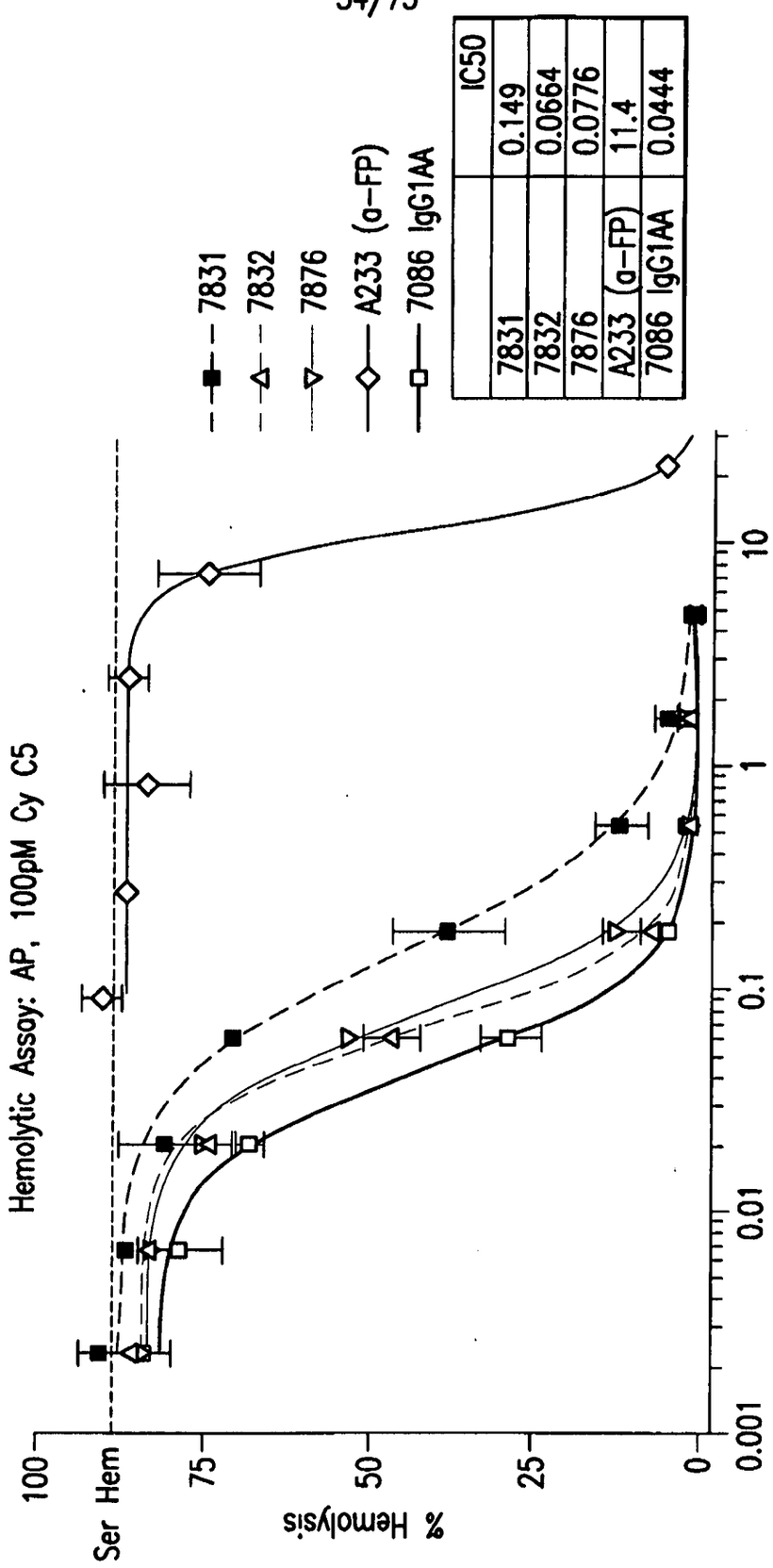

Hemolytic Assay: AP, 100pM Cy C5
% Hemolysis
Ser Hem
100
75
50
25
0
0.001
0.01
0.1
1
10
nM Fab or Ab
7831
7832
7876
A233 (a-FP)
7086 IgG1AA
IC50
7831 0.149
7832 0.0664
7876 0.0776
A233 (a-FP) 11.4
7086 IgG1AA 0.0444

FIG.11d

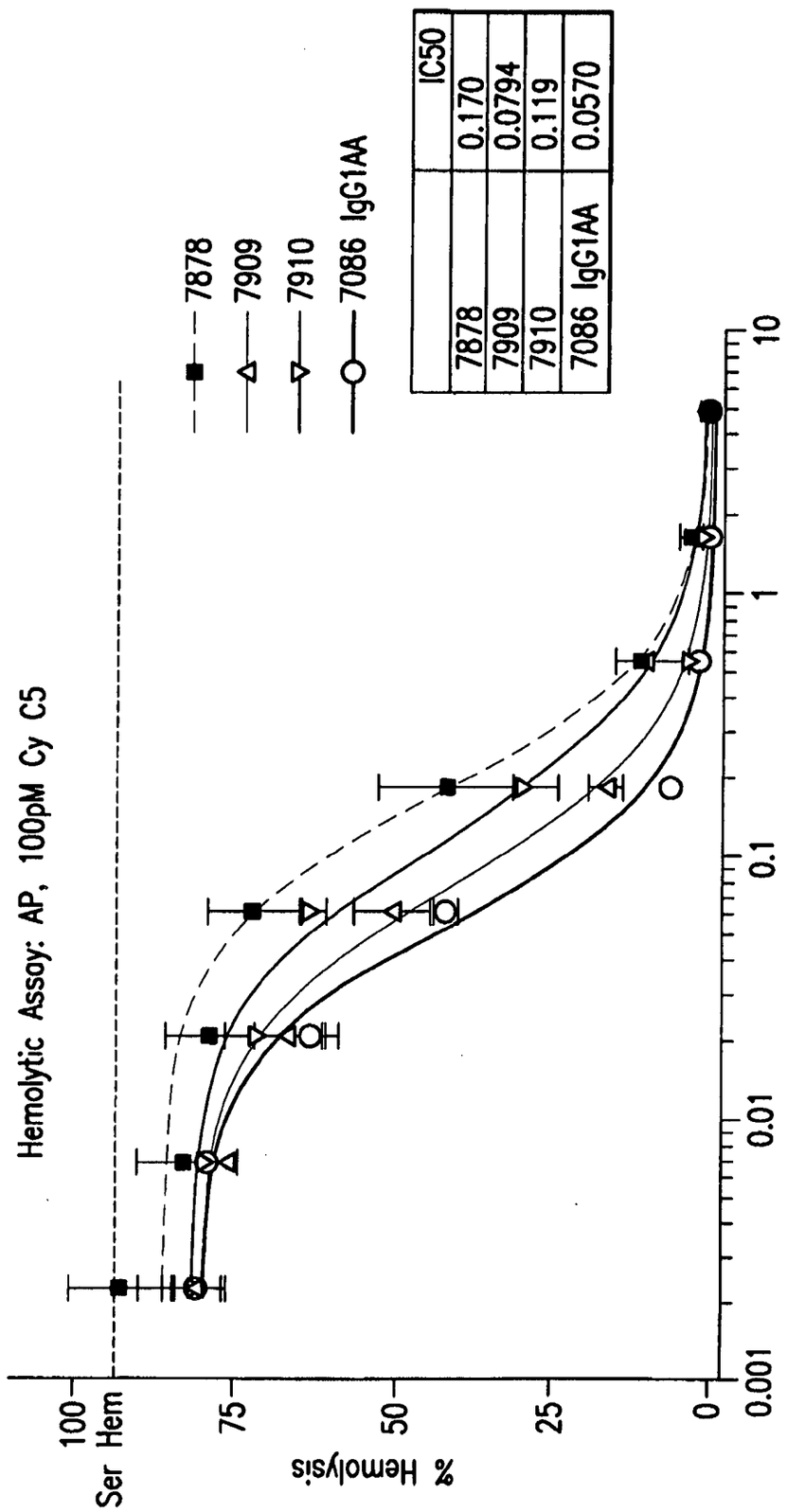

Hemolytic Assay: AP, 100pM Cy C5
% Hemolysis
100
Ser Hem
75
50
25
0
0.001
0.01
0.1
1
10
nM Fab or Ab
7878
7909
7910
7086 IgG1AA
IC50
7878 0.170
7909 0.0794
7910 0.119
7086 IgG1AA 0.0570

FIG.11e

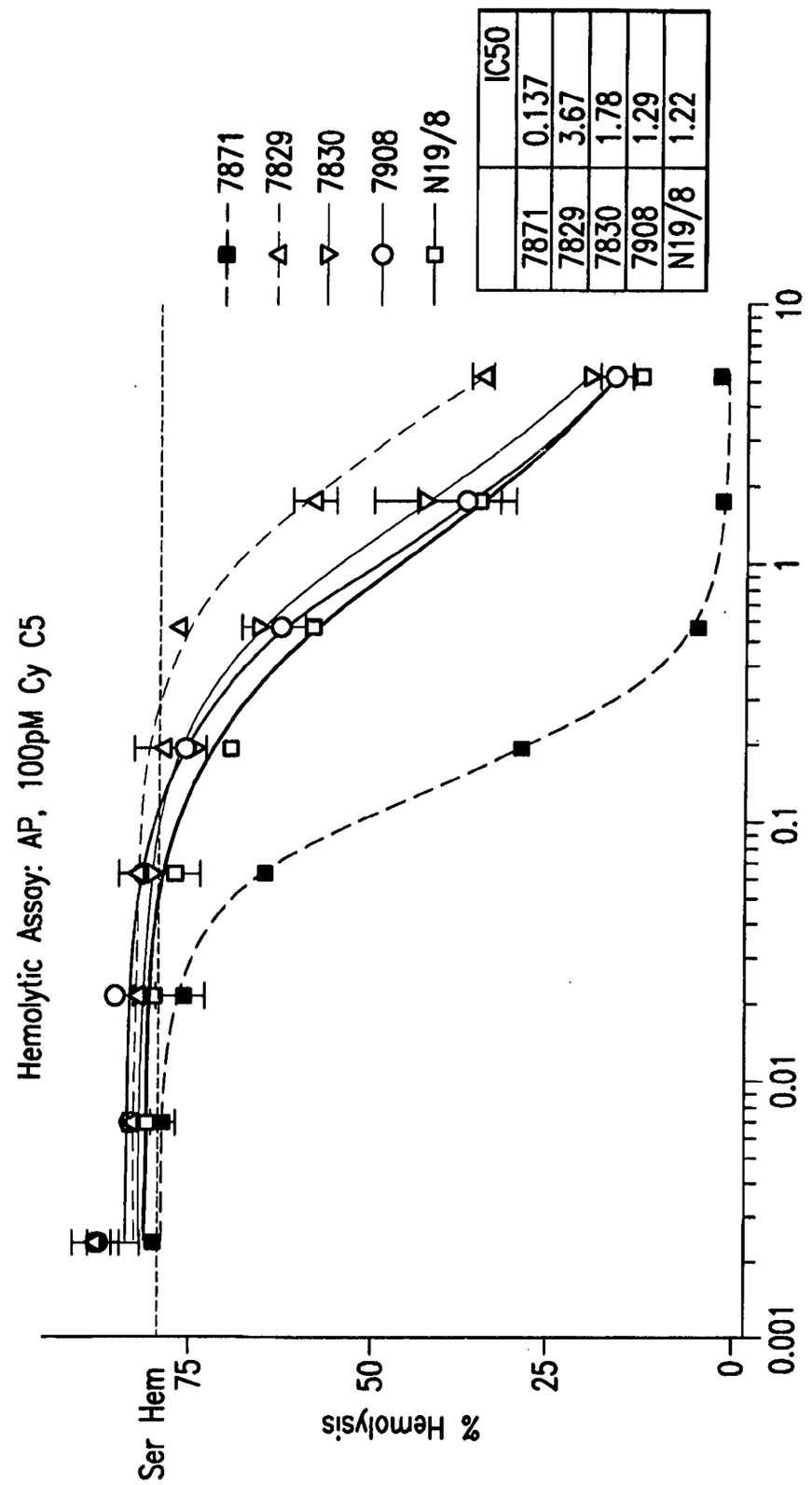
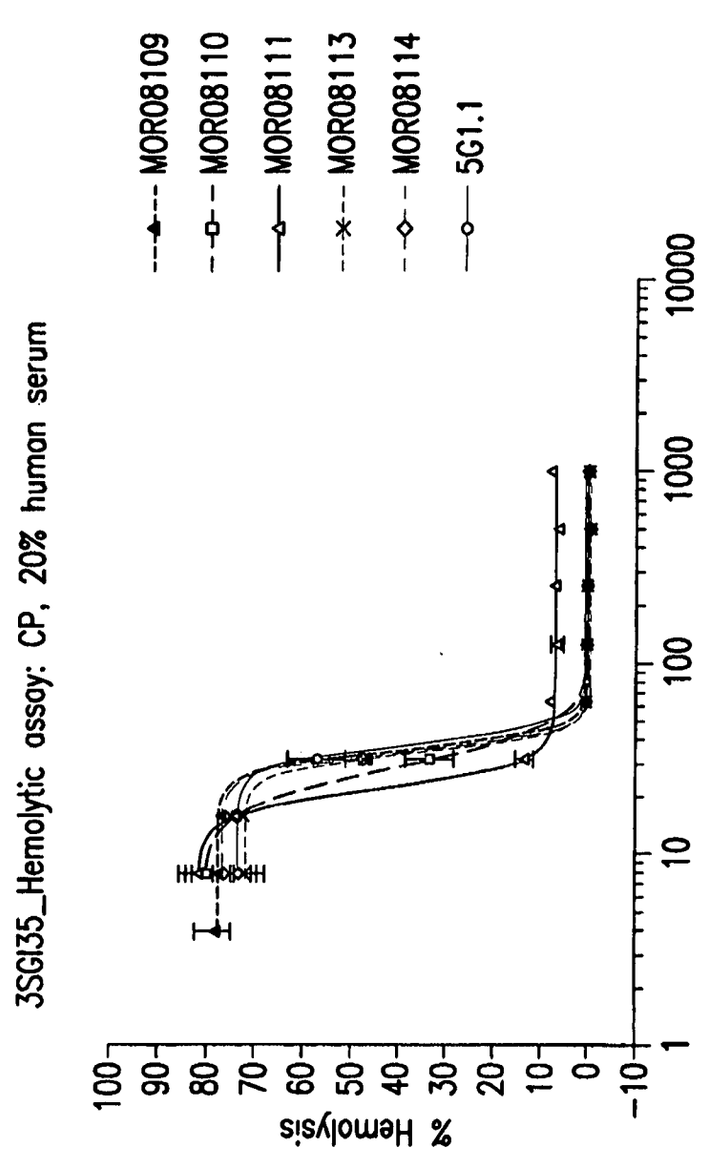

Hemolytic Assay: AP, 100pM Cy C5
7871
7829
7830
7908
N19/8
IC50
7871 0.137
7829 3.67
7830 1.78
7908 1.29
N19/8 1.22
Ser Hem
% Hemolysis
0
25
50
75
0.001
0.01
0.1
1
10
nM Fab or Ab

FIG.11f



	MOR08109	MOR08110	MOR08111	MOR08113	MOR08114	5G1.1
IC50	34.83	28.38	21.51	33.61	34.15	37.81

FIG.12

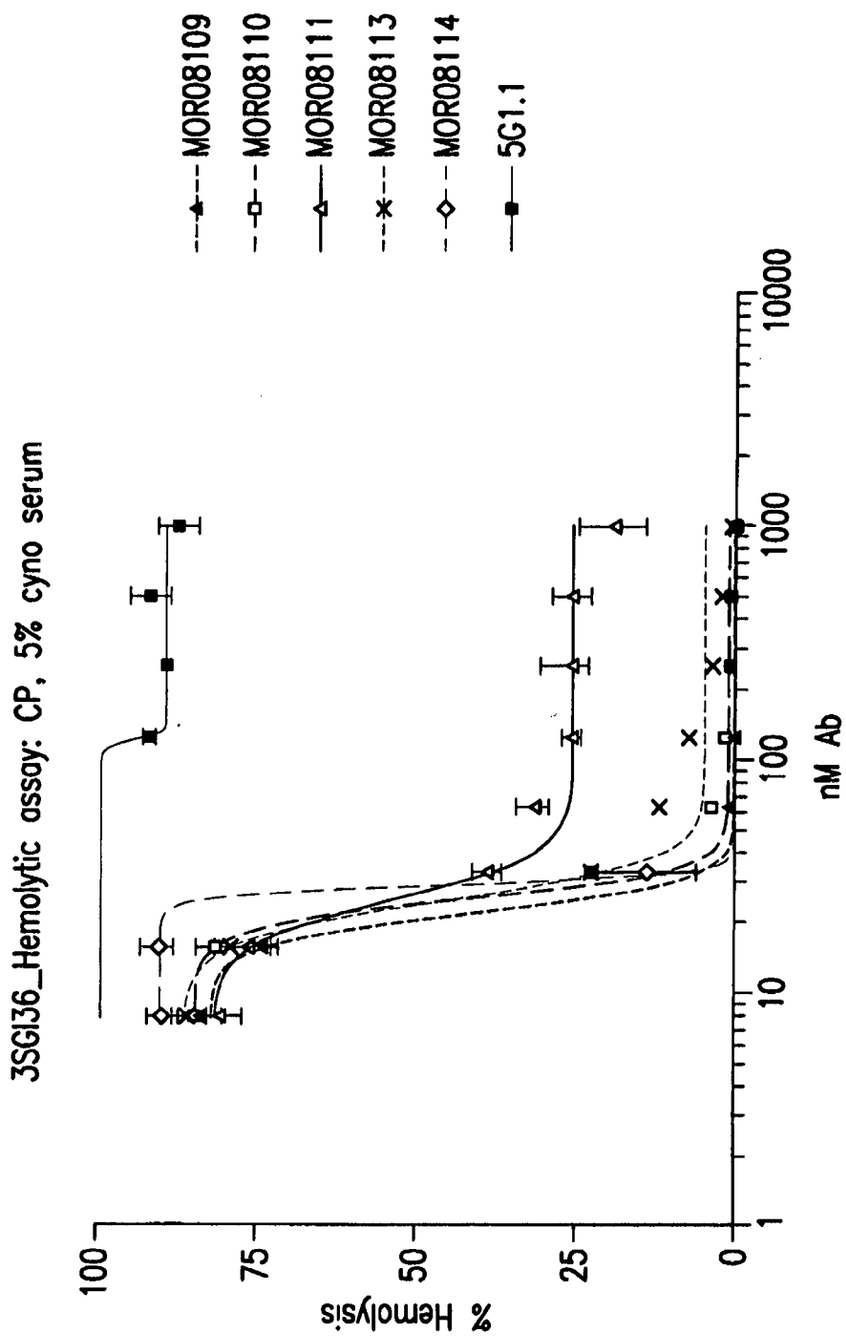

3SG136_Hemolytic assay: CP, 5% cyno serum
MOR08109
MOR08110
MOR08111
MOR08113
MOR08114
5G1.1
% Hemolysis
100
75
50
25
0
1
10
100
1000
10000
nM Ab

FIG.13

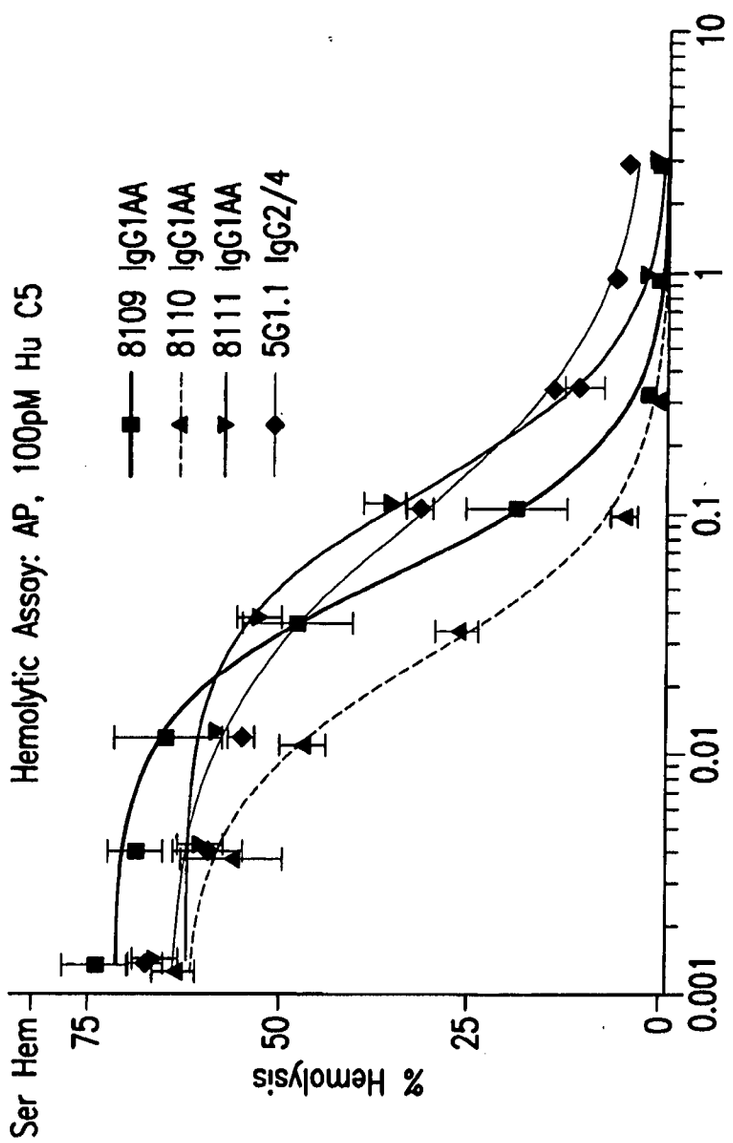

Hemolytic Assay: AP, 100pM Hu C5
8109 IgG1AA
8110 IgG1AA
8111 IgG1AA
5G1.1 IgG2/4
% Hemolysis
Ser Hem
75
50
25
0
0.001
0.01
0.1
1
10
nM Ab

FIG.14a

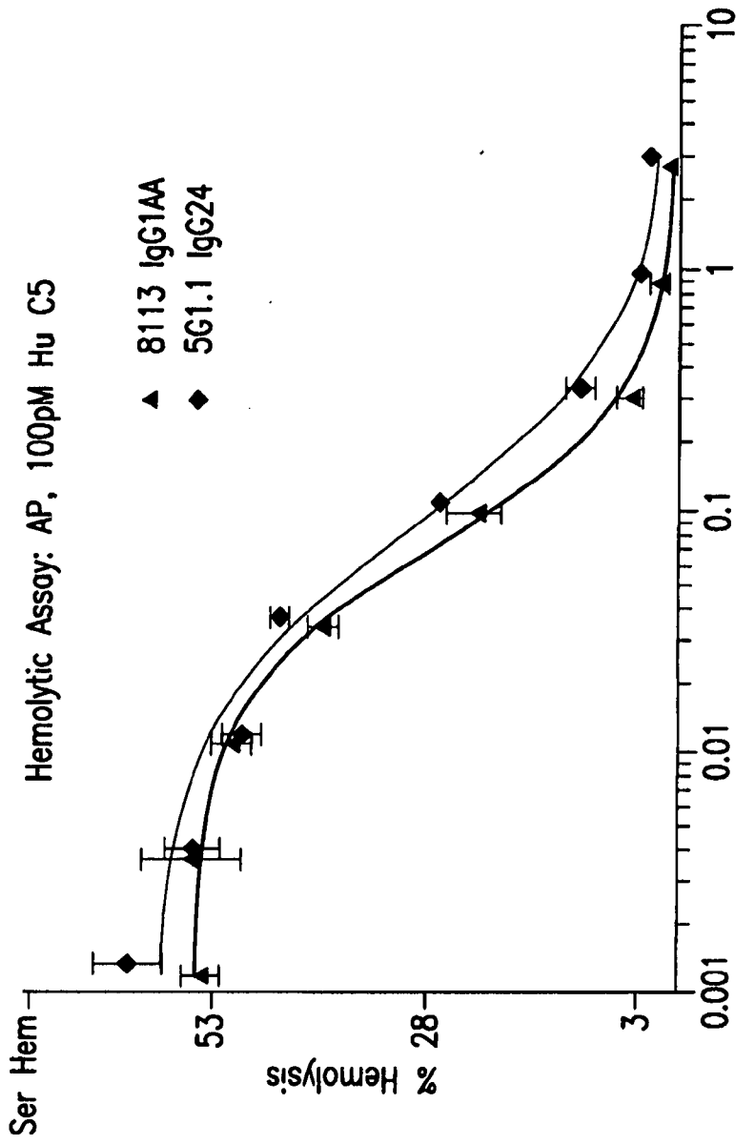

Hemolytic Assay: AP, 100pM Hu C5
8113 IgG1AA
5G1.1 IgG24
Ser Hem
53
28
3
% Hemolysis
0.001
0.01
0.1
1
10
nM Ab

FIG.14b

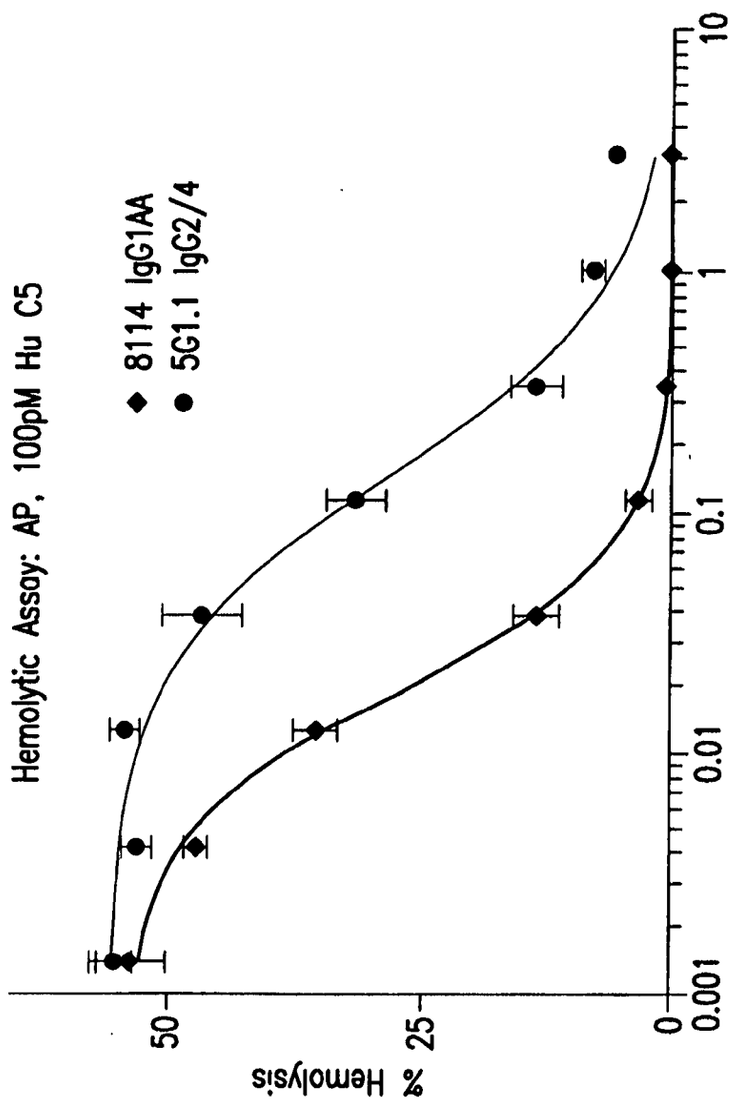

Hemolytic Assay: AP, 100pM Hu C5
8114 IgG1AA
5G1.1 IgG2/4
% Hemolysis
50
25
0
0.001
0.01
0.1
1
10
nM Ab

FIG.14c

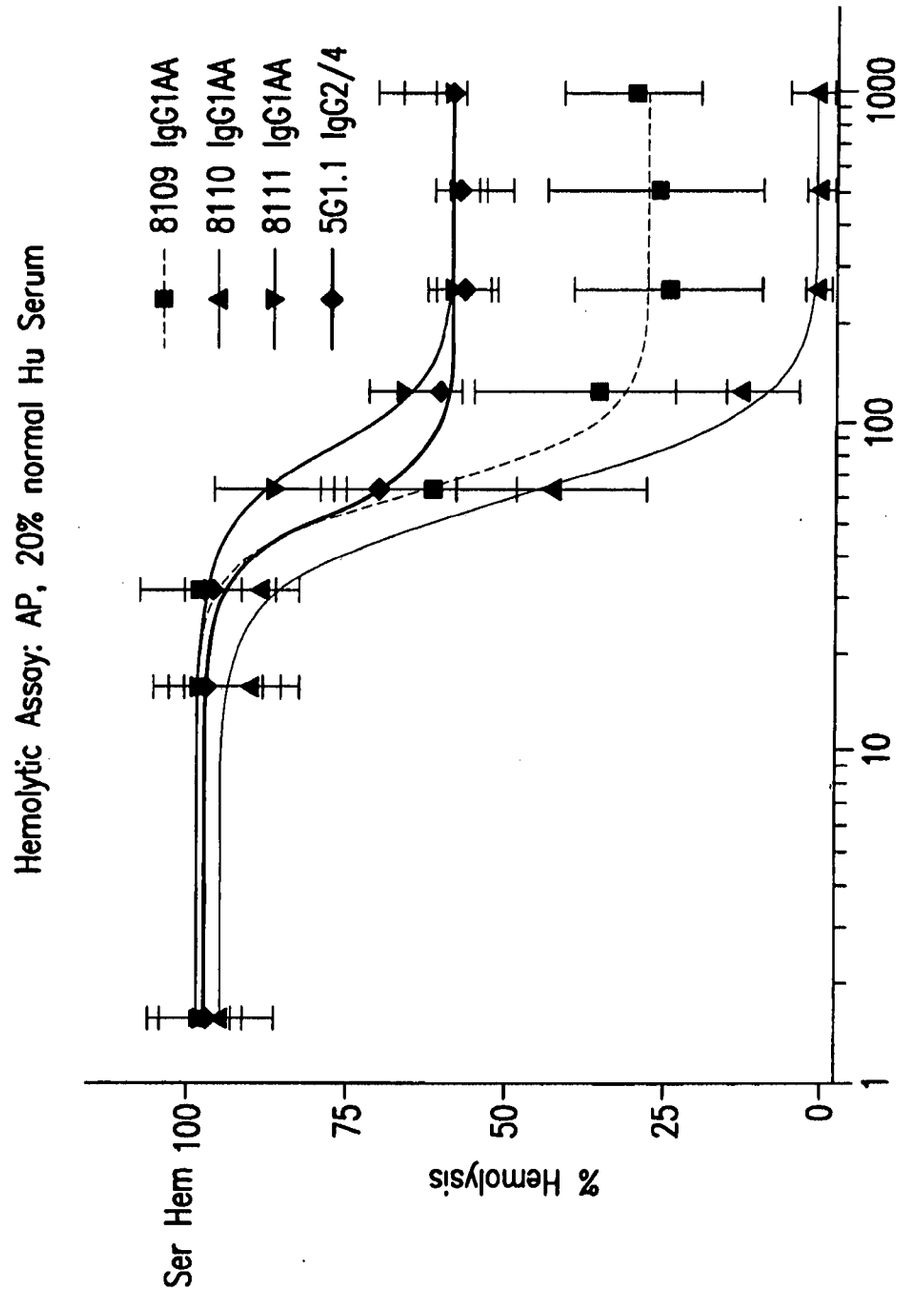

Hemolytic Assay: AP, 20% normal Hu Serum
8109 IgG1AA
8110 IgG1AA
8111 IgG1AA
5G1.1 IgG2/4
Ser Hem 100
75
50
25
0
% Hemolysis
1
10
100
1000
nM Ab

FIG.15a

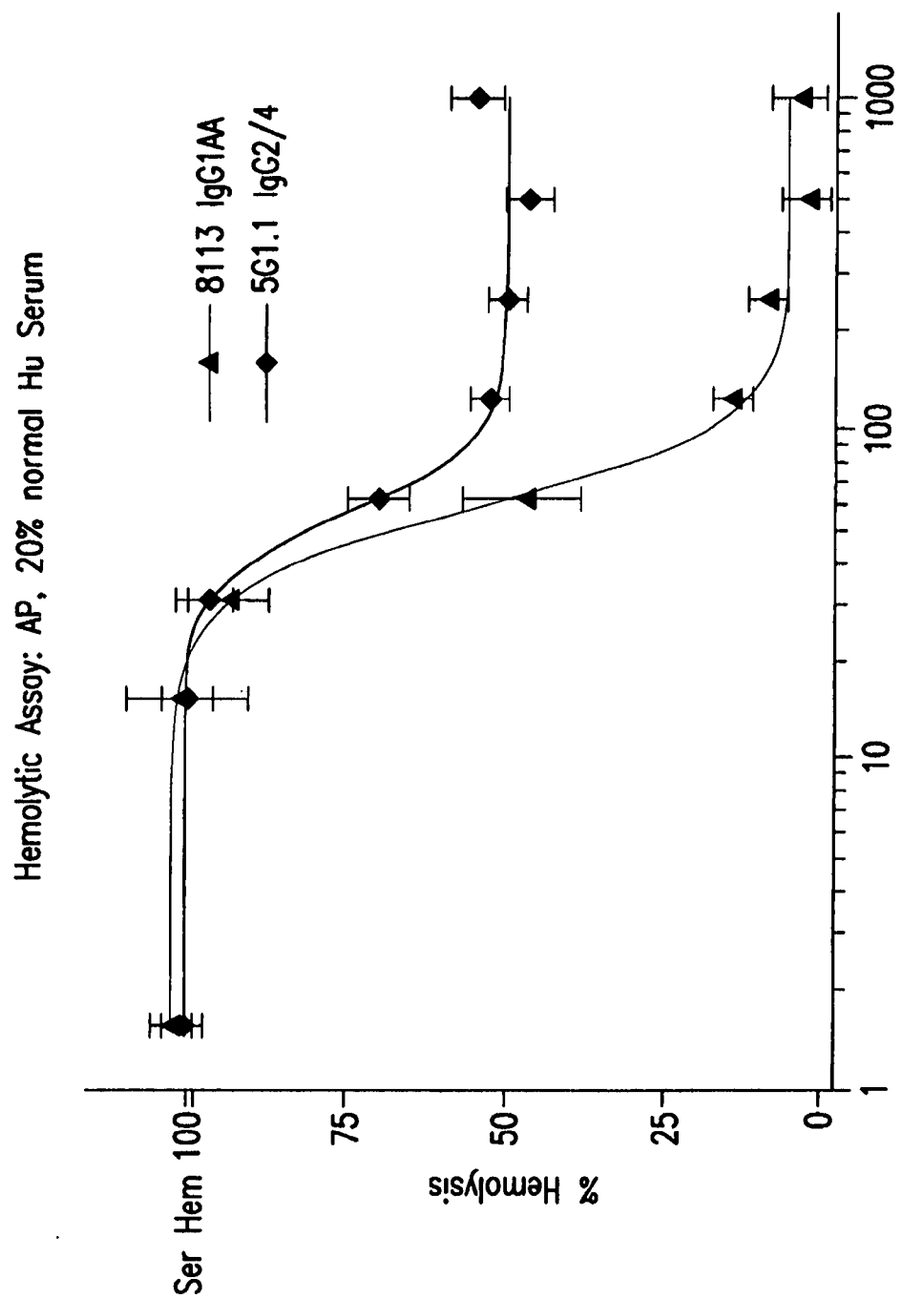

Hemolytic Assay: AP, 20% normal Hu Serum
8113 IgG1AA
5G1.1 IgG2/4
Ser Hem 100
% Hemolysis
0
25
50
75
1
10
100
1000
nM Ab

FIG.15b

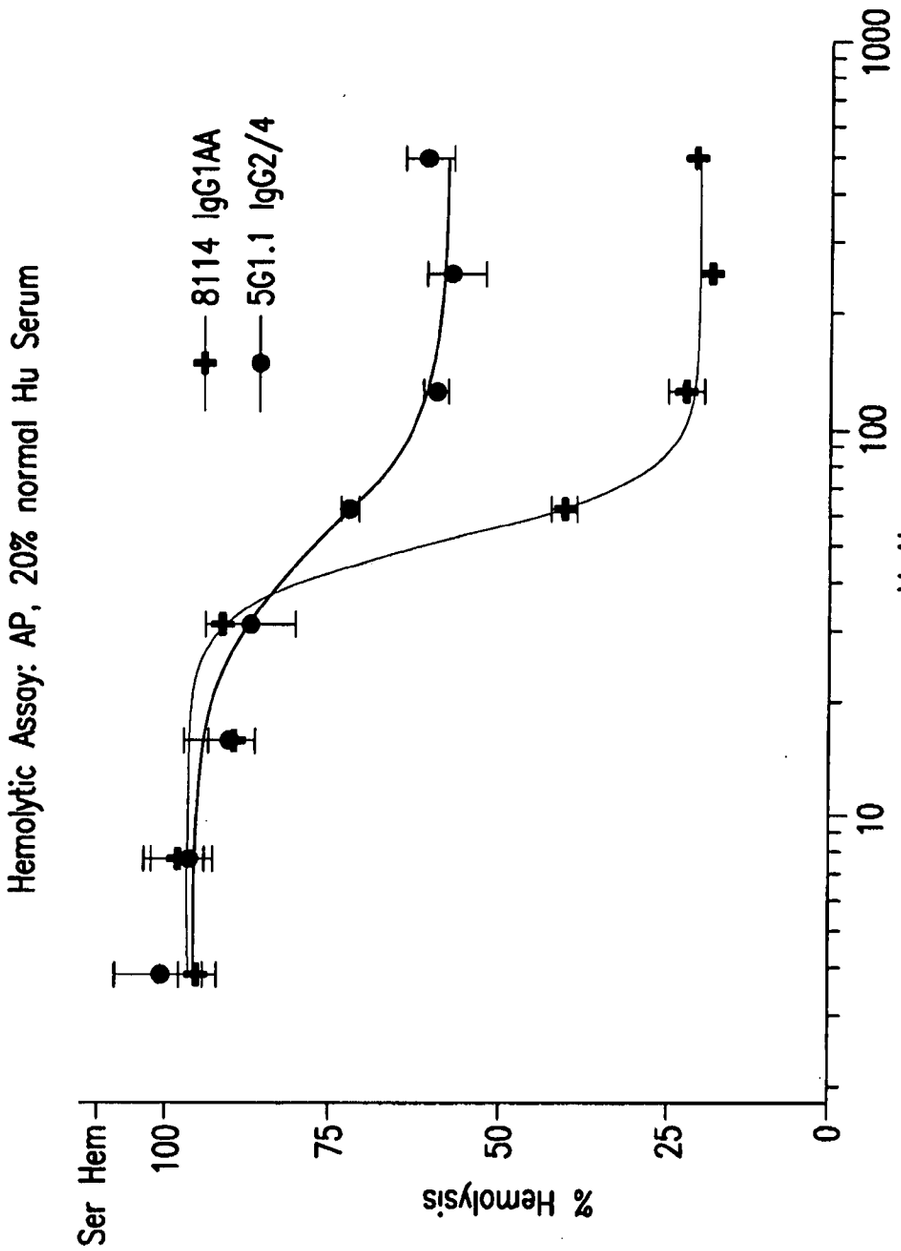

Hemolytic Assay: AP, 20% normal Hu Serum
8114 IgG1AA
5G1.1 IgG2/4
Ser Hem
100
75
50
25
0
% Hemolysis
10
100
1000
nM Ab

FIG.15c

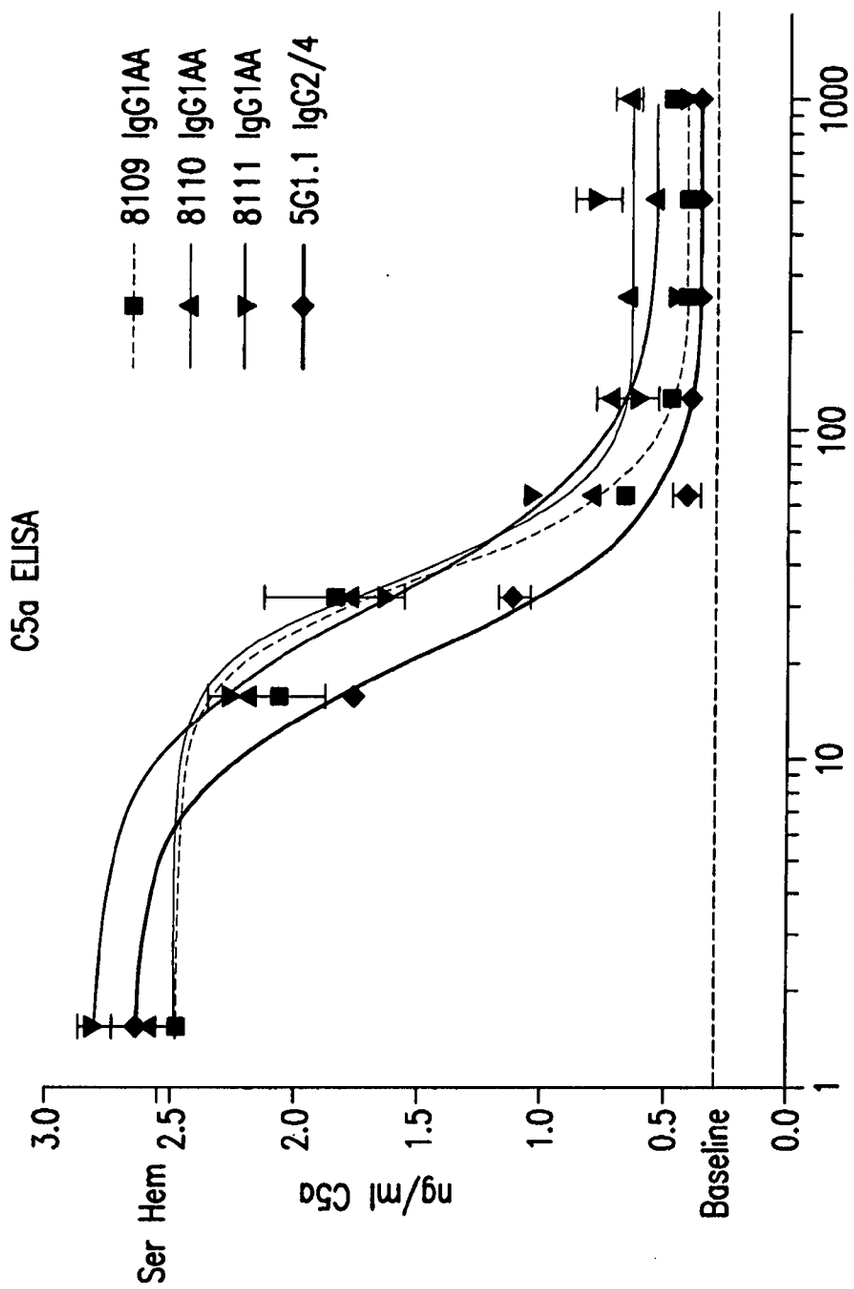

C5a ELISA
8109 IgG1AA
8110 IgG1AA
8111 IgG1AA
5G1.1 IgG2/4
ng/ml C5a
Ser Hem
Baseline
nM Ab
0.0
0.5
1.0
1.5
2.0
2.5
3.0
1
10
100
1000

FIG.15d

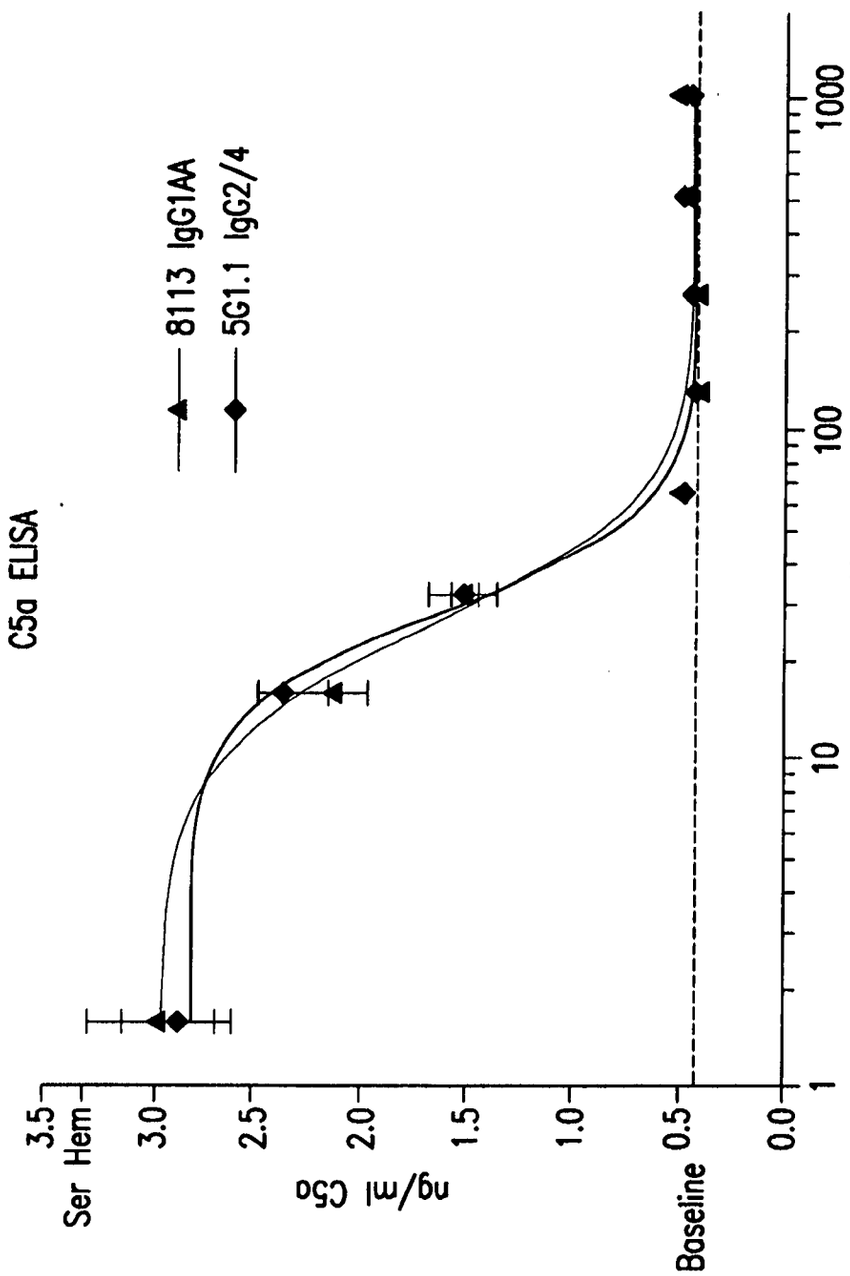

C5a ELISA
8113 IgG1AA
5G1.1 IgG2/4
ng/ml C5a
Ser Hem
Baseline
nM Ab
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1
10
100
1000

FIG.15e

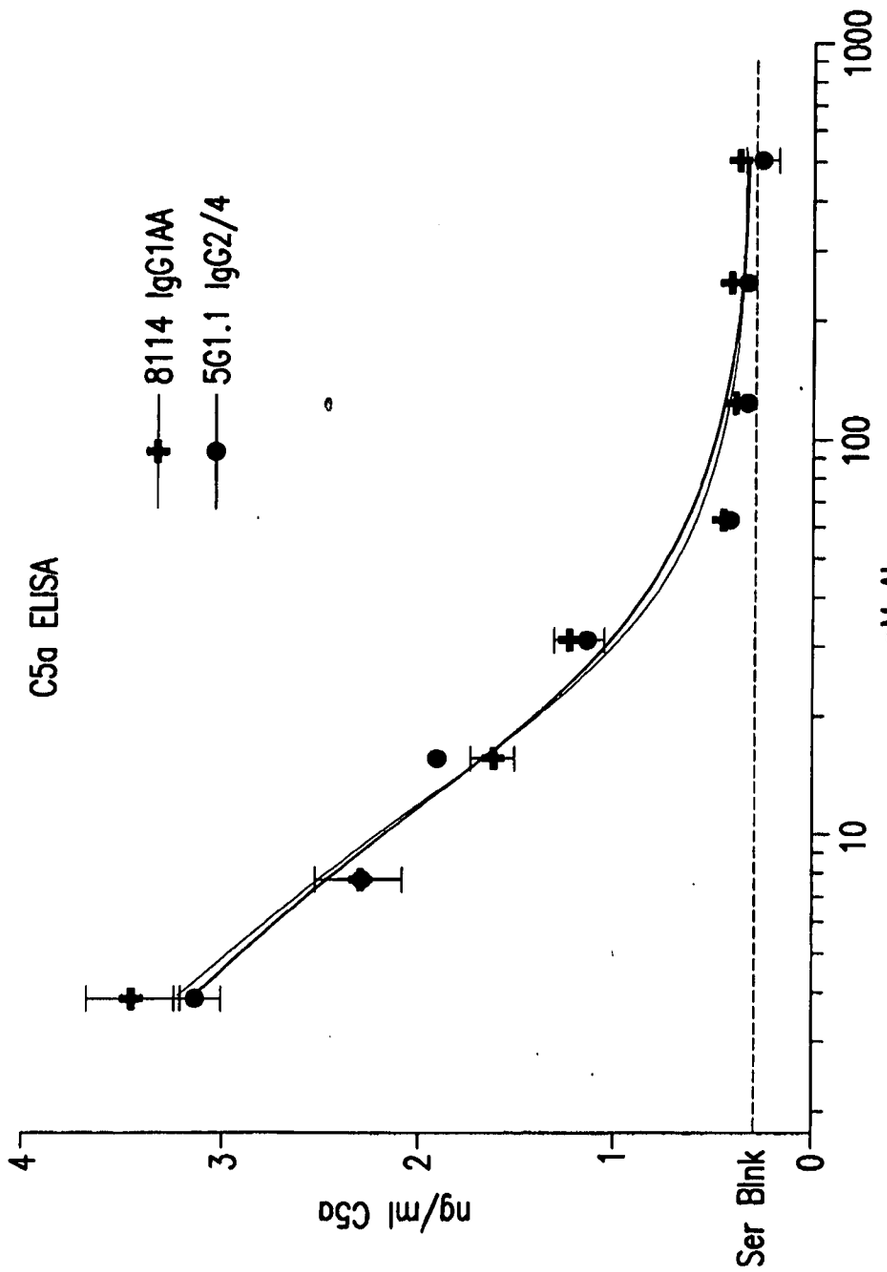

C5a ELISA
8114 IgG1AA
5G1.1 IgG2/4
ng/ml C5a
0
1
2
3
4
Ser Blnk
10
100
1000
nM Ab

FIG.15f

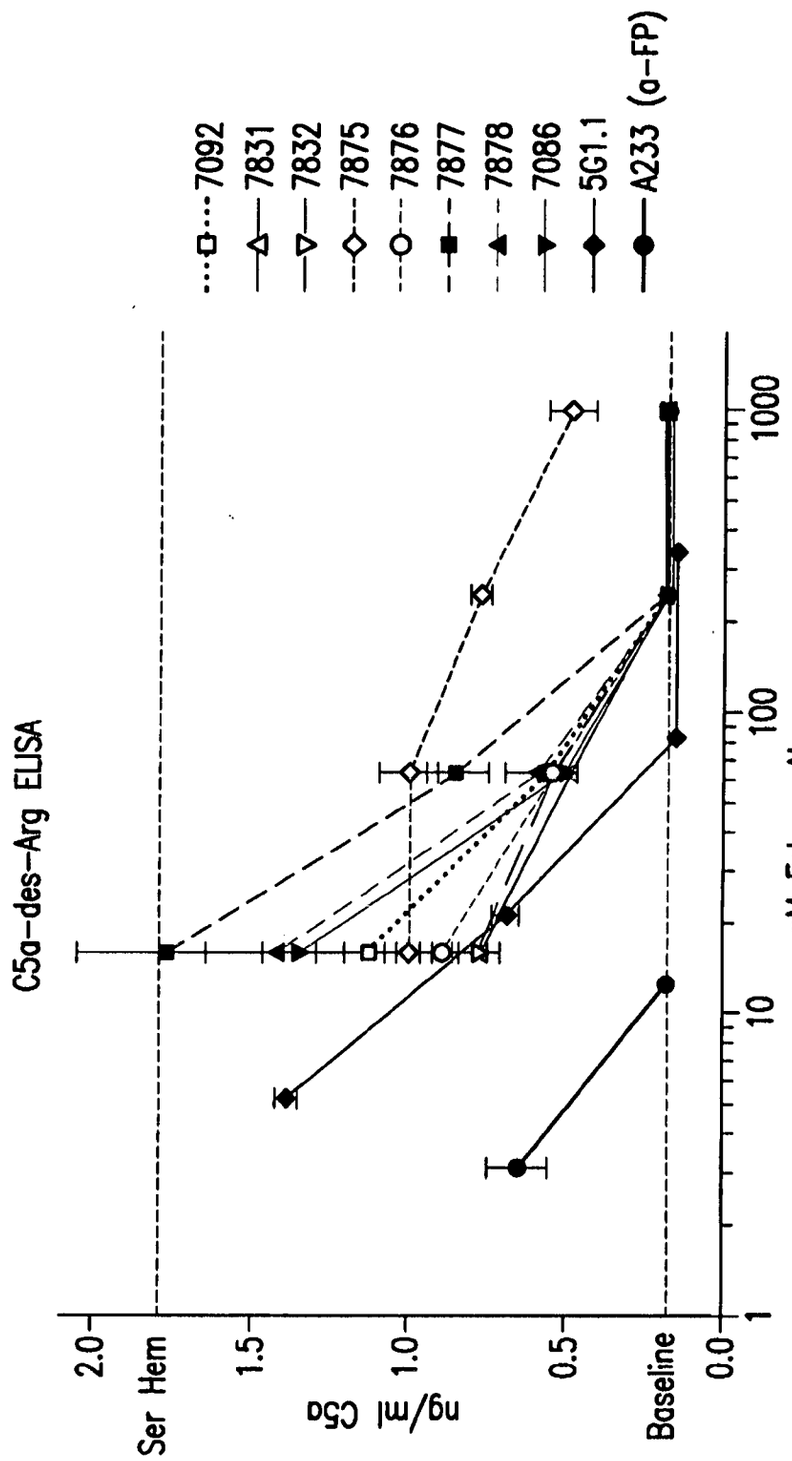

7092
7831
7832
7875
7876
7877
7878
7086
5G1.1
A233 (α-FP)
C5a-des-Arg ELISA
ng/ml C5a
2.0
1.5
1.0
0.5
0.0
Ser Hem
Baseline
1
10
100
1000
nM Fab or Ab

FIG.16a

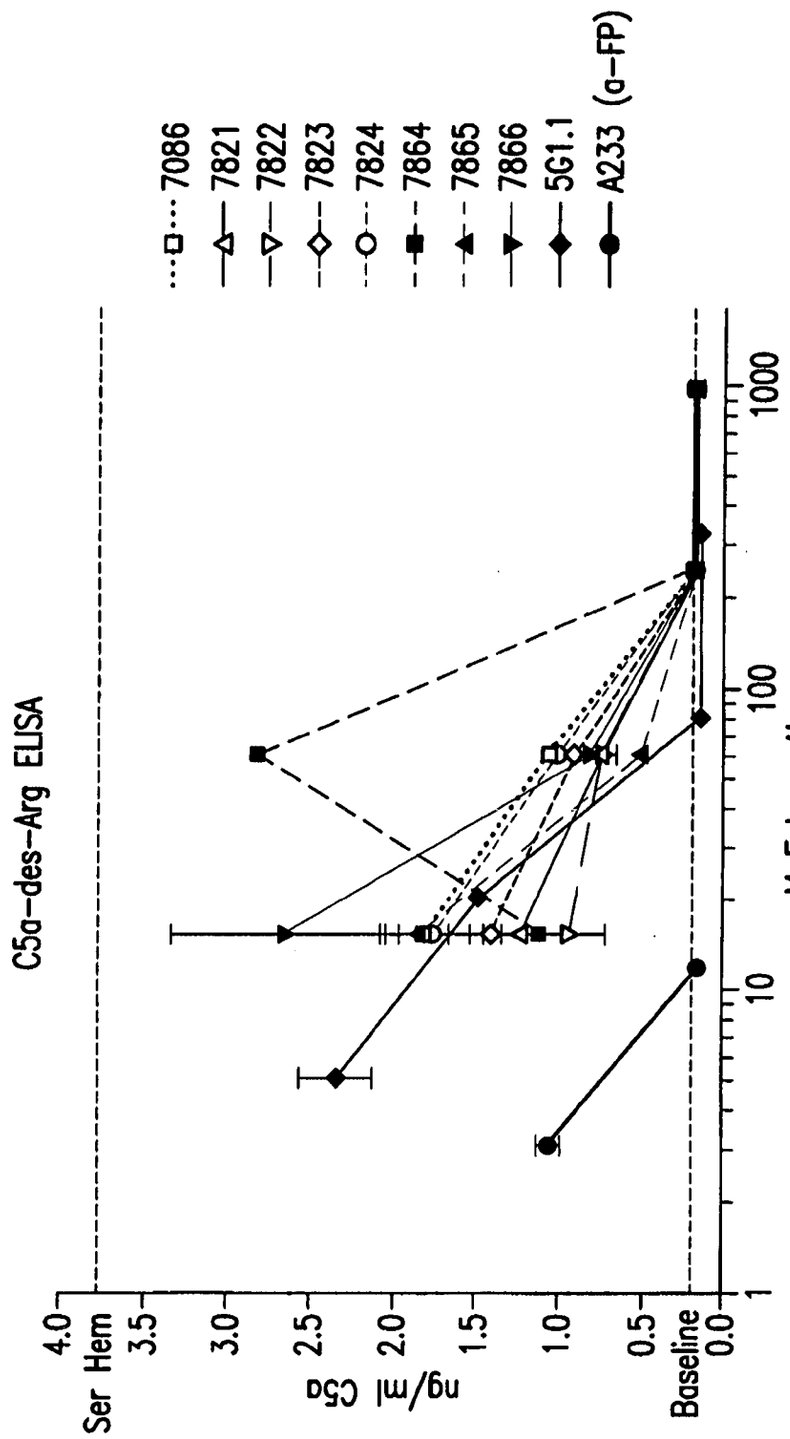

7086
7821
7822
7823
7824
7864
7865
7866
5G1.1
A233 (a-FP)
C5a-des-Arg ELISA
Ser Hem
Baseline
ng/ml C5a
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1
10
100
1000
nM Fab or Ab

FIG.16b

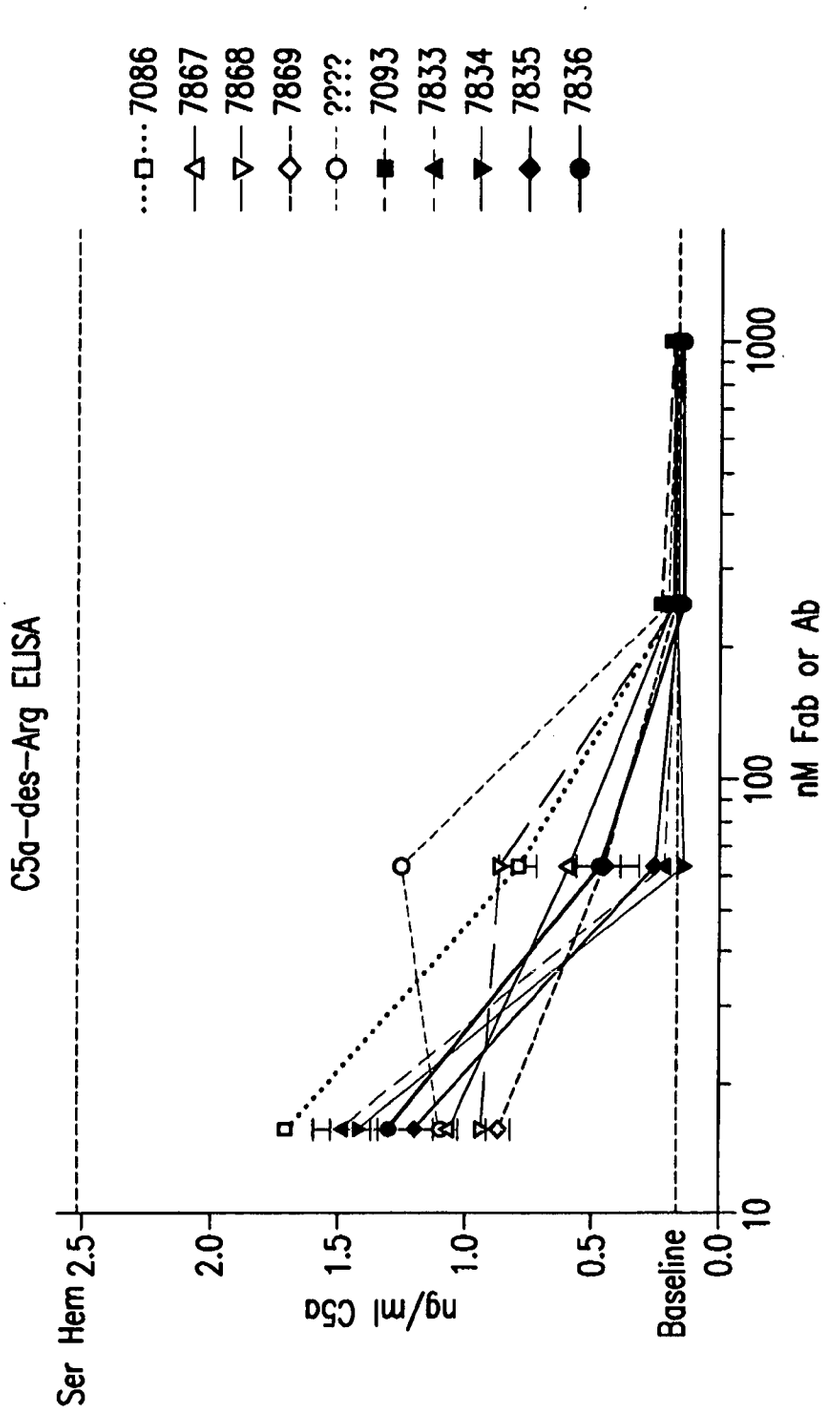

7086
7867
7868
7869
???
7093
7833
7834
7835
7836
C5a-des-Arg ELISA
Ser Hem
2.5
2.0
1.5
1.0
0.5
Baseline
0.0
ng/ml C5a
10
100
1000
nM Fab or Ab

FIG.16c

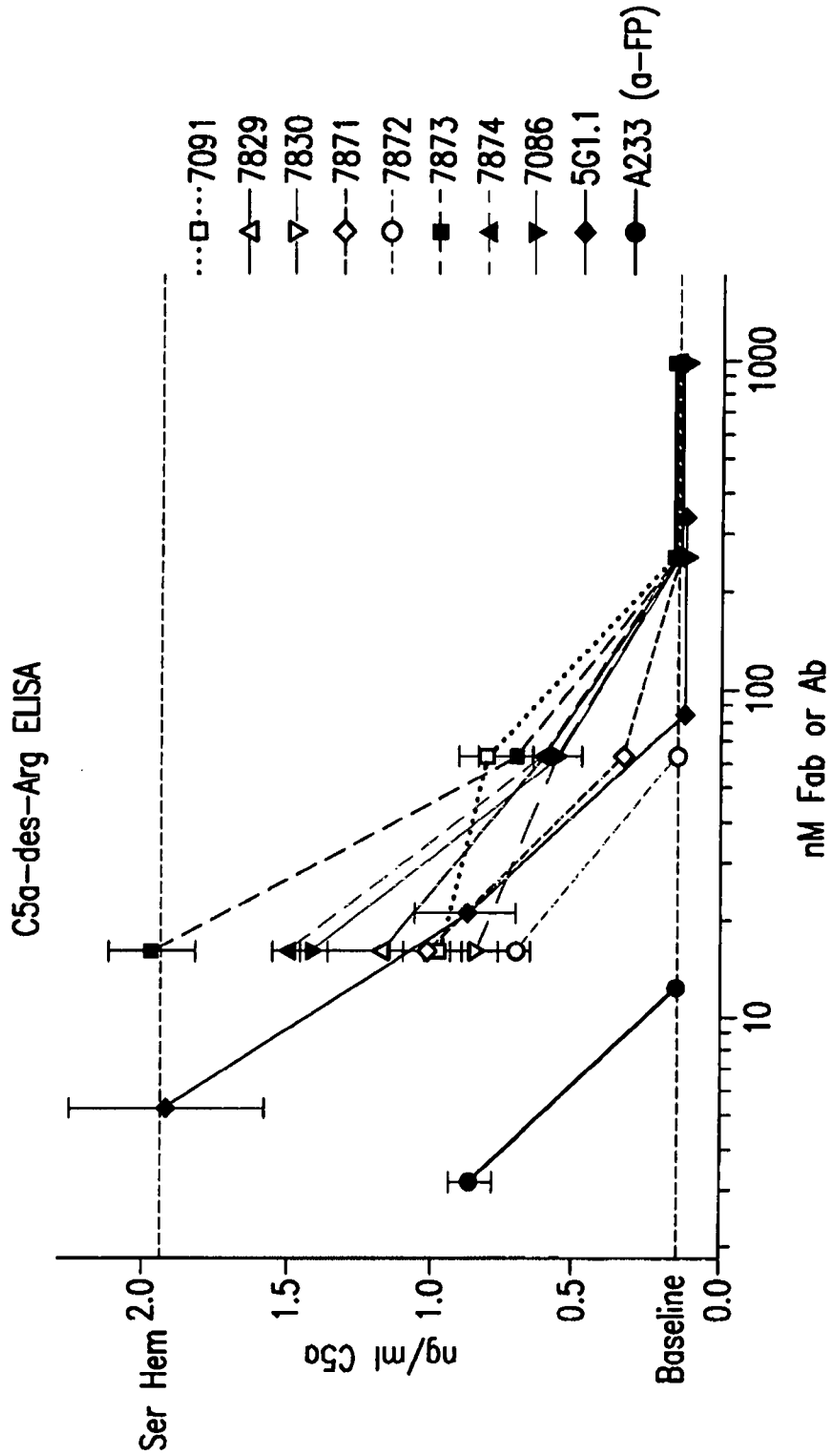

7091
7829
7830
7871
7872
7873
7874
7086
5G1.1
A233 (a-FP)
C5a-des-Arg ELISA
Ser Hem
ng/ml C5a
Baseline
2.0
1.5
1.0
0.5
0.0
10
100
1000
nM Fab or Ab

FIG.16d

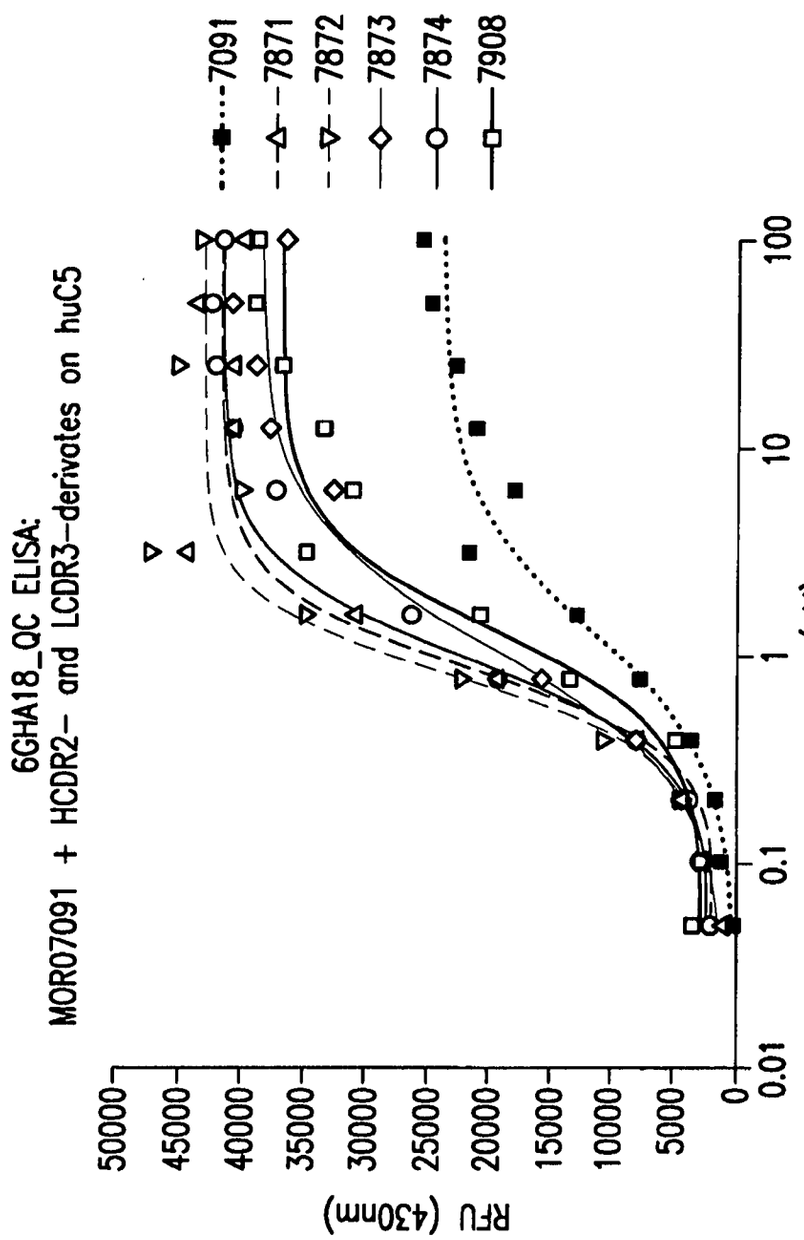

6GHA18_QC ELISA:
MOR07091 + HCDR2- and LCDR3-derivates on huC5
RFU (430nm)
conc. (nM)
7091
7871
7872
7873
7874
7908
EC50 | 7091 | 7871 | 7872 | 7873 | 7874 | 7908
1.316 | 0.8489 | 0.7889 | 1.051 | 0.9620 | 1.321

FIG.17-1

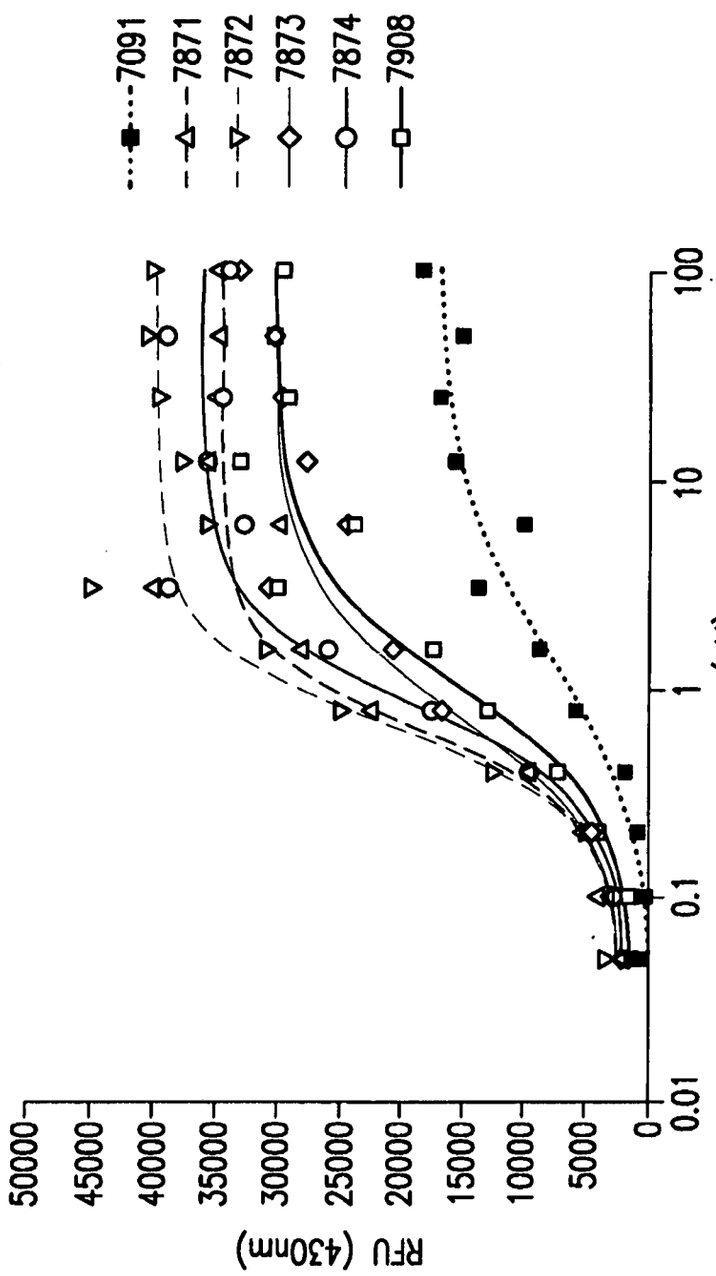

6GHA18_QC ELISA:
MOR07091 + HCDR2- and LCDR3-derivates on cynoC5
7091
7871
7872
7873
7874
7908
RFU (430nm)
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
0.01
0.1
1
10
100
conc. (nM)
EC50 | 7091 | 7871 | 7872 | 7873 | 7874 | 7908
1.316 | 0.8489 | 0.7889 | 1.051 | 0.9620 | 1.321

FIG.17-2

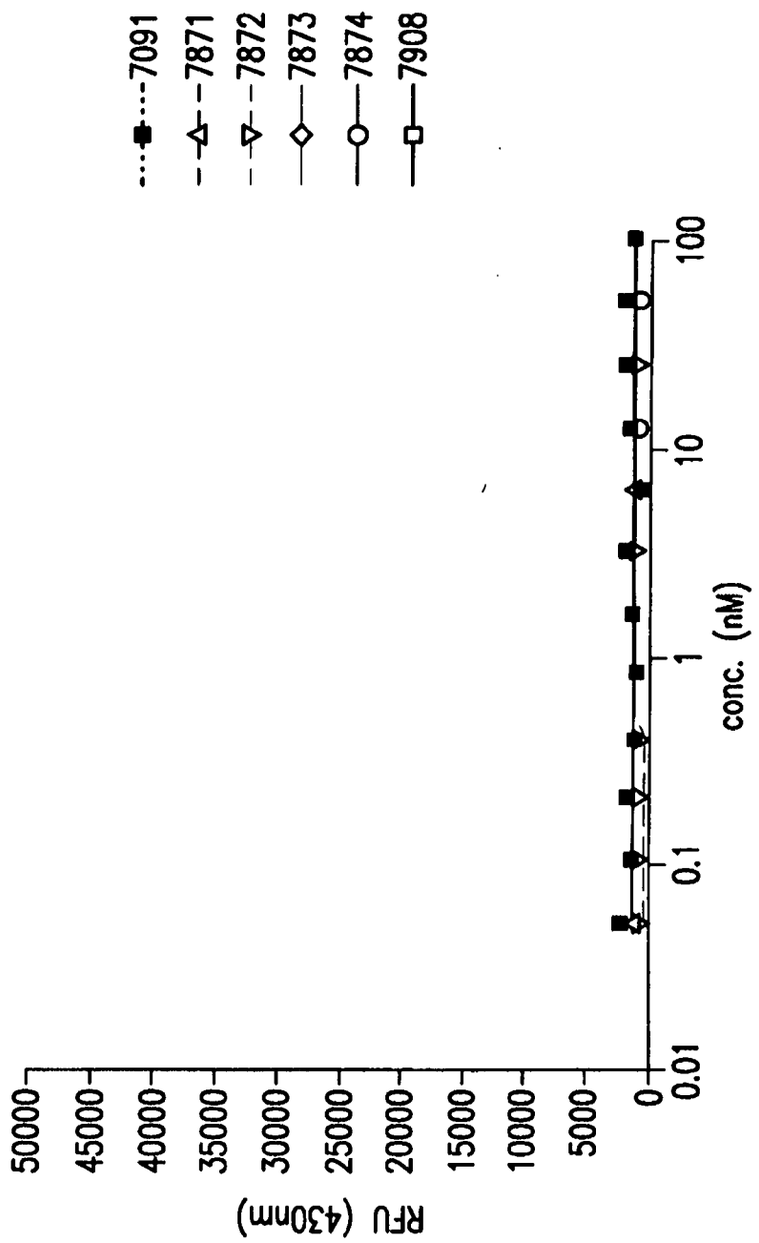

6GHA18_QC ELISA:
MOR07091 + HCDR2- and LCDR3-derivates on huC3
7091
7871
7872
7873
7874
7908
RFU (430nm)
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
0.01
0.1
1
10
100
conc. (nM)

FIG.17-3

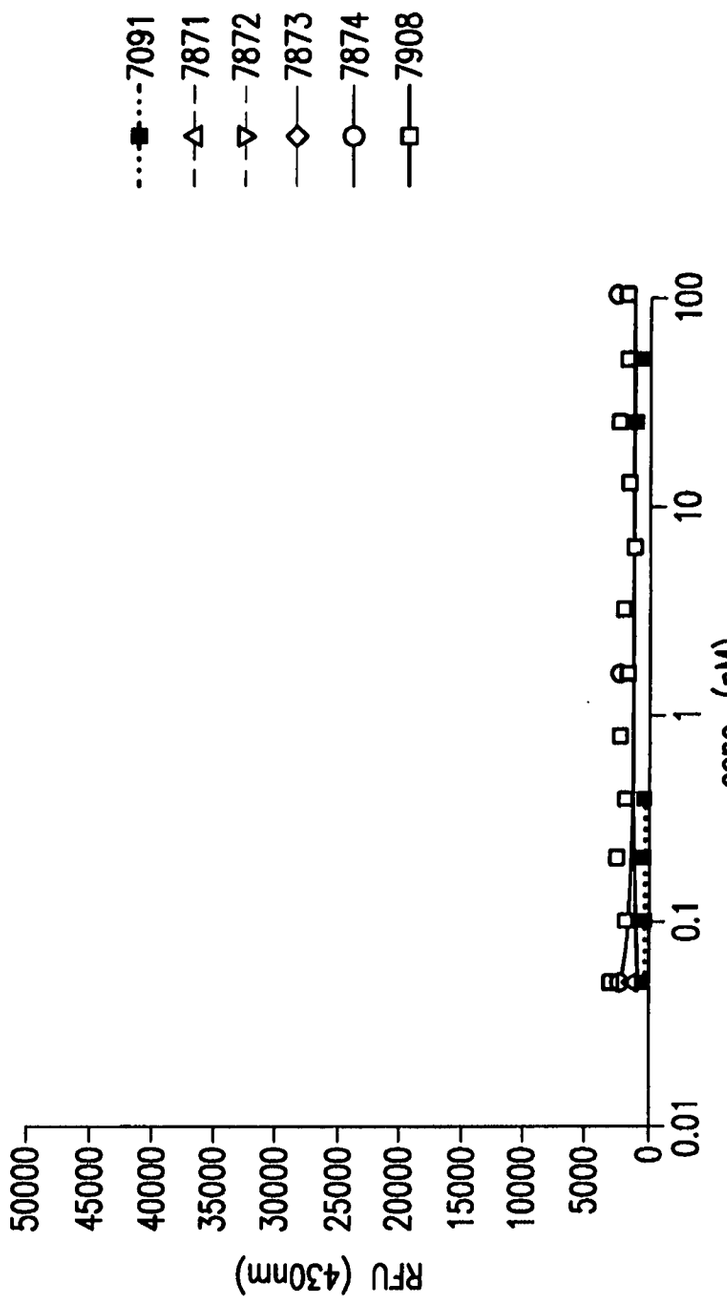

6GHA18_QC ELISA:
MOR07091 + HCDR2- and LCDR3-derivates on huC4
7091
7871
7872
7873
7874
7908
RFU (430nm)
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
0.01
0.1
1
10
100
conc. (nM)

FIG.17-4

MORO	retained binding activity	0h	4h	8h
MOR07086	88.02%			
MOR07832	69.06%			
MOR07834	66.95%			
MOR07872	82.72%			
MOR07876	78.55%			
MOR07086	92.94%			
MOR07832	74.84%			
MOR07834	92.00%			
MOR07872	90.70%			
MOR07876	75.60%			
MOR07086	89.57%			
MOR07832	91.56%			
MOR07834	86.05%			
MOR07872	72.10%			
MOR07876	70.34%			

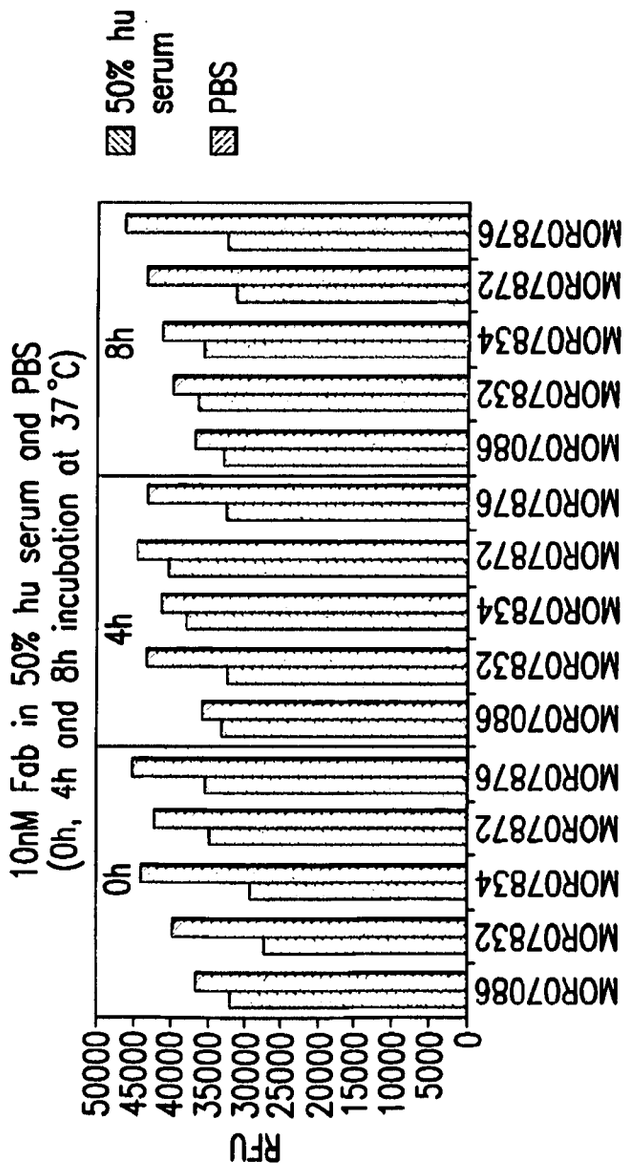


FIG.18

Rows: unlabelled Fab (100-fold excess)	Columns: biotinylated Fab							
MOR0	7086	7832	7834	7871	7872	7873	7876	7878
7086	691	2597	853	1191	825	694	1002	495
7832	668	1186	404	586	3601	499	595	251
7834	618	1727	391	625	609	455	756	560
7871	426	1384	422	758	619	1009	392	451
7872	1553	3199	773	1486	944	882	842	781
7873	800	3342	965	1414	1491	922	1188	691
7876	892	2535	652	978	1366	1394	621	701
7878	850	2643	784	1228	2218	891	1180	643
100%	36816	37112	37340	43250	41651	33768	38078	37405
competition with identical Fab			biotinylated Fab without competition = 100% signal					

FIG.19

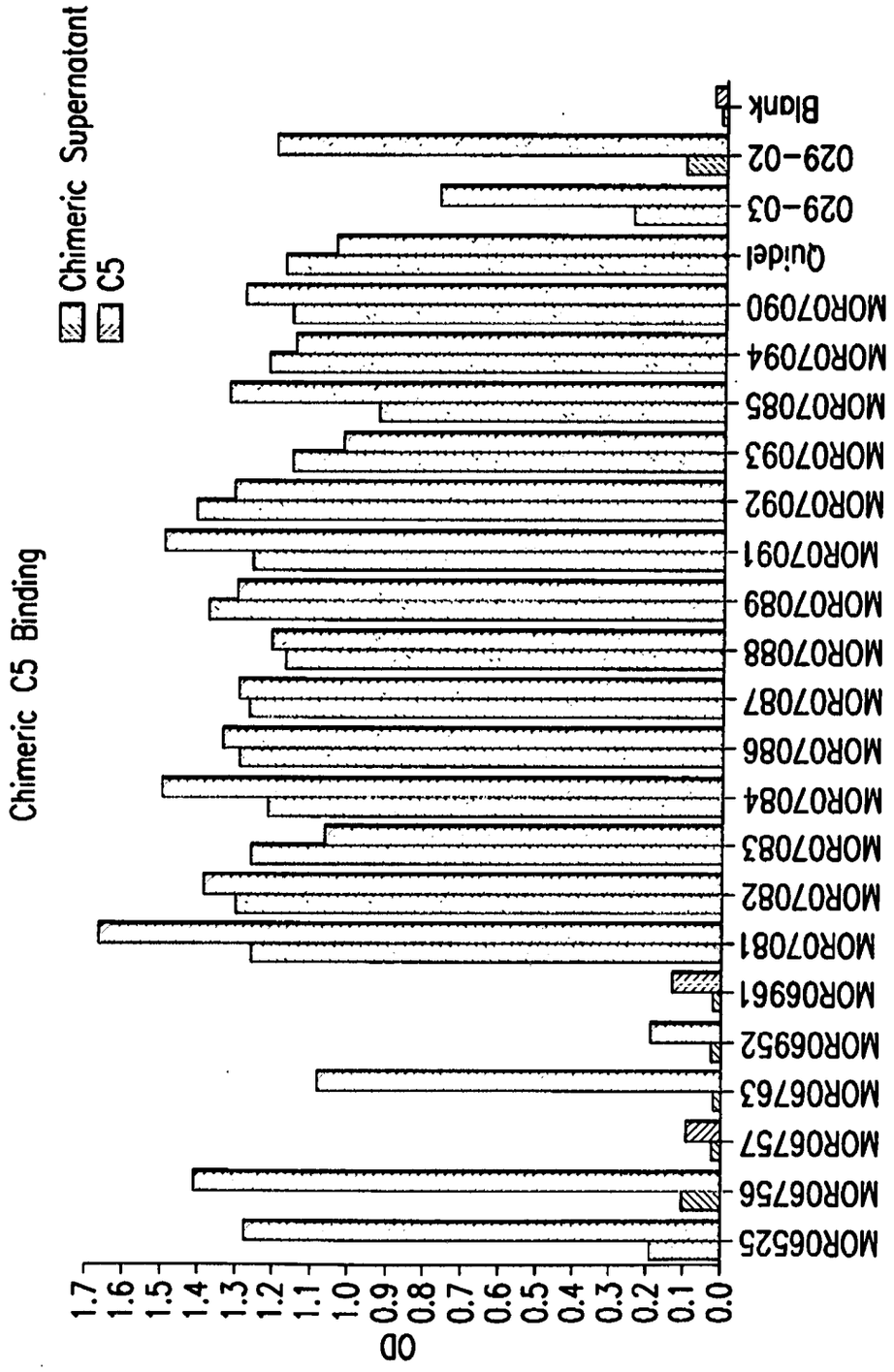

Chimeric C5 Binding
Chimeric Supernatant
C5
OD
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Fab/Mab
Blank
029-02
029-03
Quidel
MOR07090
MOR07094
MOR07085
MOR07093
MOR07092
MOR07091
MOR07089
MOR07088
MOR07087
MOR07086
MOR07084
MOR07083
MOR07082
MOR07081
MOR06961
MOR06952
MOR06763
MOR06757
MOR06756
MOR06525

FIG.20

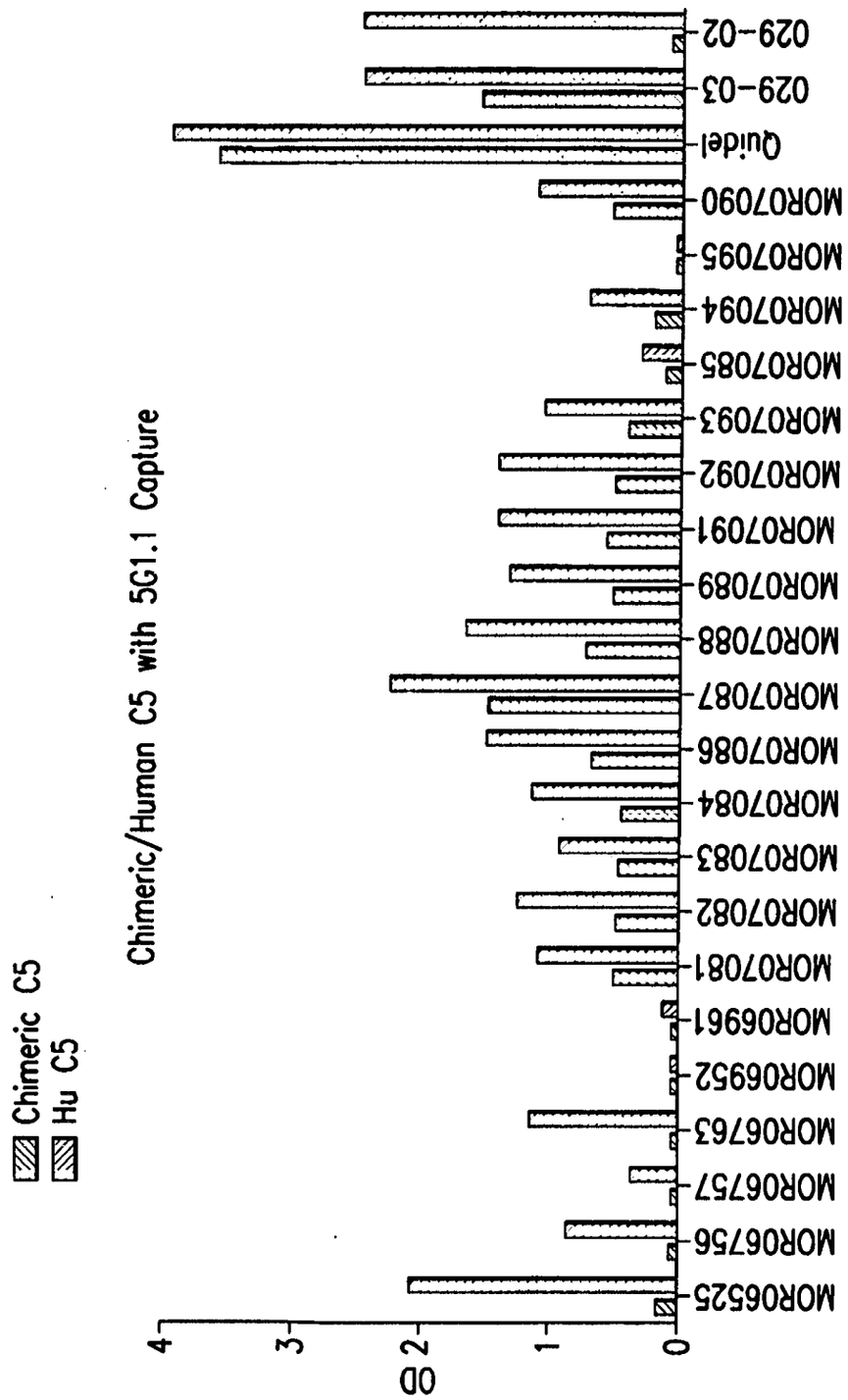

Chimeric C5
Hu C5
Chimeric/Human C5 with 5G1.1 Capture
OD
0
1
2
3
4
MOR06525
MOR06756
MOR06757
MOR06763
MOR06952
MOR06961
MOR07081
MOR07082
MOR07083
MOR07084
MOR07086
MOR07087
MOR07088
MOR07089
MOR07091
MOR07092
MOR07093
MOR07085
MOR07094
MOR07095
MOR07090
Quidel
029-03
029-02

FIG.21

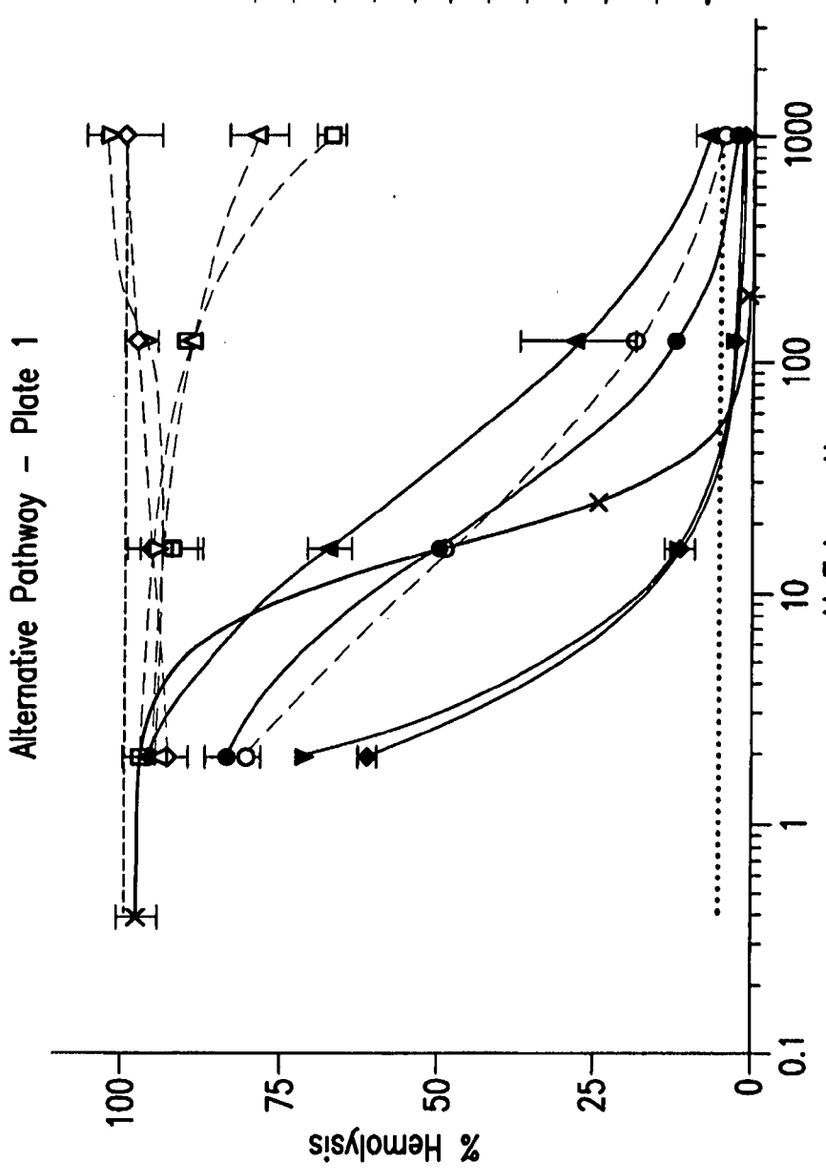

Alternative Pathway - Plate 1
% Hemolysis
100
75
50
25
0
0.1
1
10
100
1000
nM Fab or Ab
6525
6756
6757
6763
6952
6961
7081
7082
7083
Quidel a-FP
+ 6% HaMb C5 sup
C5-depleted serum

FIG.22-1

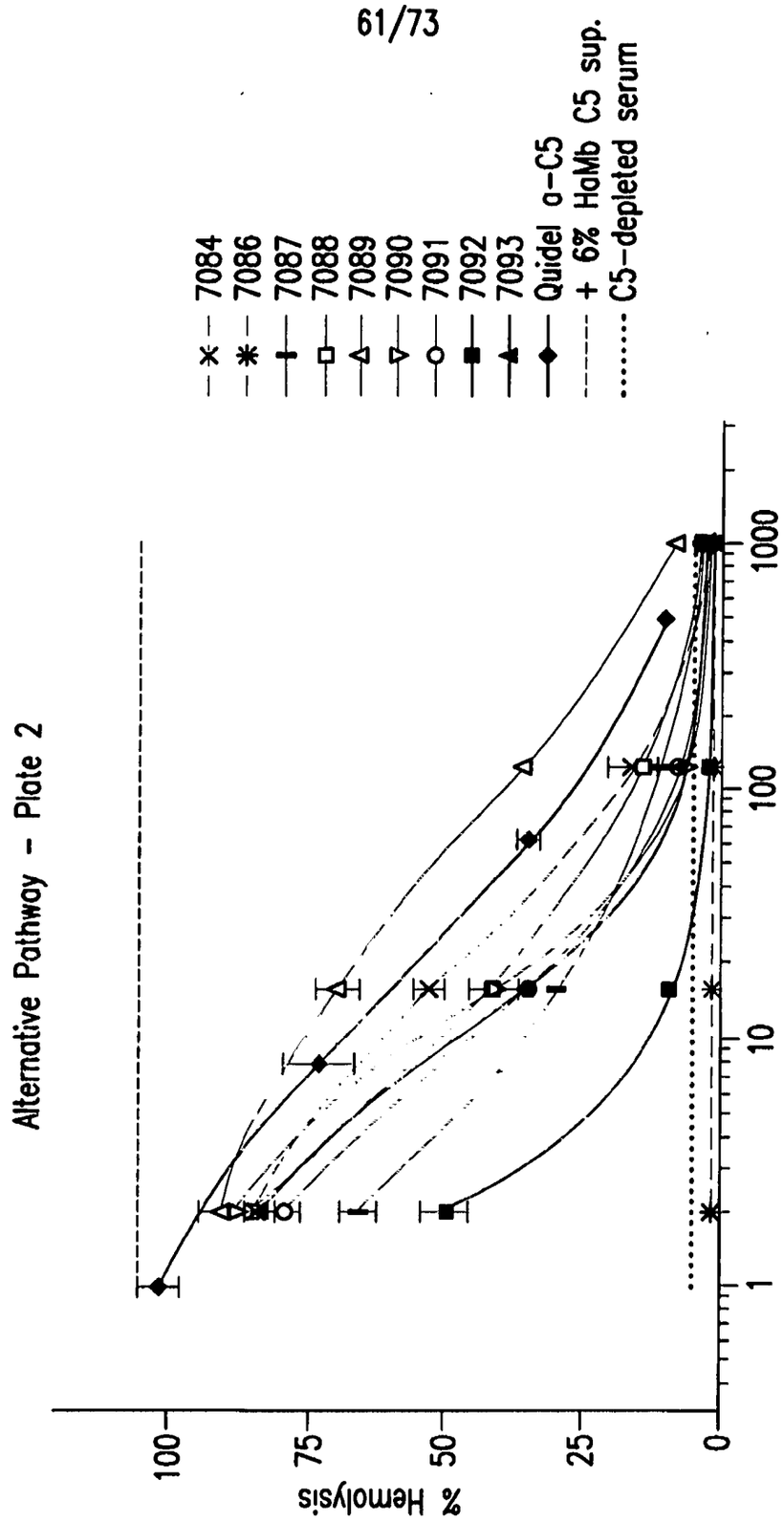

Alternative Pathway - Plate 2
% Hemolysis
0
25
50
75
100
1
10
100
1000
nM Fab or Ab
7084
7086
7087
7088
7089
7090
7091
7092
7093
Quidel a-C5
+ 6% HaMb C5 sup.
C5-depleted serum

FIG.22-2

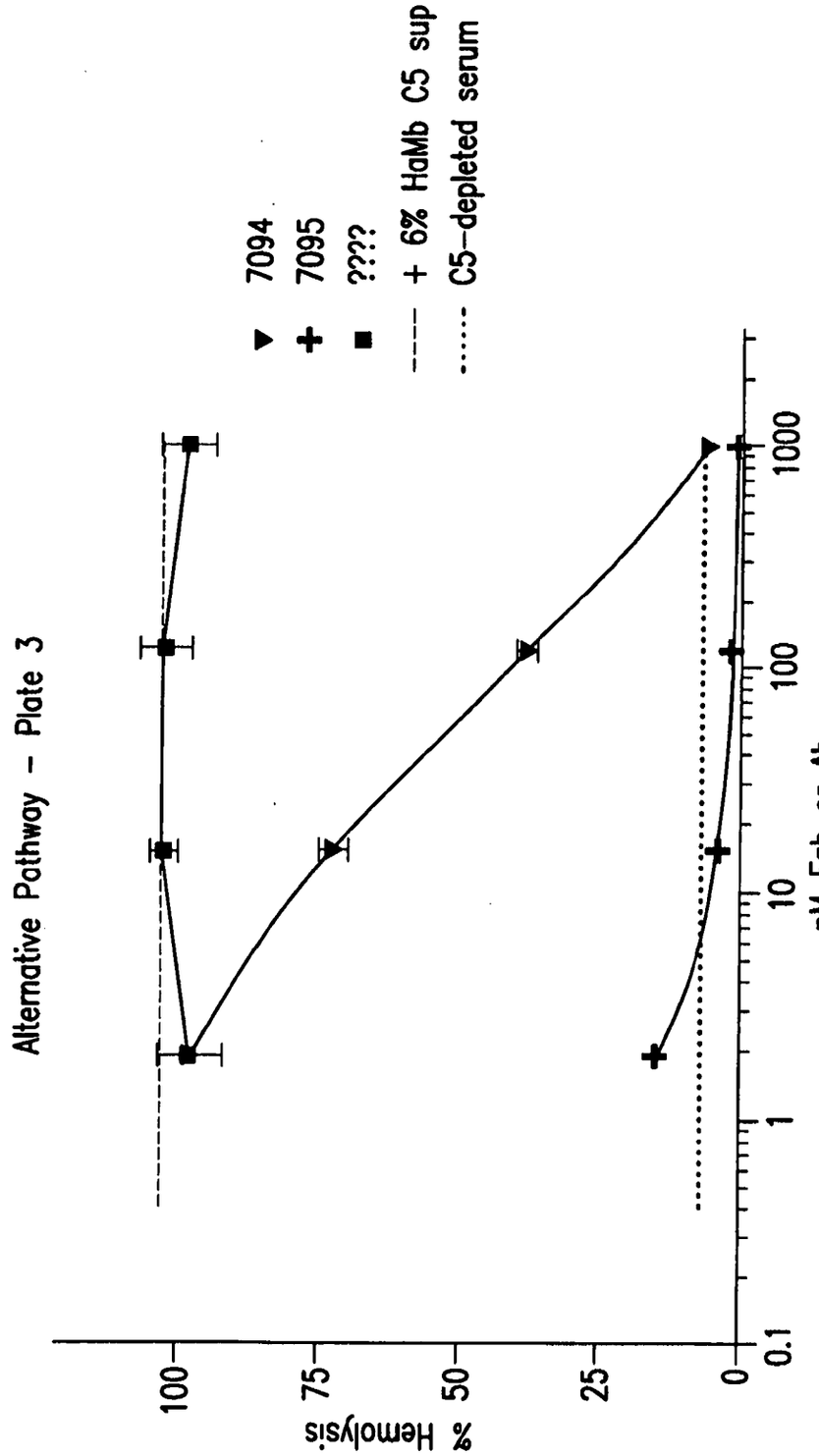

Alternative Pathway – Plate 3
% Hemolysis
100
75
50
25
0
0.1
1
10
100
1000
nM Fab or Ab
7094
7095
????
+ 6% HaMb C5 sup
C5-depleted serum

FIG.22-3

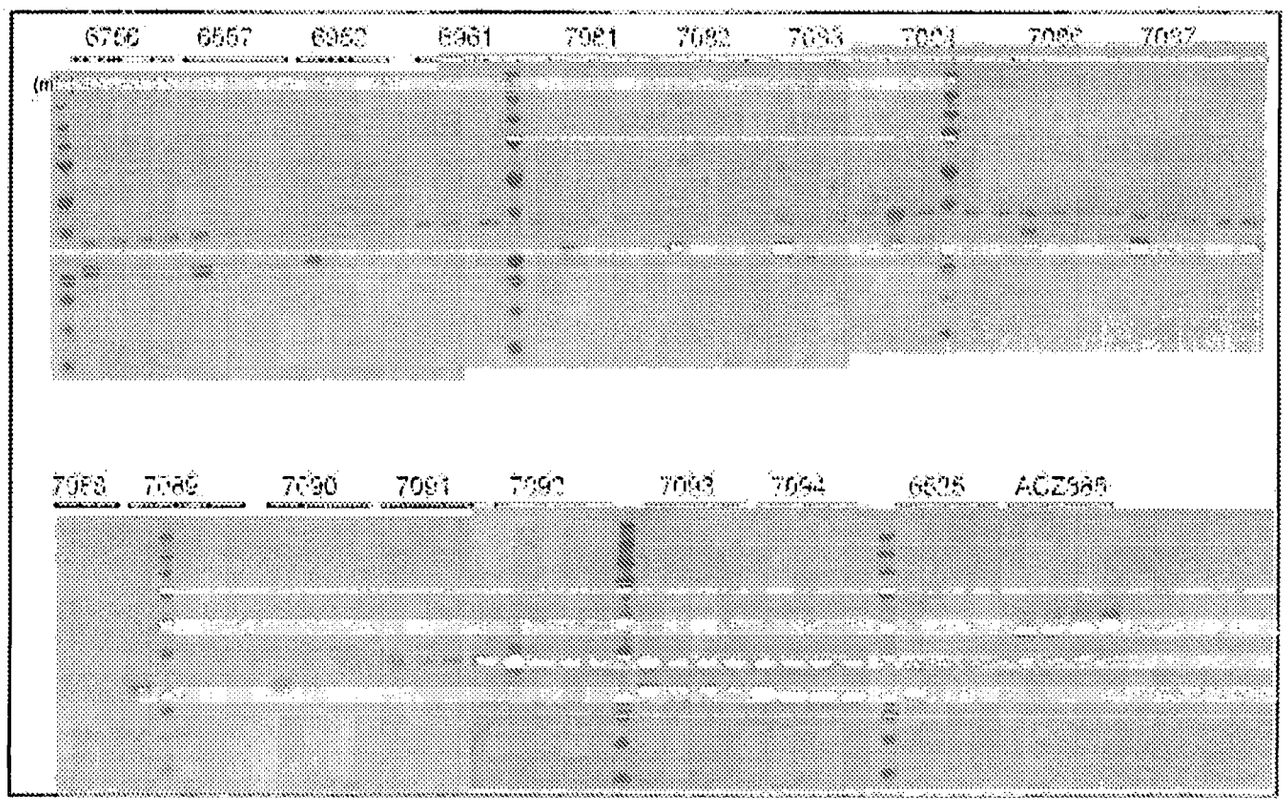

6556
6557
6962
6961
7081
7082
7083
7091
7092
7097
7088
7089
7090
7091
7092
7093
7094
6525
ACZ385

Fig. 23

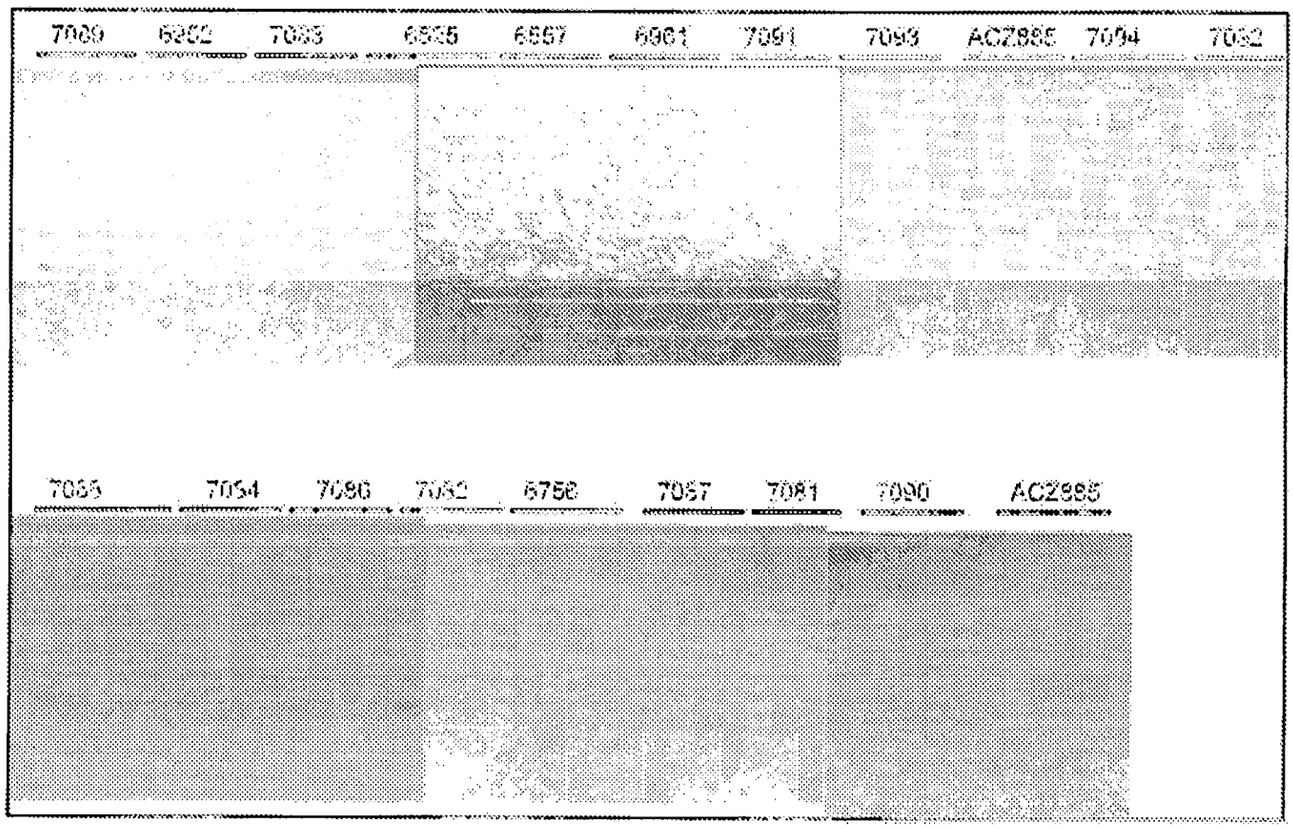

7069
6252
7083
6855
6557
6961
7091
7093
ACZ885
7094
7052
7055
7054
7086
7082
6758
7057
7081
7090
ACZ885

Fig. 24

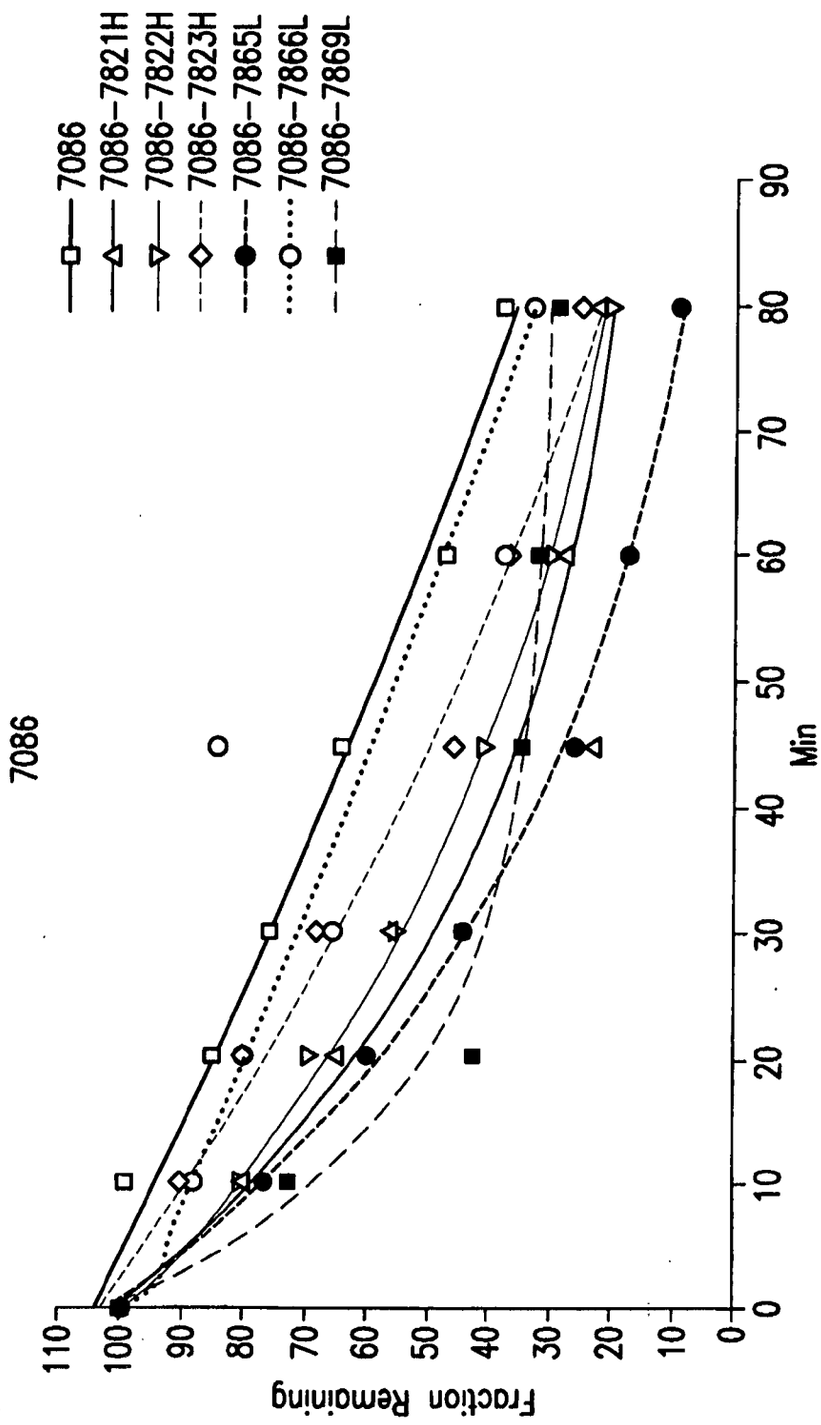

7086
7086-7821H
7086-7822H
7086-7823H
7086-7865L
7086-7866L
7086-7869L
7086
Fraction Remaining
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
Min

FIG.25-1

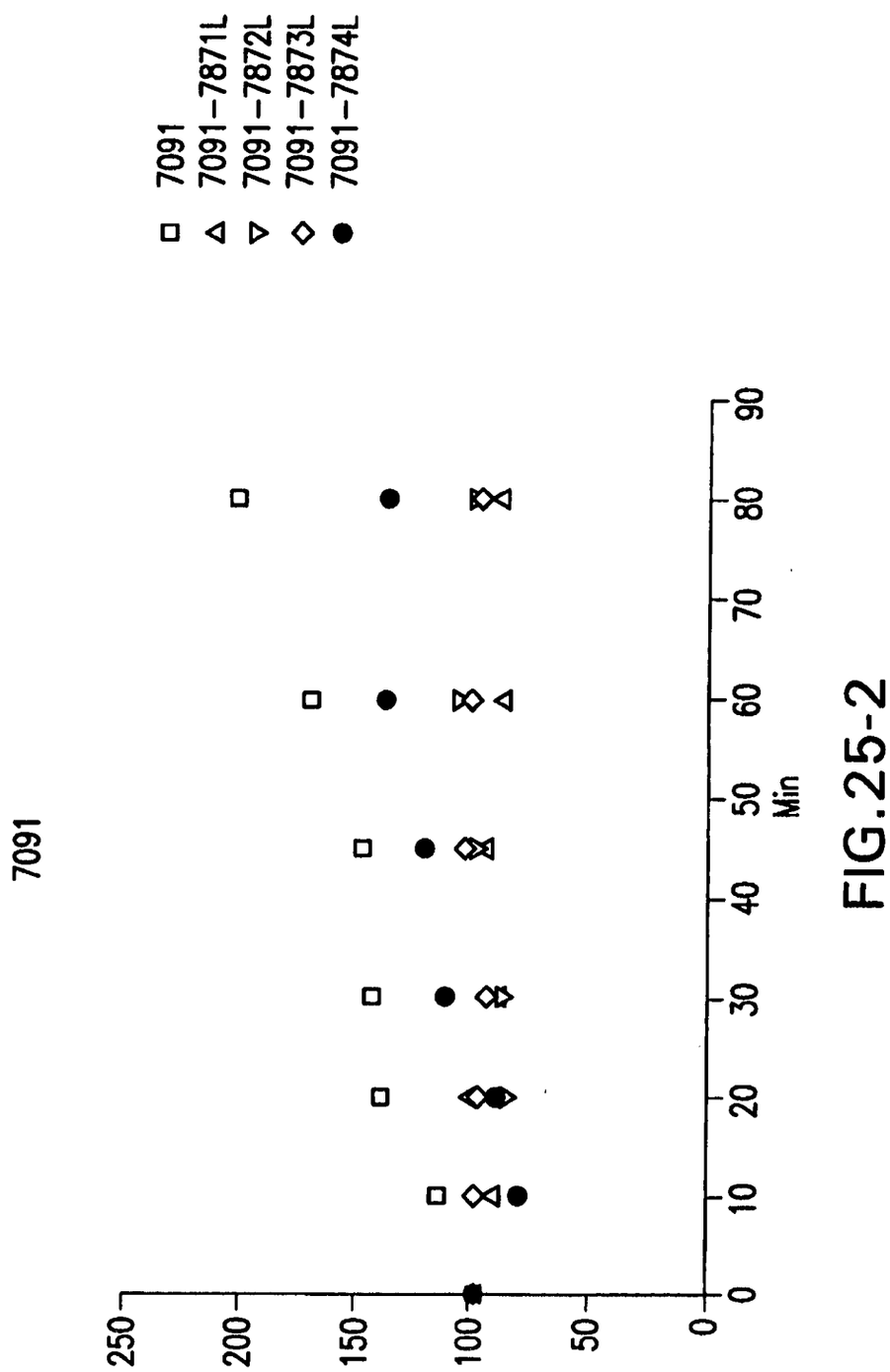

7091
7091-7871L
7091-7872L
7091-7873L
7091-7874L
7091
250
200
150
100
50
0
0
10
20
30
40
50
60
70
80
90
Min

FIG.25-2

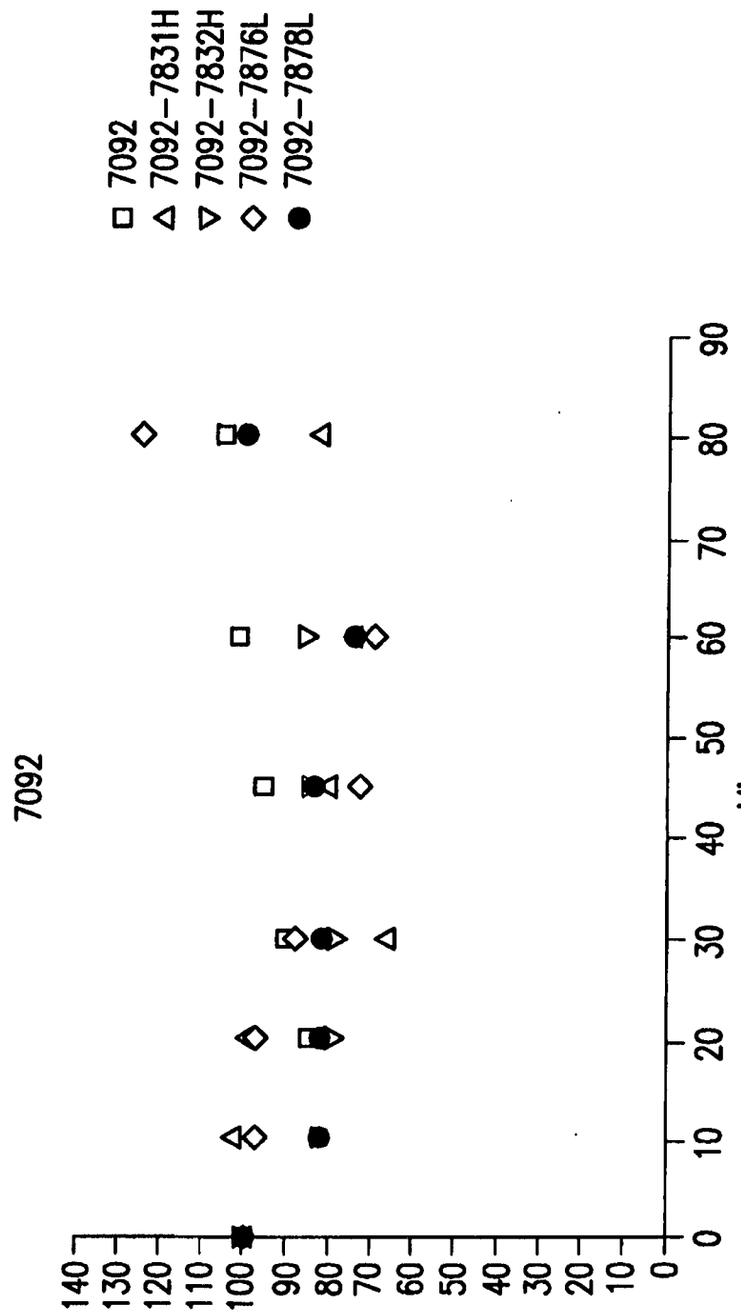

7092
7092-7831H
7092-7832H
7092-7876L
7092-7878L
7092
Min
0
10
20
30
40
50
60
70
80
90
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140

FIG.25-3

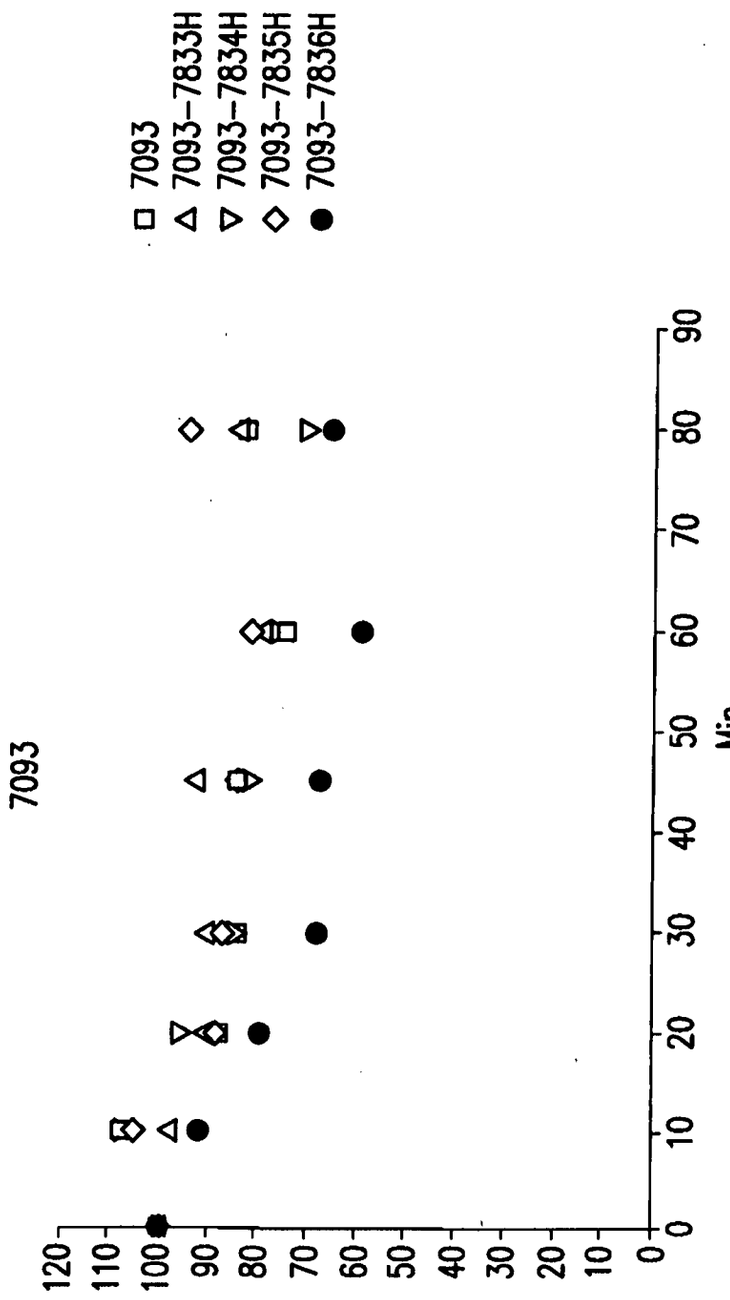

7093
7093-7833H
7093-7834H
7093-7835H
7093-7836H
7093
Min
0
10
20
30
40
50
60
70
80
90
120
110
100
90
80
70
60
50
40
30
20
10
0

FIG.25-4

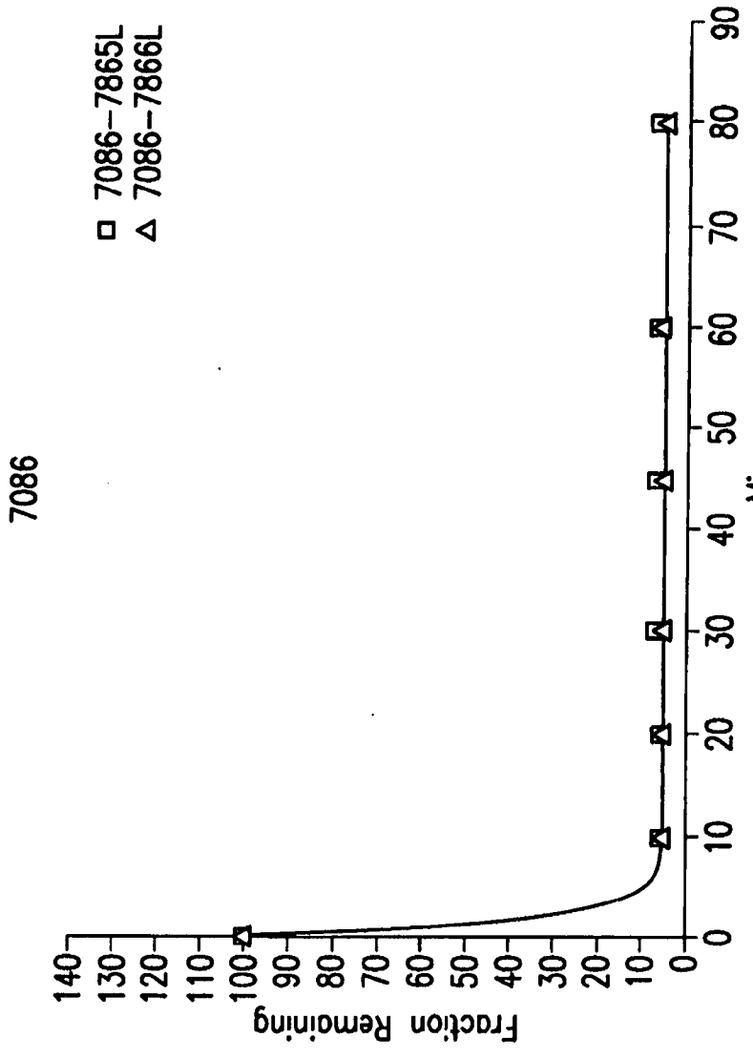

7086
7086–7865L
7086–7866L
Fraction Remaining
Min
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140

FIG.26-1

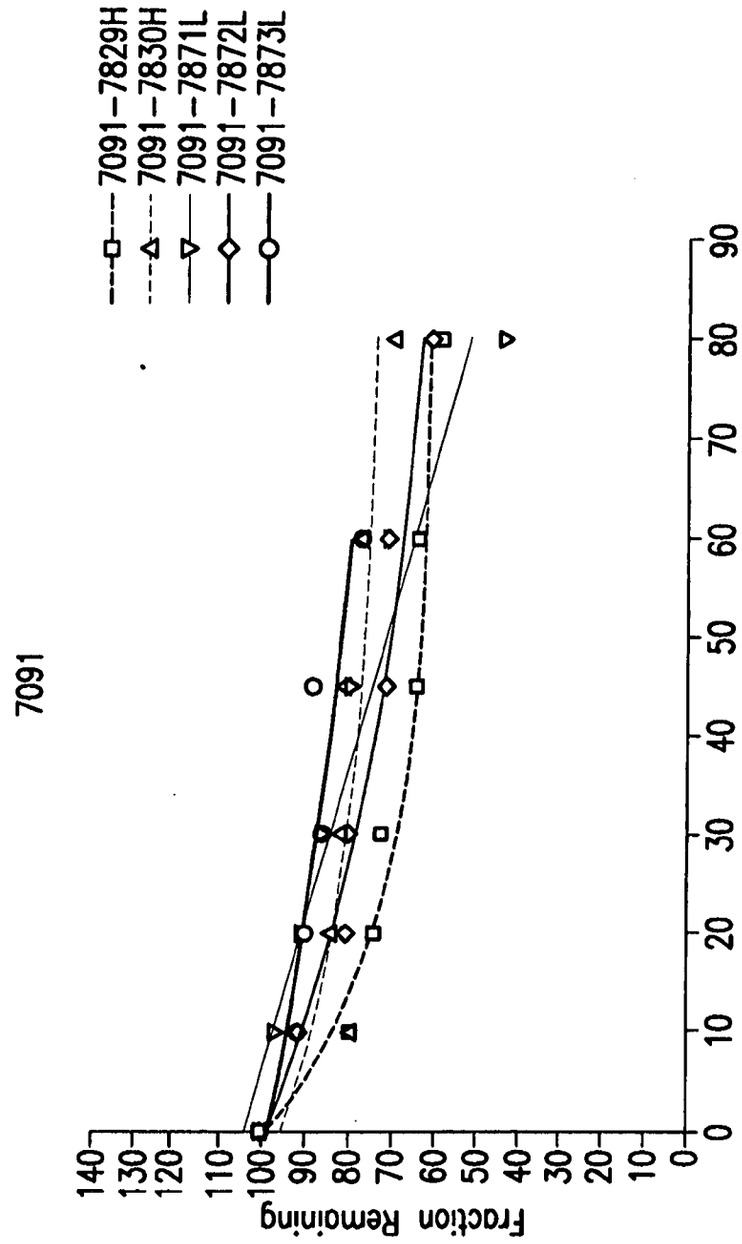

7091-7829H
7091-7830H
7091-7871L
7091-7872L
7091-7873L
7091
Fraction Remaining
Min
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140

FIG.26-2

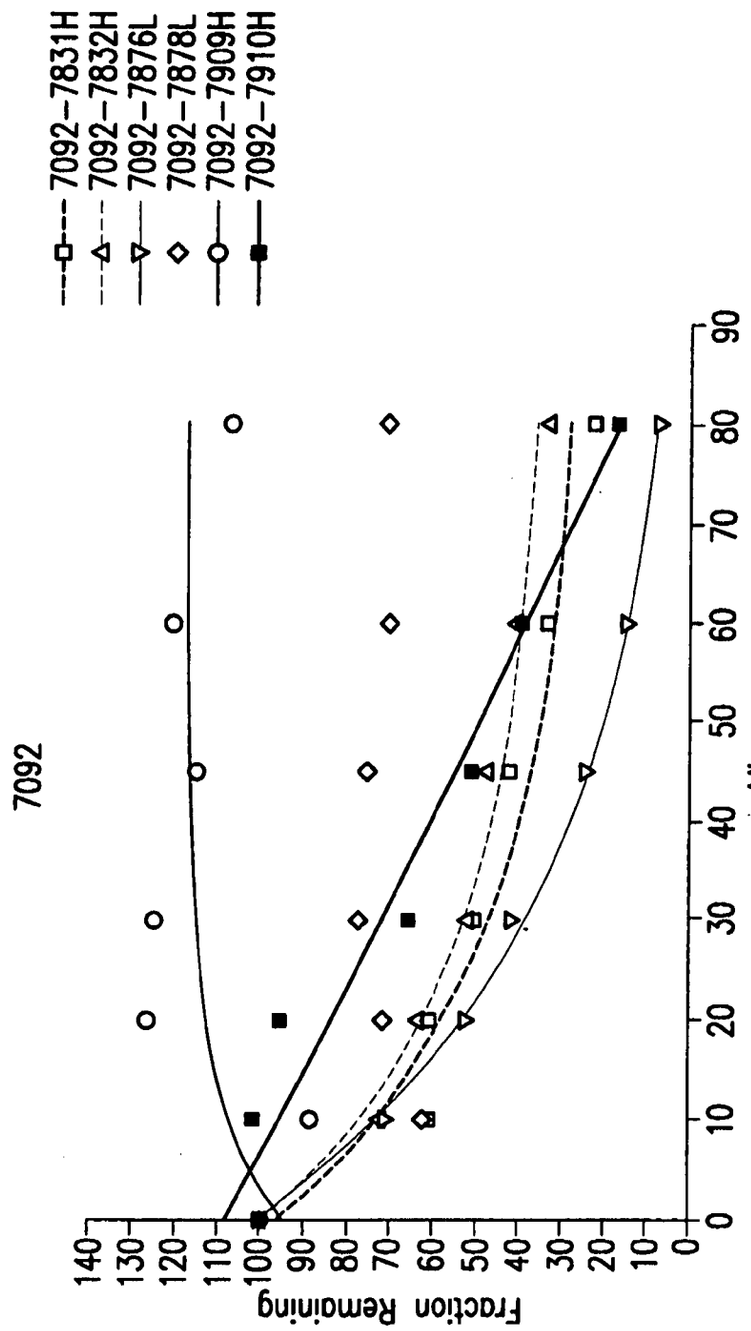

7092-7831H
7092-7832H
7092-7876L
7092-7878L
7092-7909H
7092-7910H
7092
Fraction Remaining
Min
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140

FIG.26-3

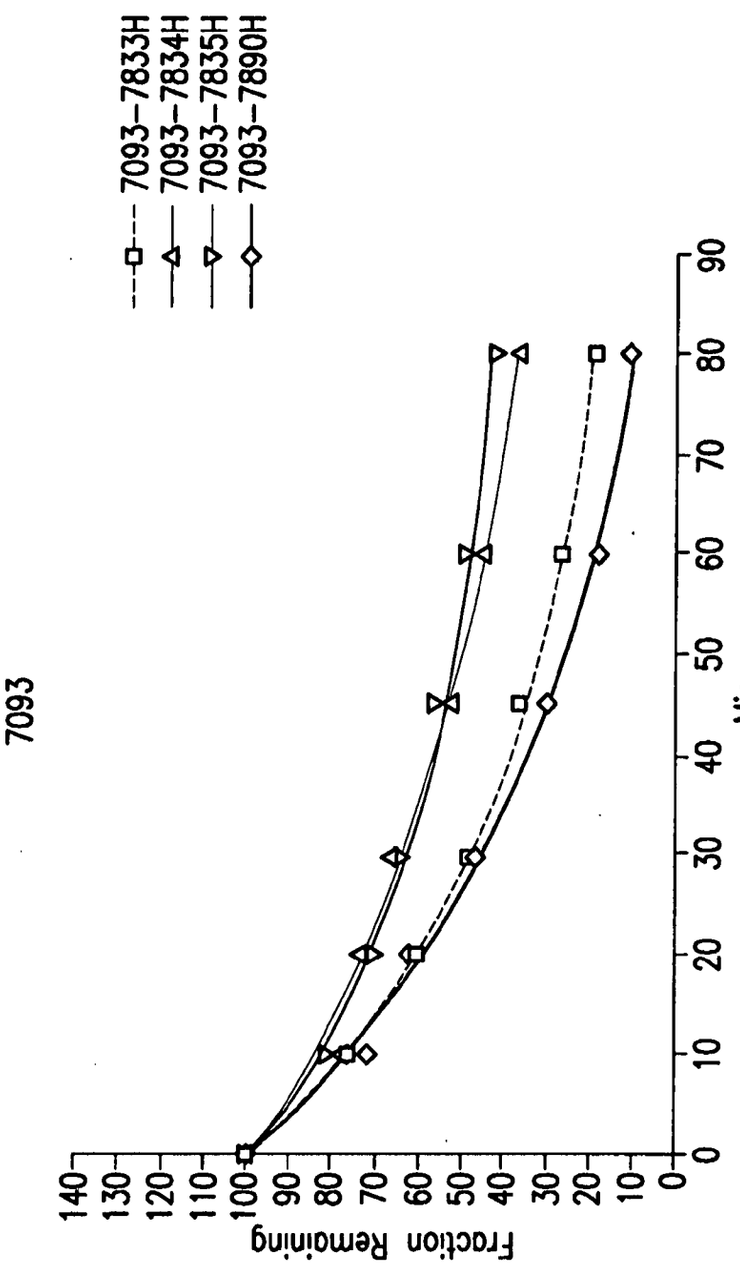

7093-7833H
7093-7834H
7093-7835H
7093-7890H
7093
Fraction Remaining
Min
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90

FIG.26-4

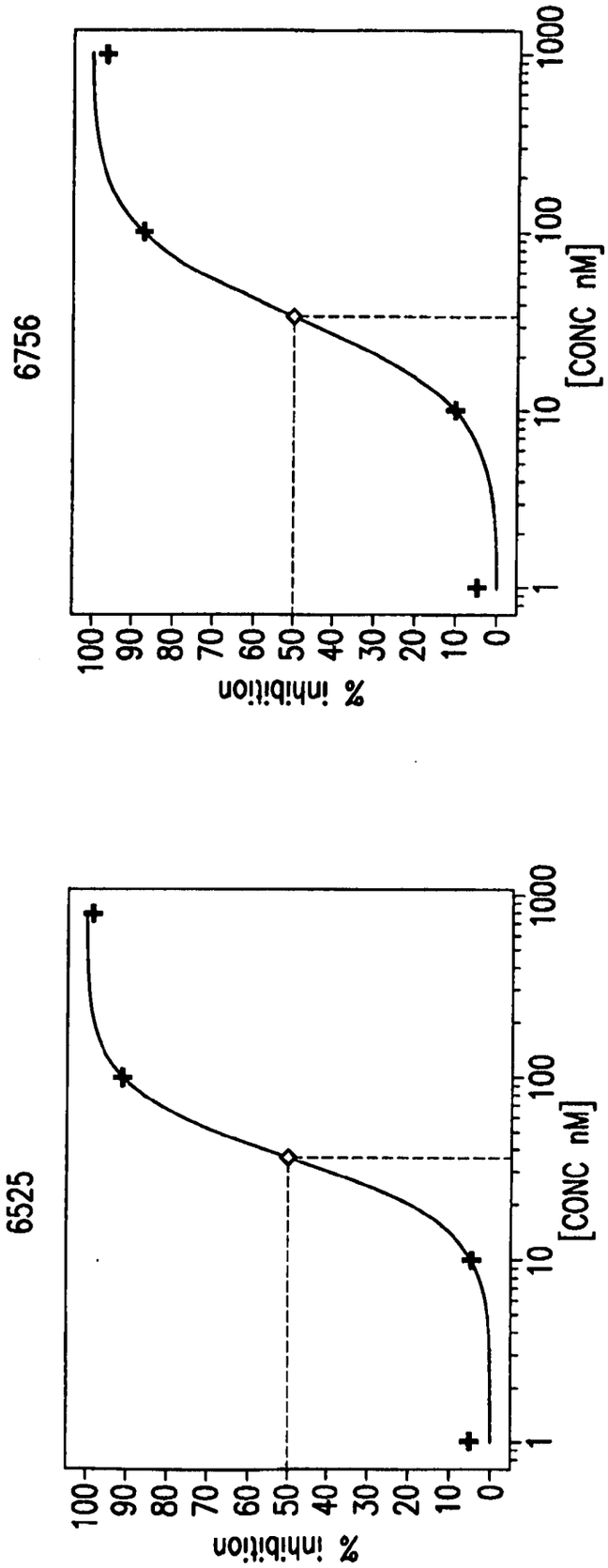

6525
% inhibition
0
10
20
30
40
50
60
70
80
90
100
1
10
100
1000
[CONC nM]
6756
% inhibition
0
10
20
30
40
50
60
70
80
90
100
1
10
100
1000
[CONC nM]

FIG.27

SEQUENCE LISTING

<110> Novartis AG

<120> Compositions and methods for antibodies targeting complement protein C5

<130> 52633-US-P

<140> 61/086,355
<141> 2008-08-05

<160> 297

<170> PatentIn version 3.3

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<213> homo sapiens

<400> 1

Ser Tyr Ala Ile Ser
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<211> 17
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<213> homo sapiens

<400> 2

Gly Ile Gly Pro Phe Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 3
<211> 7
<212> PRT
<213> homo sapiens

<400> 3

Asp Thr Pro Tyr Phe Asp Tyr
1 5

<210> 4
<211> 11
<212> PRT
<213> homo sapiens

<400> 4

Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val Tyr
1 5 10

<210> 5
<211> 7
<212> PRT
<213> homo sapiens

<400> 5

Asp Asp Ser Asn Arg Pro Ser
1 5

<210> 6
<211> 11
<212> PRT
<213> homo sapiens

<400> 6

Gln Ser Phe Asp Ser Ser Leu Asn Ala Glu Val
1 5 10

<210> 7
<211> 116
<212> PRT
<213> homo sapiens

<400> 7

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

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

Gly Gly Ile Gly Pro Phe Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 8

<211> 108
<212> PRT
<213> homo sapiens

<400> 8

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

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val
20 25 30

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

Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Ala Gln Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Ser Ser Leu Asn Ala
85 90 95

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 9
<211> 446
<212> PRT
<213> homo sapiens

<400> 9

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1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

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

Gly Gly Ile Gly Pro Phe Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 10
<211> 214
<212> PRT
<213> homo sapiens

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

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val
20 25 30

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

Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Ala Gln Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Ser Ser Leu Asn Ala
85 90 95

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln

115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

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<211> 348
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agctgcaaag cctccggagg cacttttttct tcttatgcca tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcggt atcggtccgt tttttggcac tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300

ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 12
<211> 324
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<213> homo sapiens

<400> 12
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acctgctccg gcgacagcat ccccaactac tacgtgtact ggtaccagca gaagcccggc 120

caggcccccg tgctggtgat ctacgacgac agcaaccggc ccagcggcat ccccgagcgg 180

ttcagcggca gcaacagcgg caacaccgcc accctgacca tttccagagc acaggcaggc 240

gacgaggccg actactactg ccagagcttc gacagcagcc tgaacgccga ggtgttcggc 300

ggagggacca agttaaccgt ccta 324

<210> 13
<211> 1338
<212> DNA
<213> homo sapiens

<400> 13
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cctgggcagg gtctcgagtg gatgggcggt atcggtccgt tttttggcac tgcgaattac 180
gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240
atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300
ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctcagc ctccaccaag 360
ggtccatcgg tcttcccccct ggcaccctcc tccaagagca cctctggggg cacagcggcc 420
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gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc 540
ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac 600
gtgaatcaca agcccagcaa caccaaggtg gacaagagag ttgagcccaa atcttgtgac 660
aaaactcaca catgcccacc gtgcccagca cctgaagcag cgggggggacc gtcagtcttc 720
ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacatgc 780
gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 840
gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgg 900
gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 960
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cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1080
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gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320
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<210> 14
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<212> DNA
<213> homo sapiens

<400> 14
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acctgctccg gcgacagcat ccccaactac tacgtgtact ggtaccagca gaagcccggc 120

caggcccccg tgctggtgat ctacgacgac agcaaccggc ccagcggcat ccccgagcgg 180

ttcagcggca gcaacagcgg caacaccgcc accctgacca tttccagagc acaggcaggc 240

gacgaggccg actactactg ccagagcttc gacagcagcc tgaacgccga ggtgttcggc 300

ggagggacca agttaaccgt cctaggtcag cccaaggctg ccccctcggt cactctgttc 360

ccgccctcct ctgaggagct tcaagccaac aaggccacac tggtgtgtct cataagtgac 420

ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgaa 600

gggagcaccg tggagaagac agtggccccc acagaatgtt ca 642

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<211> 1338
<212> DNA
<213> homo sapiens

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tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcggcaggcc 120

ccaggccagg gcctggagtg gatgggcggc atcggcccat tcttcggcac cgccaactac 180

gcccagaagt tccagggcag ggtcaccatc accgccgacg agagcaccag caccgcctac 240

atggagctgt ccagcctgag aagcgaggac accgccgtgt actactgcgc cagagacacc 300

ccctacttcg actactgggg ccagggcacc ctggtgaccg tgagcagcgc tagcaccaag 360

ggccccagcg tgttccccct ggccccccagc agcaagagca cctccggcgg cacagccgcc 420

ctgggctgcc tggtgaagga ctacttcccc gagcccgtga ccgtgtcctg gaacagcgga 480

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ctgtccagcg tggtgacagt gcccagcagc agcctgggca cccagaccta catctgcaac 600

gtgaaccaca agcccagcaa caccaaggtg gacaagagag tggagcccaa gagctgcgac 660

aagacccaca cctgcccccc ctgcccagcc cccgaagctg caggcggccc ttccgtgttc 720

ctgttccccc ccaagcccaa ggacaccctg atgatcagca ggacccccga ggtgacctgc 780

gtggtggtgg acgtgagcca cgaggaccca gaggtgaagt tcaactggta cgtggacggc 840

gtggaggtgc acaacgccaa gaccaagccc agagaggagc agtacaacag cacctacagg 900

gtggtgtccg tgctgaccgt gctgcaccag gactggctga acggcaaaga atacaagtgc 960

aaggtctcca acaaggccct gcctgccccc atcgaaaaga ccatcagcaa ggccaagggc 1020

cagccacggg agccccaggt gtacaccctg cccccttctc gggaggagat gaccaagaac 1080

caggtgtccc tgacctgtct ggtgaagggc ttctacccca gcgacatcgc cgtggagtgg 1140

gagagcaacg gccagcccga gaacaactac aagaccaccc ccccagtgct ggacagcgac 1200

ggcagcttct tcctgtacag caagctgacc gtggacaaga gcaggtggca gcagggcaac 1260

gtgttcagct gcagcgtgat gcacgaggcc ctgcacaacc actacaccca gaagagcctg 1320

agcctgtcac ccggcaag 1338

<210> 16
<211> 642
<212> DNA
<213> homo sapiens

<400> 16
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acctgcagcg gcgacagcat ccccaactac tacgtgtact ggtatcagca gaagcccggc 120

caggcccccg tgctggtgat ctacgacgac agcaacaggc ccagcggcat ccccgagagg 180

ttcagcggca gcaacagcgg caacaccgcc accctgacca tcagcagagc ccaggccggc 240

gacgaggccg actactactg ccagagcttc gacagctcac tgaacgccga ggtgttcggc 300

ggagggacca agctgaccgt gctgggccag cctaaggctg cccccagcgt gaccctgttc 360

ccccccagca gcgaggagct gcaggccaac aaggccaccc tggtgtgcct gatcagcgac 420

ttctacccag gcgccgtgac cgtggcctgg aaggccgaca gcagccccgt gaaggccggc 480

gtggagacca ccaccccag caagcagagc aacaacaagt acgccgccag cagctacctg 540

agcctgaccc ccgagcagtg gaagagccac aggtcctaca gctgccaggt gacccacgag 600

ggcagcaccg tggaaaagac cgtggcccca accgagtgca gc 642

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<211> 4
<212> PRT
<213> homo sapiens

<400> 17

Asn Tyr Ile Ser
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<210> 18
<211> 17
<212> PRT
<213> homo sapiens

<400> 18

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 19
<211> 8
<212> PRT
<213> homo sapiens

<400> 19

Tyr Glu Tyr Gly Gly Phe Asp Ile
1 5

<210> 20
<211> 11
<212> PRT
<213> homo sapiens

<400> 20

Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val His
1 5 10

<210> 21
<211> 7
<212> PRT
<213> homo sapiens

<400> 21

Lys Asp Asn Asp Arg Pro Ser
1 5

<210> 22
<211> 9
<212> PRT
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<400> 22

Gly Thr Tyr Asp Ile Glu Ser Tyr Val
1 5

<210> 23
<211> 116
<212> PRT
<213> homo sapiens

<400> 23

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

35 40 45

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 24
<211> 106
<212> PRT
<213> homo sapiens

<400> 24

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Tyr Asp Ile Glu Ser Tyr Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 25
<211> 446
<212> PRT
<213> homo sapiens

<400> 25

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 26
<211> 212
<212> PRT
<213> homo sapiens

<400> 26

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val

20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Tyr Asp Ile Glu Ser Tyr Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125

Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140

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

Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175

Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190

Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205

Thr Glu Cys Ser
210

<210> 27
<211> 348
<212> DNA
<213> homo sapiens

<400> 27
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agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctgatg attcttatac tgagtattct 180

ccttctttttc agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 28
<211> 318
<212> DNA
<213> homo sapiens

<400> 28
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tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cggtacttat gatattgagt cttatgtgtt tggcggcggc 300

acgaagttaa ccgtccta 318

<210> 29
<211> 1338
<212> DNA
<213> homo sapiens

<400> 29
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agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctgatg attcttatac tgagtattct 180

ccttctttttc agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc ctccaccaag 360

ggtccatcgg tcttcccccct ggcaccctcc tccaagagca cctctggggg cacagcggcc 420

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 480

gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc 540

ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac 600

gtgaatcaca agcccagcaa caccaaggtg gacaagagag ttgagcccaa atcttgtgac 660

aaaactcaca catgcccacc gtgcccagca cctgaagcag cgggggggacc gtcagtcttc 720

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacatgc 780

gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 840

gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgg 900

gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 960

aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggg 1020

cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1080

caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg 1140

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac 1200

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320

tccctgtctc cgggtaaa 1338

<210> 30
<211> 636
<212> DNA
<213> homo sapiens

<400> 30
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tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cggtacttat gatattgagt cttatgtgtt tggcggcggc 300

acgaagttaa ccgtcctagg tcagcccaag gctgcccccc cggtcactct gttcccgccc 360

tcctctgagg agcttcaagc caacaaggcc acactggtgt gtctcataag tgacttctac 420

ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag 480

accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg 540

acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaagggagc 600

accgtggaga agacagtggc ccctacagaa tgttca 636

<210> 31
<211> 1338
<212> DNA
<213> homo sapiens

<400> 31
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agctgcaagg gcagcggcta cagcttcacc aactacatca gctgggtgcg gcagatgccc 120

ggcaagggcc tggagtggat gggcatcatc gaccccgacg acagctacac cgagtacagc 180

cccagcttcc agggccaggt gaccatcagc gccgacaaga gcatcagcac cgcctacctg 240

cagtggagca gcctgaaggc cagcgacacc gccatgtact actgcgccag atacgagtac 300

ggcggcttcg acatctgggg ccagggcacc ctggtgaccg tcagctcagc tagcaccaag 360

ggccccagcg tgttcccctt ggccccccagc agcaagagca cctccggcgg cacagccgcc 420

ctgggctgcc tggtgaagga ctacttcccc gagcccgtga ccgtgtcctg gaacagcgga 480

gccctgacca gcggcgtgca caccttcccc gccgtgctgc agagcagcgg cctgtacagc 540

ctgtccagcg tggtgacagt gcccagcagc agcctgggca cccagaccta catctgcaac 600

gtgaaccaca agcccagcaa caccaaggtg gacaagagag tggagcccaa gagctgcgac 660

aagacccaca cctgcccccc ctgcccagcc cccgaagctg caggcggccc ttccgtgttc 720

ctgttccccc ccaagcccaa ggacaccctg atgatcagca ggacccccga ggtgacctgc 780

gtggtggtgg acgtgagcca cgaggaccca gaggtgaagt tcaactggta cgtggacggc 840

gtggaggtgc acaacgccaa gaccaagccc agagaggagc agtacaacag cacctacagg 900

gtggtgtccg tgctgaccgt gctgcaccag gactggctga acggcaaaga atacaagtgc 960

aaggtctcca acaaggccct gcctgccccc atcgaaaaga ccatcagcaa ggccaagggc 1020

cagccacggg agccccaggt gtacaccctg ccccctctc gggaggagat gaccaagaac 1080

caggtgtccc tgacctgtct ggtgaagggc ttctacccca gcgacatcgc cgtggagtgg 1140

gagagcaacg gccagcccga gaacaactac aagaccaccc ccccagtgct ggacagcgac 1200

ggcagcttct tcctgtacag caagctgacc gtggacaaga gcaggtggca gcagggcaac 1260

gtgttcagct gcagcgtgat gcacgaggcc ctgcacaacc actacaccca gaagagcctg 1320

agcctgtcac ccggcaag 1338

<210> 32
<211> 636
<212> DNA
<213> homo sapiens

<400> 32
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agctgcagcg gcgacaacat cggcaacagc tacgtgcact ggtatcagca gaagcccggc 120

caggcccccg tgctggtgat ctacaaggac aacgacaggc ccagcggcat ccccgagagg 180

ttcagcggca gcaactccgg caacaccgcc accctgacca tcagcggcac ccaggccgag 240

gacgaggccg actactactg cggcacctac gacatcgagt catacgtgtt cggcggaggg 300

accaagctga ccgtgctggg ccagcctaag gctgccccca gcgtgaccct gttccccccc 360

agcagcgagg agctgcaggc caacaaggcc accctggtgt gcctgatcag cgacttctac 420

ccaggcgccg tgaccgtggc ctggaaggcc gacagcagcc ccgtgaaggc cggcgtggag 480

accaccaccc ccagcaagca gagcaacaac aagtacgccg ccagcagcta cctgagcctg 540

acccccgagc agtggaagag ccacaggtcc tacagctgcc aggtgaccca cgagggcagc 600

accgtggaaa agaccgtggc cccaaccgag tgcagc 636

<210> 33
<211> 7
<212> PRT
<213> homo sapiens

<400> 33

Thr Ser Gly Gly Gly Val Ser
1 5

<210> 34
<211> 16
<212> PRT
<213> homo sapiens

<400> 34

Asn Ile Asp Asp Ala Asp Ile Lys Asp Tyr Ser Pro Ser Leu Lys Ser
1 5 10 15

<210> 35
<211> 7
<212> PRT
<213> homo sapiens

<400> 35

Gly Pro Tyr Gly Phe Asp Ser
1 5

<210> 36
<211> 14
<212> PRT
<213> homo sapiens

<400> 36

Thr Gly Thr Ser Ser Asp Ile Gly Thr Tyr Asn Tyr Val Ser
1 5 10

<210> 37
<211> 7
<212> PRT
<213> homo sapiens

<400> 37

Asp Asp Ser Asn Arg Pro Ser
1 5

<210> 38
<211> 9
<212> PRT
<213> homo sapiens

<400> 38

Gln Ser Tyr Asp Ser Gln Ser Ile Val
1 5

<210> 39
<211> 117
<212> PRT
<213> homo sapiens

<400> 39

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

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Gly Pro Tyr Gly Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 40
<211> 109
<212> PRT
<213> homo sapiens

<400> 40

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Thr Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Asp Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe

50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Gln
85 90 95

Ser Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 41
<211> 447
<212> PRT
<213> homo sapiens

<400> 41

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

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Gly Pro Tyr Gly Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser

165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 42
<211> 215
<212> PRT
<213> homo sapiens

<400> 42

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Thr Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Asp Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Gln
85 90 95

Ser Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
100 105 110

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
115 120 125

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
165 170 175

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180 185 190

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
195 200 205

Val Ala Pro Thr Glu Cys Ser
210 215

<210> 43
<211> 351
<212> DNA
<213> homo sapiens

<400> 43
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acctgtacct tttccggatt tagcctgtct acttctggtg gtggtgtgtc ttggattcgc 120

cagccgcctg ggaaagccct cgagtggctg gctaatattg atgatgctga tattaaggat 180

tattctcctt ctcttaagtc tcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240

gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgtggt 300

ccttatggtt ttgattcttg gggccaaggc accctggtga cggttagctc a 351

<210> 44
<211> 327
<212> DNA
<213> homo sapiens

<400> 44
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tcgtgtacgg gtactagcag cgatattggt acttataatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgatt ctaatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc cagtcttatg attctcagtc tattgtgttt 300

ggcggcggca cgaagttaac cgtccta 327

<210> 45
<211> 1341
<212> DNA
<213> homo sapiens

<400> 45
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acctgtacct tttccggatt tagcctgtct acttctggtg gtggtgtgtc ttggattcgc 120

cagccgcctg ggaaagccct cgagtggctg gctaatattg atgatgctga tattaaggat 180

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gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgtggt 300

ccttatggtt ttgattcttg gggccaaggc accctggtga cggttagctc agcctccacc 360

aagggtccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420
gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480
ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540
tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 600
aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt 660
gacaaaactc acacatgccc accgtgccca gcacctgaag cagcgggggg accgtcagtc 720
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tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 840
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cgggtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 960
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gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320
ctctccctgt ctccgggtaa a 1341

<210> 46
<211> 645
<212> DNA
<213> homo sapiens

<400> 46
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tcgtgtacgg gtactagcag cgatattggt acttataatt atgtgtcttg gtaccagcag 120
catcccggga aggcgccgaa acttatgatt tatgatgatt ctaatcgtcc ctcaggcgtg 180
agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
caagcggaag acgaagcgga ttattattgc cagtcttatg attctcagtc tattgtgttt 300
ggcggcggca cgaagttaac cgtcctaggt cagcccaagg ctgccccctc ggtcactctg 360
ttcccgccct cctctgagga gcttcaagcc aacaaggcca cactggtgtg tctcataagt 420
gacttctacc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg 480
ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540
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gaagggagca ccgtggagaa gacagtggcc cctacagaat gttca 645

<210> 47
<211> 1341
<212> DNA
<213> homo sapiens

<400> 47
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acttgcacct tcagcggctt cagcctgagc accagcggag ggggcgtgag ctggatcagg 120

cagcccccag gtaaggccct ggagtggctg gccaatatcg acgacgccga tatcaaggac 180

tacagcccca gcctgaagag caggctgacc atcagcaagg acaccagcaa gaaccaggtg 240

gtgctgacca tgaccaatat ggaccccgtg gacaccgcca cctactactg cgccagaggc 300

ccctacggct tcgacagctg gggccagggc accctggtga ccgtcagctc agctagcacc 360

aagggcccca gcgtgttccc cctggccccc agcagcaaga gcacctccgg cggcacagcc 420

gccctgggct gcctggtgaa ggactacttc cccgagcccg tgaccgtgtc ctggaacagc 480

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aacgtgaacc acaagcccag caacaccaag gtggacaaga gagtggagcc caagagctgc 660

gacaagaccc acacctgccc ccctgccca gccccgaag ctgcaggcgg ccccttccgtg 720

ttcctgttcc ccccaagcc caaggacacc ctgatgatca gcaggacccc cgaggtgacc 780

tgcgtggtgg tggacgtgag ccacgaggac ccagaggtga agttcaactg gtacgtggac 840

ggcgtggagg tgcacaacgc caagaccaag cccagagagg agcagtacaa cagcacctac 900

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aaccaggtgt ccctgacctg tctggtgaag ggcttctacc ccagcgacat cgccgtggag 1140

tgggagagca acggccagcc cgagaacaac tacaagacca cccccccagt gctggacagc 1200

gacggcagct tcttcctgta cagcaagctg accgtggaca agagcaggtg gcagcagggc 1260

aacgtgttca gctgcagcgt gatgcacgag gccctgcaca accactacac ccagaagagc 1320

ctgagcctgt cacccggcaa g 1341

<210> 48
<211> 645
<212> DNA
<213> homo sapiens

<400> 48
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agctgcaccg gcacctccag cgatatcggc acctacaact acgtgagctg gtatcagcag 120

caccccggca aggcccccaa gctgatgatc tacgacgaca gcaacaggcc cagcggcgtg 180

agcaacaggt tcagcggcag caagagcggc aacaccgcca gcctgacaat cagcggcctg 240

caggccgagg acgaggccga ctactactgc cagagctacg acagccagtc aatcgtgttc 300

ggcggaggga ccaagctgac cgtgctgggc cagcctaagg ctgccccctg cgtgaccctg 360

ttccccccca gcagcgagga gctgcaggcc aacaaggcca ccctggtgtg cctgatcagc 420

gacttctacc caggcgccgt gaccgtggcc tggaaggccg acagcagccc cgtgaaggcc 480

ggcgtggaga ccaccacccc cagcaagcag agcaacaaca agtacgccgc cagcagctac 540

ctgagcctga cccccgagca gtggaagagc cacaggtcct acagctgcca ggtgacccac 600

gagggcagca ccgtggaaaa gaccgtggcc ccaaccgagt gcagc 645

<210> 49
<211> 17
<212> PRT
<213> homo sapiens

<400> 49

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 50
<211> 9
<212> PRT
<213> homo sapiens

<400> 50

Ala Thr Trp Gly Ser Glu Asp Gln Val
1 5

<210> 51
<211> 116
<212> PRT
<213> homo sapiens

<400> 51

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

35 40 45

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 52
<211> 106
<212> PRT
<213> homo sapiens

<400> 52

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Gly Ser Glu Asp Gln Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 53
<211> 446
<212> PRT
<213> homo sapiens

<400> 53

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro

245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 54
<211> 212
<212> PRT
<213> homo sapiens

<400> 54

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val

20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Gly Ser Glu Asp Gln Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125

Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140

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

Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175

Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190

Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205

Thr Glu Cys Ser
210

<210> 55
<211> 348
<212> DNA
<213> homo sapiens

<400> 55
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agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatc gatccggatg atagctatac ccgttattct 180

ccgagctttc agggacaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 56
<211> 318
<212> DNA
<213> homo sapiens

<400> 56
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tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cgctacttgg ggttctgagg atcaggtgtt tggcggcggc 300

acgaagttaa ccgtccta 318

<210> 57
<211> 1338
<212> DNA
<213> homo sapiens

<400> 57
gaggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatc gatccggatg atagctatac ccgttattct 180

ccgagctttc agggacaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc ctccaccaag 360

ggtccatcgg tcttcccccc tggcaccctcc tccaagagca cctctggggg cacagcggcc 420

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 480

gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc 540

ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac 600

gtgaatcaca agcccagcaa caccaaggtg gacaagagag ttgagcccaa atcttgtgac 660

aaaactcaca catgcccacc gtgcccagca cctgaagcag cgggggggacc gtcagtcttc 720

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggaccccctga ggtcacatgc 780

gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 840

gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgg 900

gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 960

aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggg 1020

cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1080

caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg 1140

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac 1200

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320

tccctgtctc cgggtaaa 1338

<210> 58
<211> 636
<212> DNA
<213> homo sapiens

<400> 58
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tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cgctacttgg ggttctgagg atcaggtgtt tggcggcggc 300

acgaagttaa ccgtcctagg tcagcccaag gctgccccct cggtcactct gttcccgccc 360

tcctctgagg agcttcaagc caacaaggcc acactggtgt gtctcataag tgacttctac 420

ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag 480

accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg 540

acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaagggagc 600

accgtggaga agacagtggc cctacagaa tgttca 636

<210> 59
<211> 1338
<212> DNA
<213> homo sapiens

<400> 59
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agctgcaagg gcagcggcta cagcttcacc aactacatca gctgggtgcg gcagatgccc 120

ggcaagggcc tggagtggat gggcatcatc gaccccgacg acagctacac caggtacagc 180

cccagcttcc agggccaggt gaccatcagc gccgacaaga gcatcagcac cgcctacctg 240

cagtggagca gcctgaaggc cagcgacacc gccatgtact actgcgccag atacgagtac 300

ggcggcttcg acatctgggg ccagggcacc ctggtgaccg tcagctcagc tagcaccaag 360

ggccccagcg tgttcccccc ggcccccagc agcaagagca cctccggcgg cacagccgcc 420

ctgggctgcc tggtgaagga ctacttcccc gagcccgtga ccgtgtcctg gaacagcgga 480

gccctgacca gcggcgtgca caccttcccc gccgtgctgc agagcagcgg cctgtacagc 540

ctgtccagcg tggtgacagt gcccagcagc agcctgggca cccagaccta catctgcaac 600

gtgaaccaca agcccagcaa caccaaggtg gacaagagag tggagcccaa gagctgcgac 660

aagacccaca cctgcccccc ctgcccagcc cccgaagctg caggcggccc ttccgtgttc 720

ctgttccccc ccaagcccaa ggacaccctg atgatcagca ggacccccga ggtgacctgc 780

gtggtggtgg acgtgagcca cgaggaccca gaggtgaagt tcaactggta cgtggacggc 840

gtggaggtgc acaacgccaa gaccaagccc agagaggagc agtacaacag cacctacagg 900

gtggtgtccg tgctgaccgt gctgcaccag gactggctga acggcaaaga atacaagtgc 960

aaggtctcca acaaggccct gcctgccccc atcgaaaaga ccatcagcaa ggccaagggc 1020

cagccacggg agccccaggt gtacaccctg ccccctctc gggaggagat gaccaagaac 1080

caggtgtccc tgacctgtct ggtgaagggc ttctacccca gcgacatcgc cgtggagtgg 1140

gagagcaacg gccagcccga gaacaactac aagaccaccc ccccagtgct ggacagcgac 1200

ggcagcttct tcctgtacag caagctgacc gtggacaaga gcaggtggca gcagggcaac 1260

gtgttcagct gcagcgtgat gcacgaggcc ctgcacaacc actacaccca gaagagcctg 1320

agcctgtcac ccggcaag 1338

<210> 60
<211> 636
<212> DNA
<213> homo sapiens

<400> 60
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agctgcagcg gcgacaatat cggcaacagc tacgtgcact ggtatcagca gaagcccggc 120

caggcccccg tgctggtgat ctacaaggac aacgacaggc ccagcggcat ccccgagagg 180

ttcagcggca gcaactccgg caacaccgcc accctgacaa tcagcggcac ccaggccgag 240

gacgaggccg actactactg cgccacctgg ggctcagagg accaggtgtt cggcggaggg 300

accaagctga ccgtgctggg ccagcctaag gctgccccca gcgtgaccct gttccccccc 360

agcagcgagg agctgcaggc caacaaggcc accctggtgt gcctgatcag cgacttctac 420

ccaggcgccg tgaccgtggc ctggaaggcc gacagcagcc ccgtgaaggc cggcgtggag 480

accaccaccc ccagcaagca gagcaacaac aagtacgccg ccagcagcta cctgagcctg 540

acccccgagc agtggaagag ccacaggtcc tacagctgcc aggtgaccca cgagggcagc 600

accgtggaaa agaccgtggc cccaaccgag tgcagc 636

<210> 61
<211> 5
<212> PRT
<213> homo sapiens

<400> 61

Ser Tyr Tyr Ile Gly
1 5

<210> 62
<211> 17
<212> PRT
<213> homo sapiens

<400> 62

Ile Ile Asp Pro Thr Asp Ser Gln Thr Ala Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 63
<211> 8
<212> PRT
<213> homo sapiens

<400> 63

Tyr Met Met Arg Gly Phe Asp His
1 5

<210> 64
<211> 11
<212> PRT
<213> homo sapiens

<400> 64

Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala Tyr
1 5 10

<210> 65
<211> 7
<212> PRT
<213> homo sapiens

<400> 65

Lys Asp Asn Asn Arg Pro Ser
1 5

<210> 66
<211> 10
<212> PRT

<213> homo sapiens

<400> 66

Gln Thr Trp Asp Thr Gly Glu Ser Gly Val
1 5 10

<210> 67
<211> 117
<212> PRT
<213> homo sapiens

<400> 67

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Thr Asp Ser Gln Thr Ala Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 68
<211> 107
<212> PRT
<213> homo sapiens

<400> 68

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr

35 40 45

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Thr Gly Glu Ser Gly
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 69
<211> 447
<212> PRT
<213> homo sapiens

<400> 69

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Thr Asp Ser Gln Thr Ala Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser

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145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400
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Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 70
<211> 213
<212> PRT
<213> homo sapiens

<400> 70

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Thr Gly Glu Ser Gly
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110

Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125

Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140

Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160

Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
165 170 175

Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
180 185 190

Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
195 200 205

Pro Thr Glu Cys Ser
210

<210> 71
<211> 351
<212> DNA
<213> homo sapiens

<400> 71
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agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt attgatccta ctgattctca gactgcttat 180

tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc a 351

<210> 72
<211> 321
<212> DNA
<213> homo sapiens

<400> 72
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tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttgg gatactggtg agtctggtgt gtttggcggc 300

ggcacgaagt taaccgtcct a 321

<210> 73
<211> 1341
<212> DNA
<213> homo sapiens

<400> 73
gaggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt attgatccta ctgattctca gactgcttat 180

tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300
atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc agcctccacc 360
aagggtccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420
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ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540
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aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt 660
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gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260
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ctctccctgt ctccgggtaa a 1341

<210> 74
<211> 639
<212> DNA
<213> homo sapiens

<400> 74
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caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ccagacttgg gatactggtg agtctggtgt gtttggcggc 300
ggcacgaagt taaccgtcct aggtcagccc aaggctgccc cctcggtcac tctgttcccg 360
ccctcctctg aggagcttca agccaacaag gccacactgg tgtgtctcat aagtgacttc 420
tacccgggag ccgtgacagt ggcctggaag gcagatagca gccccgtcaa ggcgggagtg 480
gagaccacca caccctccaa acaaagcaac aacaagtacg cggccagcag ctatctgagc 540

ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgaaggg 600

agcaccgtgg agaagacagt ggcccctaca gaatgttca 639

<210> 75
<211> 1341
<212> DNA
<213> homo sapiens

<400> 75
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cccggcaagg gcctggagtg gatgggcatc atcgacccca ccgacagcca gaccgcctac 180

agccccagct tccagggcca ggtgaccatc agcgccgaca agagcatcag caccgcctac 240

ctgcagtgga gcagcctgaa ggccagcgac accgccatgt actactgcgc ccggtacatg 300

atgaggggct tcgaccactg gggtcagggc accctggtga ccgtcagctc agctagcacc 360

aagggcccca gcgtgttccc cctggccccc agcagcaaga gcacctccgg cggcacagcc 420

gccctgggct gcctggtgaa ggactacttc cccgagcccg tgaccgtgtc ctggaacagc 480

ggagccctga ccagcggcgt gcacaccttc cccgccgtgc tgcagagcag cggcctgtac 540

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aacgtgaacc acaagcccag caacaccaag gtggacaaga gagtggagcc caagagctgc 660

gacaagaccc acacctgccc ccctgccca gccccgaag ctgcaggcgg ccttccgtg 720

ttcctgttcc ccccaagcc caaggacacc ctgatgatca gcaggacccc cgaggtgacc 780

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agggtggtgt ccgtgctgac cgtgctgcac caggactggc tgaacggcaa agaatacaag 960

tgcaaggtct ccaacaaggc cctgcctgcc cccatcgaaa agaccatcag caaggccaag 1020

ggccagccac gggagcccca ggtgtacacc ctgccccctt ctcgggagga gatgaccaag 1080

aaccaggtgt ccctgacctg tctggtgaag ggcttctacc ccagcgacat cgccgtggag 1140

tgggagagca acggccagcc cgagaacaac tacaagacca cccccccagt gctggacagc 1200

gacggcagct tcttcctgta cagcaagctg accgtggaca agagcaggtg gcagcagggc 1260

aacgtgttca gctgcagcgt gatgcacgag gccctgcaca accactacac ccagaagagc 1320

ctgagcctgt cacccggcaa g 1341

<210> 76
<211> 639
<212> DNA
<213> homo sapiens

<400> 76
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agctgcagcg gcgacagcct gggcgactac tacgcctact ggtatcagca gaagccccggc 120

caggcccccg tgctggtgat ctacaaggac aacaacaggc ccagcggcat ccccgagagg 180

ttcagcggca gcaacagcgg caacaccgcc accctgacaa tcagcggcac ccaggccgag 240

gacgaggccg actactactg ccagacctgg gacaccggcg agtcaggcgt gttcggcgga 300

gggaccaagc tgaccgtgct gggtcagcct aaggctgccc ccagcgtgac cctgttcccc 360

cccagcagcg aggagctgca ggccaacaag gccaccctgg tgtgcctgat cagcgacttc 420

tacccaggcg ccgtgaccgt ggcctggaag gccgacagca gccccgtgaa ggccggcgtg 480

gagaccacca cccccagcaa gcagagcaac aacaagtacg ccgccagcag ctacctgagc 540

ctgacccccg agcagtggaa gagccacagg tcctacagct gccaggtgac ccacgagggc 600

agcaccgtgg aaaagaccgt ggccccaacc gagtgcagc 639

<210> 77
<211> 17
<212> PRT
<213> homo sapiens

<400> 77

Ile Ile Asp Pro Ser Asp Ser His Thr Thr Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 78
<211> 11
<212> PRT
<213> homo sapiens

<400> 78

Gln Thr Trp Asp Ile Leu Pro His Gly Leu Val
1 5 10

<210> 79
<211> 117
<212> PRT
<213> homo sapiens

<400> 79

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr

20 25 30

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

Gly Ile Ile Asp Pro Ser Asp Ser His Thr Thr Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 80
<211> 108
<212> PRT
<213> homo sapiens

<400> 80

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Ile Leu Pro His Gly
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 81

<211> 447
<212> PRT
<213> homo sapiens

<400> 81

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

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

Gly Ile Ile Asp Pro Ser Asp Ser His Thr Thr Tyr Ser Pro Ser Phe
    50                  55                  60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
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225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 82
<211> 214
<212> PRT
<213> homo sapiens

<400> 82

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln

eolf-seql

1 5 10 15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Ile Leu Pro His Gly
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 83
<211> 351
<212> DNA
<213> homo sapiens

<400> 83
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agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atcgatccgt ctgatagcca taccacttat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc a 351

<210> 84
<211> 324
<212> DNA
<213> homo sapiens

<400> 84
agttacgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttgg gatattcttc ctcatggtct tgtgtttggc 300

ggcggcacga agttaaccgt ccta 324

<210> 85
<211> 1341
<212> DNA
<213> homo sapiens

<400> 85
gaggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atcgatccgt ctgatagcca taccacttat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc agcctccacc 360

aagggtccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 600

aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt 660

gacaaaactc acacatgccc accgtgccca gcacctgaag cagcgggggg accgtcagtc 720

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tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1020

gggcagcccc gagaaccaca ggtgtacacc ctgccccccat cccgggagga gatgaccaag 1080

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1140

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gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320

ctctccctgt ctccgggtaa a 1341

<210> 86
<211> 642
<212> DNA
<213> homo sapiens

<400> 86
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tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttgg gatattcttc ctcatggtct tgtgtttggc 300

ggcggcacga agttaaccgt cctaggtcag cccaaggctg cccctcggt cactctgttc 360

ccgccctcct ctgaggagct tcaagccaac aaggccacac tggtgtgtct cataagtgac 420

ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgaa 600

gggagcaccg tggagaagac agtggccct acagaatgtt ca 642

<210> 87
<211> 1341
<212> DNA
<213> homo sapiens

<400> 87
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agctgcaagg gcagcggcta cagcttcacc agctactaca tcggctgggt gcggcagatg 120

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aagggcccca gcgtgttccc cctggccccc agcagcaaga gcacctccgg cggcacagcc 420

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aacgtgaacc acaagcccag caacaccaag gtggacaaga gagtggagcc caagagctgc 660

gacaagaccc acacctgccc ccctgccca gccccgaag ctgcaggcgg ccctccgtg 720

ttcctgttcc ccccaagcc caaggacacc ctgatgatca gcaggacccc cgaggtgacc 780

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aaccaggtgt ccctgacctg tctggtgaag ggcttctacc ccagcgacat cgccgtggag 1140

tgggagagca acggccagcc cgagaacaac tacaagacca ccccccccagt gctggacagc 1200

gacggcagct tcttcctgta cagcaagctg accgtggaca agagcaggtg gcagcagggc 1260

aacgtgttca gctgcagcgt gatgcacgag gccctgcaca accactacac ccagaagagc 1320

ctgagcctgt cacccggcaa g 1341

<210> 88
<211> 642
<212> DNA
<213> homo sapiens

<400> 88
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agctgcagcg gcgacagcct gggcgactac tacgcctact ggtatcagca gaagcccggc 120

caggcccccg tgctggtgat ctacaaggac aacaacaggc ccagcggcat ccccgagagg 180

ttcagcggca gcaacagcgg caacaccgcc accctgacaa tcagcggcac ccaggccgag 240

gacgaggccg actactactg ccagacttgg gatattcttc ctcatggtct tgtgttcggc 300

ggagggacca agctgaccgt gctgggtcag cctaaggctg cccccagcgt gaccctgttc 360

ccccccagca gcgaggagct gcaggccaac aaggccaccc tggtgtgcct gatcagcgac 420

ttctacccag gcgccgtgac cgtggcctgg aaggccgaca gcagccccgt gaaggccggc 480

gtggagacca ccaccccccag caagcagagc aacaacaagt acgccgccag cagctacctg 540

agcctgaccc ccgagcagtg gaagagccac aggtcctaca gctgccaggt gacccacgag 600

ggcagcaccg tggaaaagac cgtggcccca accgagtgca gc 642

<210> 89
<211> 11
<212> PRT
<213> homo sapiens

<400> 89

Gln Ala Trp Thr Asp Ser Pro Thr Gly Leu Val
1 5 10

<210> 90
<211> 108
<212> PRT
<213> homo sapiens

<400> 90

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Thr Asp Ser Pro Thr Gly
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 91
<211> 214
<212> PRT
<213> homo sapiens

<400> 91

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala

20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Thr Asp Ser Pro Thr Gly
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 92
<211> 324
<212> DNA
<213> homo sapiens

<400> 92
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tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccaggcttgg actgattctc ctactggtct tgtgtttggc 300

ggcggcacga agttaaccgt ccta 324

<210> 93
<211> 642
<212> DNA
<213> homo sapiens

<400> 93
agttacgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccaggcttgg actgattctc ctactggtct tgtgtttggc 300

ggcggcacga agttaaccgt cctaggtcag cccaaggctg cccccтcggt cactctgttc 360

ccgccctcct ctgaggagct tcaagccaac aaggccacac tggtgtgtct cataagtgac 420

ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgaa 600

gggagcaccg tggagaagac agtggccccт acagaatgtt ca 642

<210> 94
<211> 642
<212> DNA
<213> homo sapiens

<400> 94
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agctgcagcg gcgacagcct gggcgactac tacgcctact ggtatcagca gaagcccggc 120

caggcccccg tgctggtgat ctacaaggac aacaacaggc ccagcggcat ccccgagagg 180

ttcagcggca gcaacagcgg caacaccgcc accctgacaa tcagcggcac ccaggccgag 240

gacgaggccg actactactg ccaggcttgg actgattctc ctactggtct tgtgttcggc 300

ggagggacca agctgaccgt gctgggtcag cctaaggctg cccccagcgt gaccctgttc 360

ccccccagca gcgaggagct gcaggccaac aaggccaccc tggtgtgcct gatcagcgac 420

ttctacccag gcgccgtgac cgtggcctgg aaggccgaca gcagccccgt gaaggccggc 480

gtggagacca ccacccccag caagcagagc aacaacaagt acgccgccag cagctacctg 540

agcctgaccc ccgagcagtg gaagagccac aggtcctaca gctgccaggt gacccacgag 600

ggcagcaccg tggaaaagac cgtggccccа accgagtgca gc 642

<210> 95
<211> 17
<212> PRT
<213> homo sapiens

<400> 95

Ile Ile Asp Pro Thr Asp Ser Tyr Thr Val Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 96
<211> 117
<212> PRT
<213> homo sapiens

<400> 96

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Thr Asp Ser Tyr Thr Val Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 97
<211> 447
<212> PRT
<213> homo sapiens

<400> 97

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Thr Asp Ser Tyr Thr Val Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 98
<211> 353
<212> DNA
<213> homo sapiens

<400> 98
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agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt attgatccta ctgattctta tactgtttat 180

tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc agc 353

<210> 99
<211> 1343
<212> DNA
<213> homo sapiens

<400> 99
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cctgggaagg gtctcgagtg gatgggcatt attgatccta ctgattctta tactgtttat 180

tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc agcgcctcca 360

ccaagggtcc atcggtcttc cccctggcac cctcctccaa gagcacctct gggggcacag 420

cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg tcgtggaact 480

caggcgccct gaccagcggc gtgcacacct tcccggctgt cctacagtcc tcaggactct 540

actccctcag cagcgtggtg accgtgccct ccagcagctt gggcacccag acctacatct 600

gcaacgtgaa tcacaagccc agcaacacca aggtggacaa gagagttgag cccaaatctt 660

gtgacaaaac tcacacatgc ccaccgtgcc cagcacctga agcagcgggg ggaccgtcag 720

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catgcgtggt ggtggacgtg agccacgaag accctgaggt caagttcaac tggtacgtgg 840

acggcgtgga ggtgcataat gccaagacaa agccgcggga ggagcagtac aacagcacgt 900

accgggtggt cagcgtcctc accgtcctgc accaggactg gctgaatggc aaggagtaca 960

agtgcaaggt ctccaacaaa gccctcccag ccccatcga gaaaaccatc tccaaagcca 1020

aagggcagcc ccgagaacca caggtgtaca ccctgccccc atcccgggag gagatgacca 1080

agaaccaggt cagcctgacc tgcctggtca aaggcttcta tcccagcgac atcgccgtgg 1140

agtgggagag caatgggcag ccggagaaca actacaagac cacgcctccc gtgctggact 1200

ccgacggctc cttcttcctc tacagcaagc tcaccgtgga caagagcagg tggcagcagg 1260

ggaacgtctt ctcatgctcc gtgatgcatg aggctctgca caaccactac acgcagaaga 1320

gcctctccct gtctccgggt aaa 1343

<210> 100
<211> 1341
<212> DNA
<213> homo sapiens

<400> 100
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cccggcaagg gcctggagtg gatgggcatt attgatccta ctgattctta tactgtttat 180
tctccttctt ttcagggtca ggtgaccatc agcgccgaca agagcatcag caccgcctac 240
ctgcagtgga gcagcctgaa ggccagcgac accgccatgt actactgcgc ccggtacatg 300
atgaggggct tcgaccactg gggtcagggc accctggtga ccgtcagctc agctagcacc 360
aagggcccca gcgtgttccc cctggccccc agcagcaaga gcacctccgg cggcacagcc 420
gccctgggct gcctggtgaa ggactacttc cccgagcccg tgaccgtgtc ctggaacagc 480
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agcctgtcca gcgtggtgac agtgcccagc agcagcctgg gcacccagac ctacatctgc 600
aacgtgaacc acaagcccag caacaccaag gtggacaaga gagtggagcc caagagctgc 660
gacaagaccc acacctgccc ccctgcccca gccccccgaag ctgcaggcgg ccctttccgtg 720
ttcctgttcc ccccccaagcc caaggacacc ctgatgatca gcaggacccc cgaggtgacc 780
tgcgtggtgg tggacgtgag ccacgaggac ccagaggtga agttcaactg gtacgtggac 840
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agggtggtgt ccgtgctgac cgtgctgcac caggactggc tgaacggcaa agaatacaag 960
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aaccaggtgt ccctgacctg tctggtgaag ggcttctacc ccagcgacat cgccgtggag 1140
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gacggcagct tcttcctgta cagcaagctg accgtggaca agagcaggtg gcagcagggc 1260
aacgtgttca gctgcagcgt gatgcacgag gccctgcaca accactacac ccagaagagc 1320
ctgagcctgt cacccggcaa g 1341

<210> 101
<211> 10
<212> PRT
<213> homo sapiens

<400> 101

Ser Thr Trp Asp Ile Glu Pro Thr Tyr Val
1 5 10

<210> 102
<211> 107
<212> PRT
<213> homo sapiens

<400> 102

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ser Thr Trp Asp Ile Glu Pro Thr Tyr
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 103
<211> 213
<212> PRT
<213> homo sapiens

<400> 103

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ser Thr Trp Asp Ile Glu Pro Thr Tyr
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala

100 105 110

Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125

Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140

Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160

Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
165 170 175

Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
180 185 190

Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
195 200 205

Pro Thr Glu Cys Ser
210

<210> 104
<211> 321
<212> DNA
<213> homo sapiens

<400> 104
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tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ctctacttgg gatattgagc ctacttatgt gtttggcggc 300

ggcacgaagt taaccgtcct a 321

<210> 105
<211> 639
<212> DNA
<213> homo sapiens

<400> 105
agttacgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ctctacttgg gatattgagc ctacttatgt gtttggcggc 300

ggcacgaagt taaccgtcct aggtcagccc aaggctgccc cctcggtcac tctgttcccg 360

ccctcctctg aggagcttca agccaacaag gccacactgg tgtgtctcat aagtgacttc 420

tacccgggag ccgtgacagt ggcctggaag gcagatagca gccccgtcaa ggcgggagtg 480

gagaccacca caccctccaa acaaagcaac aacaagtacg cggccagcag ctatctgagc 540

ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgaaggg 600

agcaccgtgg agaagacagt ggcccctaca gaatgttca 639

<210> 106
<211> 639
<212> DNA
<213> homo sapiens

<400> 106
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agctgcagcg gcgacaatat cggcaacagc tacgtgcact ggtatcagca gaagcccggc 120

caggcccccg tgctggtgat ctacaaggac aacgacaggc ccagcggcat ccccgagagg 180

ttcagcggca gcaactccgg caacaccgcc accctgacaa tcagcggcac ccaggccgag 240

gacgaggccg actactactg ctctacttgg gatattgagc ctacttatgt gttcggcgga 300

gggaccaagc tgaccgtgct gggccagcct aaggctgccc ccagcgtgac cctgttcccc 360

cccagcagcg aggagctgca ggccaacaag gccaccctgg tgtgcctgat cagcgacttc 420

tacccaggcg ccgtgaccgt ggcctggaag gccgacagca gccccgtgaa ggccggcgtg 480

gagaccacca cccccagcaa gcagagcaac aacaagtacg ccgccagcag ctacctgagc 540

ctgacccccg agcagtggaa gagccacagg tcctacagct gccaggtgac ccacgagggc 600

agcaccgtgg aaaagaccgt ggccccaacc gagtgcagc 639

<210> 107
<211> 17
<212> PRT
<213> homo sapiens

<400> 107

Ile Ile Asp Pro Gln Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 108
<211> 116
<212> PRT

<213> homo sapiens

<400> 108

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Gln Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 109
<211> 446
<212> PRT
<213> homo sapiens

<400> 109

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Gln Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

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Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 110
<211> 348
<212> DNA
<213> homo sapiens

<400> 110
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agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctcagg attcttatac tgagtattct 180

ccttcttttc agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

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ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 111
<211> 1338
<212> DNA
<213> homo sapiens

<400> 111
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agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctcagg attcttatac tgagtattct 180

ccttcttttc agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc ctccaccaag 360

ggtccatcgg tcttcccccc ggcaccctcc tccaagagca cctctggggg cacagcggcc 420

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 480

gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc 540

ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac 600

gtgaatcaca agcccagcaa caccaaggtg gacaagagag ttgagcccaa atcttgtgac 660

aaaactcaca catgcccacc gtgcccagca cctgaagcag cgggggggacc gtcagtcttc 720

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggaccccctga ggtcacatgc 780

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gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 960

aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggg 1020

cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1080

caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg 1140

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac 1200

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320

tccctgtctc cgggtaaa 1338

<210> 112
<211> 1338
<212> DNA
<213> homo sapiens

<400> 112
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agctgcaagg gcagcggcta cagcttcacc aactacatca gctgggtgcg gcagatgccc 120

ggcaagggcc tggagtggat gggcatcatc gaccccccagg acagctacac cgagtacagc 180

cccagcttcc agggccaggt gaccatcagc gccgacaaga gcatcagcac cgcctacctg 240

cagtggagca gcctgaaggc cagcgacacc gccatgtact actgcgccag atacgagtac 300

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gccctgacca gcggcgtgca caccttcccc gccgtgctgc agagcagcgg cctgtacagc 540

ctgtccagcg tggtgacagt gcccagcagc agcctgggca cccagaccta catctgcaac 600

gtgaaccaca agcccagcaa caccaaggtg gacaagagag tggagcccaa gagctgcgac 660

aagacccaca cctgcccccc ctgcccagcc cccgaagctg caggcggccc ttccgtgttc 720

ctgttccccc ccaagcccaa ggacaccctg atgatcagca ggacccccga ggtgacctgc 780

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gtggaggtgc acaacgccaa gaccaagccc agagaggagc agtacaacag cacctacagg 900

gtggtgtccg tgctgaccgt gctgcaccag gactggctga acggcaaaga atacaagtgc 960

aaggtctcca acaaggccct gcctgccccc atcgaaaaga ccatcagcaa ggccaagggc 1020

cagccacggg agccccaggt gtacaccctg ccccctctc gggaggagat gaccaagaac 1080

caggtgtccc tgacctgtct ggtgaagggc ttctacccca gcgacatcgc cgtggagtgg 1140

gagagcaacg gccagcccga gaacaactac aagaccaccc ccccagtgct ggacagcgac 1200

ggcagcttct tcctgtacag caagctgacc gtggacaaga gcaggtggca gcagggcaac 1260

gtgttcagct gcagcgtgat gcacgaggcc ctgcacaacc actacaccca gaagagcctg 1320

agcctgtcac ccggcaag 1338

<210> 113
<211> 17
<212> PRT
<213> homo sapiens

<400> 113

Ile Ile Asp Pro Glu Asp Ser His Thr Glu Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 114
<211> 116
<212> PRT
<213> homo sapiens

<400> 114

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Glu Asp Ser His Thr Glu Tyr Ser Pro Ser Phe Gln

50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 115
<211> 446
<212> PRT
<213> homo sapiens

<400> 115

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Glu Asp Ser His Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly

145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

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Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 116
<211> 348
<212> DNA
<213> homo sapiens

<400> 116
gaggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctgagg attctcatac tgagtattct 180

ccttcttttc agggtcaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 117
<211> 1338
<212> DNA
<213> homo sapiens

<400> 117
gaggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctgagg attctcatac tgagtattct 180

ccttcttttc agggtcaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc ctccaccaag 360

ggtccatcgg tcttcccccc ggcaccctcc tccaagagca cctctggggg cacagcggcc 420

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 480

gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc 540

ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac 600

gtgaatcaca agcccagcaa caccaaggtg gacaagagag ttgagcccaa atcttgtgac 660

aaaactcaca catgcccacc gtgcccagca cctgaagcag cgggggggacc gtcagtcttc 720

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacatgc 780

gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 840

gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgg 900

gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 960

aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggg 1020

cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1080

caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg 1140

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac 1200

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320

tccctgtctc cgggtaaa 1338

<210> 118
<211> 1338
<212> DNA
<213> homo sapiens

<400> 118
gaggtgcagc tggtgcagag cggagccgag gtgaaaaagc ccggtgagag cctgaagatc 60

agctgcaagg gcagcggcta cagcttcacc aactacatca gctgggtgcg gcagatgccc 120

ggcaagggcc tggagtggat gggcatcatc gaccccgagg acagccatac cgagtacagc 180

cccagcttcc agggccaggt gaccatcagc gccgacaaga gcatcagcac cgcctacctg 240

cagtggagca gcctgaaggc cagcgacacc gccatgtact actgcgccag atacgagtac 300

ggcggcttcg acatctgggg ccagggcacc ctggtgaccg tcagctcagc tagcaccaag 360

ggccccagcg tgttccccct ggccccccagc agcaagagca cctccggcgg cacagccgcc 420

ctgggctgcc tggtgaagga ctacttcccc gagccccgtga ccgtgtcctg gaacagcgga 480

gccctgacca gcggcgtgca caccttcccc gccgtgctgc agagcagcgg cctgtacagc 540

ctgtccagcg tggtgacagt gcccagcagc agcctgggca cccagaccta catctgcaac 600

gtgaaccaca agcccagcaa caccaaggtg gacaagagag tggagcccaa gagctgcgac 660

aagacccaca cctgccccc ctgcccagcc cccgaagctg caggcggccc ttccgtgttc 720

ctgttccccc ccaagcccaa ggacaccctg atgatcagca ggacccccga ggtgacctgc 780

gtggtggtgg acgtgagcca cgaggaccca gaggtgaagt tcaactggta cgtggacggc 840

gtggaggtgc acaacgccaa gaccaagccc agagaggagc agtacaacag cacctacagg 900

gtggtgtccg tgctgaccgt gctgcaccag gactggctga acggcaaaga atacaagtgc 960

aaggtctcca acaaggccct gcctgccccc atcgaaaaga ccatcagcaa ggccaagggc 1020

cagccacggg agccccaggt gtacaccctg cccccttctc gggaggagat gaccaagaac 1080

caggtgtccc tgacctgtct ggtgaagggc ttctacccca gcgacatcgc cgtggagtgg 1140

gagagcaacg gccagcccga gaacaactac aagaccaccc ccccagtgct ggacagcgac 1200

ggcagcttct tcctgtacag caagctgacc gtggacaaga gcaggtggca gcagggcaac 1260

gtgttcagct gcagcgtgat gcacgaggcc ctgcacaacc actacaccca gaagagcctg 1320

agcctgtcac ccggcaag 1338

<210> 119
<211> 17
<212> PRT
<213> homo sapiens

<400> 119

Asn Ile Gly Pro Phe Phe Gly Ile Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 120
<211> 11
<212> PRT
<213> homo sapiens

<400> 120

Gln Thr Tyr Asp Asp Gly Ser Thr Ala Glu Val
1 5 10

<210> 121
<211> 116
<212> PRT
<213> homo sapiens

<400> 121

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

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

Gly Asn Ile Gly Pro Phe Phe Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 122
<211> 108
<212> PRT
<213> homo sapiens

<400> 122

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val
20 25 30

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

Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Asp Asp Gly Ser Thr Ala
85 90 95

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 123
<211> 442
<212> PRT
<213> homo sapiens

<400> 123

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

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

Gly Asn Ile Gly Pro Phe Phe Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe
180 185 190

Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro
210 215 220

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
225 230 235 240

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
245 250 255

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
260 265 270

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
275 280 285

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
290 295 300

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305 310 315 320

Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
325 330 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
340 345 350

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
355 360 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
370 375 380

Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe
385 390 395 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
405 410 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
420 425 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 124
<211> 214
<212> PRT
<213> homo sapiens

<400> 124

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val
20 25 30

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

Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Asp Asp Gly Ser Thr Ala
85 90 95

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 125
<211> 348
<212> DNA
<213> homo sapiens

<400> 125
caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60

agctgcaaag cctccggagg cacttttttct tcttatgcca tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcaat atcggtccgt tttttggcat tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300

ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 126
<211> 324
<212> DNA

<213> homo sapiens

<400> 126
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctat tcctaattat tatgtttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttat gatgatggtt ctactgctga ggtgtttggc 300

ggcggcacga agttaaccgt tctt 324

<210> 127
<211> 1326
<212> DNA
<213> homo sapiens

<400> 127
caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60

agctgcaaag cctccggagg cacttttttct tcttatgcca tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcaat atcggtccgt tttttggcat tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300

ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctcagc ttccaccaag 360

ggccccagcg tgttcccccct ggcccccctgc agcagaagca ccagcgagag cacagccgcc 420

ctgggctgcc tggtgaagga ctacttcccc gagcccgtga ccgtgagctg gaacagcgga 480

gccctgacca gcggcgtgca caccttcccc gccgtgctgc agagcagcgg cctgtacagc 540

ctgagcagcg tggtgaccgt gcccagcagc aacttcggca cccagaccta cacctgcaac 600

gtggaccaca agcccagcaa caccaaggtg gacaagaccg tggagcggaa gtgctgcgtg 660

gagtgccccc cctgccctgc ccctcctgtg gccggaccct ccgtgttcct gttcccccccc 720

aagcccaagg acaccctgat gatcagccgg acccccgagg tgacctgcgt ggtggtggac 780

gtgagccacg aggaccccga ggtgcagttc aactggtacg tggacggcgt ggaggtgcac 840

aacgccaaga ccaagccccg ggaggaacag ttcaacagca ccttccgggt ggtgtccgtg 900

ctgaccgtgg tgcaccagga ctggctgaac ggcaaagaat acaagtgcaa ggtgtccaac 960

aagggcctgc ctgccccccat cgagaaaacc atcagcaaga caaagggcca gcccagggaa 1020

ccccaggtgt acaccctgcc ccccagccgg gaggaaatga ccaagaacca ggtgtccctg 1080

acctgtctgg tgaagggctt ctaccccagc gacatcgccg tggagtggga gagcaacggc 1140

cagcccgaga acaactacaa gaccacccccc cccatgctgg acagcgacgg cagcttcttc 1200

ctgtacagca agctgacagt ggacaagagc cggtggcagc agggcaacgt gttcagctgc 1260

agcgtgatgc acgaggccct gcacaaccac tacacccaga agagcctgag cctgtccccc 1320

ggcaaa 1326

<210> 128
<211> 642
<212> DNA
<213> homo sapiens

<400> 128
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctat tcctaattat tatgtttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttat gatgatggtt ctactgctga ggtgtttggc 300

ggcggcacga agttaaccgt tcttggtcag cccaaggctg ccccctcggt cactctgttc 360

ccgccctcct ctgaggagct tcaagccaac aaggccacac tggtgtgtct cataagtgac 420

ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgaa 600

gggagcaccg tggagaagac agtggccccc acagaatgtt ca 642

<210> 129
<211> 1326
<212> DNA
<213> homo sapiens

<400> 129
caggtgcagc tggtgcagtc cggcgccgag gtgaagaagc ccggctcctc cgtgaaggtg 60

tcctgcaagg cctccggcgg caccttctcc tcctacgcca tctcctgggt gcggcaggcc 120

cccggccagg gcctggagtg gatgggcaac atcggccccc tcttcggcat cgccaactac 180

gcccagaagt tccagggccg ggtgaccatc accgccgacg agtccacctc caccgcctac 240

atggagctgt cctccctgcg gtccgaggac accgccgtgt actactgcgc ccgggacacc 300

ccctacttcg actactgggg ccagggcacc ctggtgaccg tgtcctccgc ctccaccaag 360

ggcccctccg tgttcccccc ggccccctgc tcccggtcca cctccgagtc caccgccgcc 420

ctgggctgcc tggtgaagga ctacttcccc gagcccgtga ccgtgtcctg gaactccggc 480

gccctgacct ccggcgtgca caccttcccc gccgtgctgc agtcctccgg cctgtactcc 540

ctgtcctccg tggtgaccgt gccctcctcc aacttcggca cccagaccta cacctgcaac 600

gtggaccaca agccctccaa caccaaggtg gacaagaccg tggagcggaa gtgctgcgtg 660

gagtgccccc cctgccccgc ccccccccgtg gccggccccct ccgtgttcct gttcccccccc 720

aagcccaagg acaccctgat gatctcccgg acccccgagg tgacctgcgt ggtggtggac 780

gtgtcccacg aggaccccga ggtgcagttc aactggtacg tggacggcgt ggaggtgcac 840

aacgccaaga ccaagccccg ggaggagcag ttcaactcca ccttccgggt ggtgtccgtg 900

ctgaccgtgg tgcaccagga ctggctgaac ggcaaggagt acaagtgcaa ggtgtccaac 960

aagggcctgc ccgccccccat cgagaagacc atctccaaga ccaagggcca gccccgggag 1020

ccccaggtgt acaccctgcc ccctcccgg gaggagatga ccaagaacca ggtgtccctg 1080

acctgcctgg tgaagggctt ctaccctcc gacatcgccg tggagtggga gtccaacggc 1140

cagcccgaga acaactacaa gaccacccccc cccatgctgg actccgacgg ctccttcttc 1200

ctgtactcca agctgaccgt ggacaagtcc cggtggcagc agggcaacgt gttctcctgc 1260

tccgtgatgc acgaggccct gcacaaccac tacacccaga agtccctgtc cctgtccccc 1320

ggcaag 1326

<210> 130
<211> 642
<212> DNA
<213> homo sapiens

<400> 130
gacatcgagc tgacccagcc ccctccgtg tccgtggccc ccggccagac cgcccggatc 60

tcctgctccg gcgactccat ccccaactac tacgtgtact ggtaccagca gaagcccggc 120

caggcccccg tgctggtgat ctacgacgac tccaaccggc cctccggcat ccccgagcgg 180

ttctccggct ccaactccgg caacaccgcc accctgacca tctccggcac ccaggccgag 240

gacgaggccg actactactg ccagacctac gacgacggct ccaccgccga ggtgttcggc 300

ggcggcacca agctgaccgt gctgggccag cctaaggctg cccccagcgt gaccctgttc 360

ccccccagca gcgaggagct gcaggccaac aaggccaccc tggtgtgcct gatcagcgac 420

ttctacccag gcgccgtgac cgtggcctgg aaggccgaca gcagccccgt gaaggccggc 480

gtggagacca ccaccccccag caagcagagc aacaacaagt acgccgccag cagctacctg 540

agcctgaccc ccgagcagtg gaagagccac aggtcctaca gctgccaggt gacccacgag 600

ggcagcaccg tggaaaagac cgtggcccca accgagtgca gc 642

<210> 131
<211> 5
<212> PRT
<213> homo sapiens

<400> 131

Ser Tyr Trp Ile Ser
1 5

<210> 132
<211> 17
<212> PRT
<213> homo sapiens

<400> 132

Ile Ile Asp Pro Asp Asp Ser Lys Thr Asn Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 133
<211> 8
<212> PRT
<213> homo sapiens

<400> 133

Arg Ser Tyr Tyr Pro Met Asp Tyr
1 5

<210> 134
<211> 15
<212> PRT
<213> homo sapiens

<400> 134

Thr Gly Thr Ser Ser Asp Val Val Gly Val Tyr Asn Phe Val Ser
1 5 10 15

<210> 135
<211> 7
<212> PRT
<213> homo sapiens

<400> 135

Tyr Val Asp Asn Arg Pro Ser
1 5

<210> 136
<211> 11
<212> PRT
<213> homo sapiens

<400> 136

Gln Ser Phe Asp Gly Phe Gly Ile Asp Met Val
1 5 10

<210> 137
<211> 117

<212> PRT
<213> homo sapiens

<400> 137

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Asp Asp Ser Lys Thr Asn Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Ser Tyr Tyr Pro Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 138
<211> 112
<212> PRT
<213> homo sapiens

<400> 138

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Val Gly Val
20 25 30

Tyr Asn Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys
35 40 45

Leu Met Ile Tyr Tyr Val Asp Asn Arg Pro Ser Gly Val Ser Asn Arg
50 55 60

Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly
65 70 75 80

Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Gly
85 90 95

Phe Gly Ile Asp Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 139
<211> 220
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (220)..(220)
<223> X can be C, EF, or CEF

<400> 139

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Asp Asp Ser Lys Thr Asn Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Ser Tyr Tyr Pro Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser

165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215 220

<210> 140
<211> 217
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (217)..(217)
<223> X can be CS or A

<400> 140

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Val Gly Val
20 25 30

Tyr Asn Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys
35 40 45

Leu Met Ile Tyr Tyr Val Asp Asn Arg Pro Ser Gly Val Ser Asn Arg
50 55 60

Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly
65 70 75 80

Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Gly
85 90 95

Phe Gly Ile Asp Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
115 120 125

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
130 135 140

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
145 150 155 160

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
165 170 175

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
180 185 190

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
195 200 205

Glu Lys Thr Val Ala Pro Thr Glu Xaa
210 215

<210> 141
<211> 351
<212> DNA
<213> homo sapiens

<400> 141
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattgga tttcttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atcgatccgg atgatagcaa gaccaattat 180

tctccgagct tcagggccca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtcgttct 300

tattatccta tggattattg gggccaaggc accctggtga cggttagctc a 351

<210> 142
<211> 336
<212> DNA
<213> homo sapiens

<400> 142
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttgtt ggtgtttata attttgtgtc ttggtaccag 120

cagcatcccg ggaaggcgcc gaaacttatg atttattatg ttgataatcg tccctcaggc 180

gtgagcaacc gttttagcgg atccaaaagc ggcaacaccg cgagcctgac cattagcggc 240

ctgcaagcgg aagacgaagc ggattattat tgccagtctt ttgatggttt tggtattgat 300

atggtgtttg gcggcggcac gaagttaacc gttctt 336

<210> 143
<211> 658
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (658)..(658)
<223> n can be TGC, GAATTC, or TGCGAATTC

<400> 143
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattgga tttcttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atcgatccgg atgatagcaa gaccaattat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtcgttct 300

tattatccta tggattattg gggccaaggc accctggtga cggttagctc agcgtcgacc 360

aaaggtccaa gcgtgtttcc gctggctccg agcagcaaaa gcaccagcgg cggcacggct 420

gccctgggct gcctggttaa agattatttc ccggaaccag tcaccgtgag ctggaacagc 480

ggggcgctga ccagcggcgt gcatacctt ccggcggtgc tgcaaagcag cggcctgtat 540

agcctgagca gcgttgtgac cgtgccgagc agcagcttag gcactcagac ctatatttgc 600

aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagtggaacc gaaaagcn 658

<210> 144
<211> 649
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (649)..(649)
<223> n can be TGCAGC or GCC

<400> 144
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttgtt ggtgtttata attttgtgtc ttggtaccag 120

cagcatcccg ggaaggcgcc gaaacttatg atttattatg ttgataatcg tccctcaggc 180

gtgagcaacc gttttagcgg atccaaaagc ggcaacaccg cgagcctgac cattagcggc 240

ctgcaagcgg aagacgaagc ggattattat tgccagtctt ttgatggttt tggtattgat 300

atggtgtttg gcggcggcac gaagttaacc gttcttggcc agccgaaagc cgcaccgagt 360

gtgacgctgt ttccgccgag cagcgaagaa ttgcaggcga acaaagcgac cctggtgtgc 420

ctgattagcg acttttatcc gggagccgtg acagtggcct ggaaggcaga tagcagcccc 480

gtcaaggcgg gagtggagac caccacaccc tccaaacaaa gcaacaacaa gtacgcggcc 540

agcagctatc tgagcctgac gcctgagcag tggaagtccc acagaagcta cagctgccag 600

gtcacgcatg aggggagcac cgtggaaaaa accgttgcgc cgactgagn 649

<210> 145
<211> 5
<212> PRT
<213> homo sapiens

<400> 145

Ser Tyr Trp Ile Ala
1 5

<210> 146
<211> 17
<212> PRT
<213> homo sapiens

<400> 146

Ile Ile Tyr Pro Gly Asp Ser Asp Thr Asn Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 147
<211> 8
<212> PRT
<213> homo sapiens

<400> 147

Ser Lys Tyr Gly Ser Phe Asp Tyr
1 5

<210> 148
<211> 14
<212> PRT
<213> homo sapiens

<400> 148

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 149
<211> 7
<212> PRT
<213> homo sapiens

<400> 149

Asn Val Asn Ser Arg Pro Ser
1 5

<210> 150

<211> 11
<212> PRT
<213> homo sapiens

<400> 150

Gln Ser Tyr Asp Asp Gly Gln Asp Asn Glu Val
1 5 10

<210> 151
<211> 117
<212> PRT
<213> homo sapiens

<400> 151

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Asn Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Ser Lys Tyr Gly Ser Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 152
<211> 111
<212> PRT
<213> homo sapiens

<400> 152

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asn Val Asn Ser Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Asp Gly
85 90 95

Gln Asp Asn Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 153
<211> 220
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (220)..(220)
<223> X can be C, EF, or CEF

<400> 153

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Asn Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Ser Lys Tyr Gly Ser Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu

115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215 220

<210> 154
<211> 216
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (216)..(216)
<223> X can be CS or A

<400> 154

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asn Val Asn Ser Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Asp Gly
85 90 95

Gln Asp Asn Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
115 120 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
130 135 140

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

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
165 170 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180 185 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205

Lys Thr Val Ala Pro Thr Glu Xaa
210 215

<210> 155
<211> 351
<212> DNA
<213> homo sapiens

<400> 155
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattgga ttgcttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atctatccgg gtgatagcga taccaattat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttctaag 300

tatggttctt ttgattattg gggccaaggc accctggtga cggttagctc a 351

<210> 156
<211> 333
<212> DNA
<213> homo sapiens

<400> 156
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt ggttataatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tataatgtta attctcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc cagtcttatg atgatggtca ggataatgag 300

gtgtttggcg gcggcacgaa gttaaccgtt ctt 333

<210> 157
<211> 658
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (658)..(658)
<223> n can be TGC, GAATTC, or TGCGAATTC

<400> 157
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattgga ttgcttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atctatccgg gtgatagcga taccaattat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttctaag 300

tatggttctt ttgattattg gggccaaggc accctggtga cggttagctc agcgtcgacc 360

aaaggtccaa gcgtgtttcc gctggctccg agcagcaaaa gcaccagcgg cggcacggct 420

gccctgggct gcctggttaa agattatttc ccggaaccag tcaccgtgag ctggaacagc 480

ggggcgctga ccagcggcgt gcataccttt ccggcggtgc tgcaaagcag cggcctgtat 540

agcctgagca gcgttgtgac cgtgccgagc agcagcttag gcactcagac ctatatttgc 600

aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagtggaacc gaaaagcn 658

<210> 158
<211> 646
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (646)..(646)
<223> n can be TGCAGC or GCC

<400> 158
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt ggttataatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tataatgtta attctcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc cagtcttatg atgatggtca ggataatgag 300

gtgtttggcg gcggcacgaa gttaaccgtt cttggccagc cgaaagccgc accgagtgtg 360

acgctgtttc cgccgagcag cgaagaattg caggcgaaca aagcgaccct ggtgtgcctg 420

attagcgact tttatccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 480

aaggcgggag tggagaccac cacaccctcc aaacaaagca acaacaagta cgcggccagc 540

agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc 600

acgcatgagg ggagcaccgt ggaaaaaacc gttgcgccga ctgagn 646

<210> 159
<211> 5
<212> PRT
<213> homo sapiens

<400> 159

Ser Tyr Ala Met His
1 5

<210> 160
<211> 17
<212> PRT
<213> homo sapiens

<400> 160

Ala Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 161
<211> 7
<212> PRT
<213> homo sapiens

<400> 161

Glu Ser Trp Phe Leu Asp Leu
1 5

<210> 162
<211> 11
<212> PRT
<213> homo sapiens

<400> 162

Arg Ala Ser Gln Ser Ile Ser Asn Trp Leu Ala
1 5 10

<210> 163
<211> 7
<212> PRT
<213> homo sapiens

<400> 163

Leu Ala Ser Ser Leu Gln Ser
1 5

<210> 164
<211> 9
<212> PRT
<213> homo sapiens

<400> 164

Gln Gln Tyr Tyr Asp Phe Ser Asp Thr
1 5

<210> 165
<211> 116
<212> PRT
<213> homo sapiens

<400> 165

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Thr Val Ser Ser
115

<210> 166
<211> 107

<212> PRT
<213> homo sapiens

<400> 166

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asn Trp
20 25 30

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

Tyr Leu Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asp Phe Ser Asp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 167
<211> 219
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (219)..(219)
<223> X can be C, EF, or CEF

<400> 167

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

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

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215

<210> 168
<211> 214
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (214)..(214)
<223> X can be C or A

<400> 168

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asn Trp
20 25 30

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

Tyr Leu Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asp Phe Ser Asp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Xaa
210

<210> 169
<211> 348
<212> DNA
<213> homo sapiens

<400> 169
caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttact tcttatgcta tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct atctcttctt ctggtagctc tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgagtct 300

tggtttcttg atcttttggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 170
<211> 321
<212> DNA
<213> homo sapiens

<400> 170
gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gtctatttct aattggctgg cttggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatctt gcttcttctt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cggtttatta ttgccagcag tattatgatt tttctgatac ctttggccag 300

ggtacgaaag ttgaaattaa a 321

<210> 171
<211> 655
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (655)..(655)
<223> n can be TGC, TAATTC, or TGCGAATTC

<400> 171
caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttact tcttatgcta tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct atctcttctt ctggtagctc tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgagtct 300

tggtttcttg atctttgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360

ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420

ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg 480

gcgctgacca gcggcgtgca taccttccg gcggtgctgc aaagcagcgg cctgtatagc 540

ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600

gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagcn 655

<210> 172
<211> 640
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature

<222> (640)..(640)
<223> n can be TGC or GCC

<400> 172
gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gtctatttct aattggctgg cttggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatctt gcttcttctt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cggtttatta ttgccagcag tattatgatt tttctgatac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacggtg gctgctccga gcgtgtttat ttttccgccg 360

agcgatgaac aactgaaaag cggcacggcg agcgtggtgt gcctgctgaa caacttttat 420

ccgcgtgaag cgaaagttca gtggaaagta gacaacgcgc tgcaaagcgg caacagccag 480

gaaagcgtga ccgaacagga tagcaaagat agcacctatt ctctgagcag caccctgacc 540

ctgagcaaag cggattatga aaaacataaa gtgtatgcgt gcgaagtgac ccatcaaggt 600

ctgagcagcc cggtgactaa atcttttaat cgtggcgagn 640

<210> 173
<211> 5
<212> PRT
<213> homo sapiens

<400> 173

Asn Tyr Gly Met His
1 5

<210> 174
<211> 16
<212> PRT
<213> homo sapiens

<400> 174

Val Ser Tyr Ala Gly Ser Phe Thr Asn Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> 175
<211> 12
<212> PRT
<213> homo sapiens

<400> 175

Ser Trp Leu Phe Gly Tyr Pro Asp Ile Phe Asp Tyr
1 5 10

<210> 176
<211> 14
<212> PRT

<213> homo sapiens

<400> 176

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 177
<211> 7
<212> PRT
<213> homo sapiens

<400> 177

Asp Val Asn Asn Arg Pro Ser
1 5

<210> 178
<211> 9
<212> PRT
<213> homo sapiens

<400> 178

Ser Ser Tyr Asp Lys Phe Gln Thr Val
1 5

<210> 179
<211> 120
<212> PRT
<213> homo sapiens

<400> 179

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ser Tyr Ala Gly Ser Phe Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Ser Trp Leu Phe Gly Tyr Pro Asp Ile Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 180
<211> 109
<212> PRT
<213> homo sapiens

<400> 180

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Asn Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Lys Phe
85 90 95

Gln Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 181
<211> 223
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (223)..(223)
<223> X can be C, EF, or CEF

<400> 181

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35 40 45

Ser Val Ser Tyr Ala Gly Ser Phe Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Ser Trp Leu Phe Gly Tyr Pro Asp Ile Phe Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

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

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215 220

<210> 182
<211> 214
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (214)..(214)
<223> X can be CS or A

<400> 182

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

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Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Asn Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Lys Phe
85 90 95

Gln Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
100 105 110

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
115 120 125

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
165 170 175

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180 185 190

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
195 200 205

Val Ala Pro Thr Glu Xaa
210

<210> 183
<211> 360
<212> DNA
<213> homo sapiens

<400> 183
caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct aattatggta tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgtt tcttatgctg gtagctttac caattatgcg 180

gatagcgtga aaggccgttt taccatttca cgtgataatt cgaaaaacac cctgtatctg 240

caaatgaaca gcctgcgtgc ggaagatacg gccgtgtatt attgcgcgcg ttcttggctt 300

tttggttatc ctgatatttt tgattattgg ggccaaggca ccctggtgac ggttagctca 360

<210> 184
<211> 327
<212> DNA
<213> homo sapiens

<400> 184
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt ggttataatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tcttcttatg ataagtttca gactgtgttt 300

ggcggcggca cgaagttaac cgttctt 327

<210> 185
<211> 667
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (667)..(667)
<223> n can be TGC, TAATTC, or TGCGAATTC

<400> 185
caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct aattatggta tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgtt tcttatgctg gtagctttac caattatgcg 180

gatagcgtga aaggccgttt taccatttca cgtgataatt cgaaaaacac cctgtatctg 240

caaatgaaca gcctgcgtgc ggaagatacg gccgtgtatt attgcgcgcg ttcttggctt 300

tttggttatc ctgatatttt tgattattgg ggccaaggca ccctggtgac ggttagctca 360

gcgtcgacca aaggtccaag cgtgtttccg ctggctccga gcagcaaaag caccagcggc 420

ggcacggctg ccctgggctg cctggttaaa gattatttcc cggaaccagt caccgtgagc 480

tggaacagcg gggcgctgac cagcggcgtg cataccttc cggcggtgct gcaaagcagc 540

ggcctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc 600

tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtggaaccg 660

aaaagcn 667

<210> 186
<211> 640
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (640)..(640)
<223> n can be TGCAGC or GCC

<400> 186
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt ggttataatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tcttcttatg ataagtttca gactgtgttt 300

ggcggcggca cgaagttaac cgttcttggc cagccgaaag ccgcaccgag tgtgacgctg 360

tttccgccga gcagcgaaga attgcaggcg aacaaagcga ccctggtgtg cctgattagc 420

gacttttatc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg 480

ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540

ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat 600

gaggggagca ccgtggaaaa aaccgttgcg ccgactgagn 640

<210> 187
<211> 116
<212> PRT
<213> homo sapiens

<400> 187

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

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

Gly Gly Ile Gly Pro Phe Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 188
<211> 108
<212> PRT
<213> homo sapiens

<400> 188

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val
20 25 30

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

Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Ser Ser Leu Asn Ala
85 90 95

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 189
<211> 219
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (219)..(219)
<223> X can be C, EF, or CEF

<400> 189

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

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

Gly Gly Ile Gly Pro Phe Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215

<210> 190
<211> 213
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (213)..(213)

<223> X can be CS or A

<400> 190

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val
20 25 30

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

Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Ser Ser Leu Asn Ala
85 90 95

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Xaa
210

<210> 191
<211> 348
<212> DNA

<213> homo sapiens

<400> 191
caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60

agctgcaaag cctccggagg cacttttttct tcttatgcca tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcggt atcggtccgt tttttggcac tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300

ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 192
<211> 324
<212> DNA
<213> homo sapiens

<400> 192
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctat tcctaattat tatgtttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtctttt gattcttctc ttaatgctga ggtgtttggc 300

ggcggcacga agttaaccgt tctt 324

<210> 193
<211> 655
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (655)..(655)
<223> n can be TGC, GAATTC, or TGCGAATTC

<400> 193
caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60

agctgcaaag cctccggagg cacttttttct tcttatgcca tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcggt atcggtccgt tttttggcac tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300

ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360

ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420

ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg 480

gcgctgacca gcggcgtgca tacctttccg gcggtgctgc aaagcagcgg cctgtatagc 540

ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600

gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagcn 655

<210> 194
<211> 637
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (637)..(637)
<223> n can be TGCAGC or GCC

<400> 194
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctat tcctaattat tatgtttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtctttt gattcttctc ttaatgctga ggtgtttggc 300

ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt 360

ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac 420

ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600

gggagcaccg tggaaaaaac cgttgcgccg actgagn 637

<210> 195
<211> 5
<212> PRT
<213> homo sapiens

<400> 195

Ser Tyr Tyr Ile Ser
1 5

<210> 196
<211> 17
<212> PRT
<213> homo sapiens

<400> 196

Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 197
<211> 19
<212> PRT
<213> homo sapiens

<400> 197

Gly Glu Ile Trp His Val His Gln Pro Tyr Lys Ser Gly Val Tyr Gly
1 5 10 15

Ala Ala Tyr

<210> 198
<211> 11
<212> PRT
<213> homo sapiens

<400> 198

Arg Ala Ser Gln Gly Ile Ser Asn Trp Leu Asn
1 5 10

<210> 199
<211> 7
<212> PRT
<213> homo sapiens

<400> 199

Gly Thr Ser Ser Leu Gln Ser
1 5

<210> 200
<211> 9
<212> PRT
<213> homo sapiens

<400> 200

Gln Gln Leu Asp Ser Phe Pro Ala Thr
1 5

<210> 201
<211> 128
<212> PRT
<213> homo sapiens

<400> 201

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Glu Ile Trp His Val His Gln Pro Tyr Lys Ser Gly Val
100 105 110

Tyr Gly Ala Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 202
<211> 107
<212> PRT
<213> homo sapiens

<400> 202

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Trp
20 25 30

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

Tyr Gly Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asp Ser Phe Pro Ala
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 203
<211> 231
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (231)..(231)
<223> X can be C, EF, or CEF

<400> 203

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30

Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Glu Ile Trp His Val His Gln Pro Tyr Lys Ser Gly Val
            100                 105                 110

Tyr Gly Ala Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
    130                 135                 140

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
                165                 170                 175

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
            180                 185                 190

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
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195 200 205

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
210 215 220

Lys Val Glu Pro Lys Ser Xaa
225 230

<210> 204
<211> 214
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (214)..(214)
<223> X can be C or A

<400> 204

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 Gly Ile Ser Asn Trp
20 25 30

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

Tyr Gly Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asp Ser Phe Pro Ala
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Xaa
210

<210> 205
<211> 384
<212> DNA
<213> homo sapiens

<400> 205
caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60

agctgcaaag cctccggagg cacttttttct tcttattata tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcggt atcattccga tttttggcac tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtggtgag 300

atttggcatg ttcatcagcc ttataagtct ggtgtttatg gtgctgctta ttggggccaa 360

ggcaccctgg tgacggttag ctca 384

<210> 206
<211> 321
<212> DNA
<213> homo sapiens

<400> 206
gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gggtatttct aattggctga attggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatggt acttcttctt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cgacttatta ttgccagcag cttgattctt ttcctgctac ctttggccag 300

ggtacgaaag ttgaaattaa a 321

<210> 207
<211> 691
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (691)..(691)
<223> n can be TGC, GAATTC, or TGCGAATTC

<400> 207
caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60

agctgcaaag cctccggagg cacttttttct tcttattata tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcggt atcattccga tttttggcac tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtggtgag 300

atttggcatg ttcatcagcc ttataagtct ggtgtttatg gtgctgctta ttggggccaa 360

ggcaccctgg tgacggttag ctcagcgtcg accaaaggtc caagcgtgtt tccgctggct 420

ccgagcagca aaagcaccag cggcggcacg gctgccctgg gctgcctggt taaagattat 480

ttcccggaac cagtcaccgt gagctggaac agcggggcgc tgaccagcgg cgtgcatacc 540

tttccggcgg tgctgcaaag cagcggcctg tatagcctga gcagcgttgt gaccgtgccg 600

agcagcagct taggcactca gacctatatt tgcaacgtga accataaacc gagcaacacc 660

aaagtggata aaaaagtgga accgaaaagc n 691

<210> 208
<211> 640
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (640)..(640)
<223> n can be TGC or GCC

<400> 208
gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gggtatttct aattggctga attggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatggt acttcttctt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cgacttatta ttgccagcag cttgattctt ttcctgctac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacggtg gctgctccga gcgtgtttat ttttccgccg 360

agcgatgaac aactgaaaag cggcacggcg agcgtggtgt gcctgctgaa caacttttat 420

ccgcgtgaag cgaaagttca gtggaaagta gacaacgcgc tgcaaagcgg caacagccag 480

gaaagcgtga ccgaacagga tagcaaagat agcacctatt ctctgagcag caccctgacc 540

ctgagcaaag cggattatga aaaacataaa gtgtatgcgt gcgaagtgac ccatcaaggt 600

ctgagcagcc cggtgactaa atcttttaat cgtggcgagn 640

<210> 209
<211> 11
<212> PRT
<213> homo sapiens

<400> 209

Gln Ser Trp Thr Asp Ser Pro Asn Thr Leu Val
1 5 10

<210> 210
<211> 117
<212> PRT
<213> homo sapiens

<400> 210

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Ser Asp Ser His Thr Thr Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 211
<211> 108
<212> PRT
<213> homo sapiens

<400> 211

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Thr Asp Ser Pro Asn Thr
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 212
<211> 220
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (220)..(220)
<223> X can be C, EF, or CEF

<400> 212

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Ser Asp Ser His Thr Thr Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu

100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215 220

<210> 213
<211> 213
<212>. PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (213)..(213)
<223> X can be CS or A

<400> 213

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Thr Asp Ser Pro Asn Thr
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Xaa
210

<210> 214
<211> 351
<212> DNA
<213> homo sapiens

<400> 214
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atcgatccgt ctgatagcca taccacttat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc a 351

<210> 215
<211> 324
<212> DNA
<213> homo sapiens

<400> 215
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttgg actgattctc ctaatactct tgtgtttggc 300

ggcggcacga agttaaccgt tctt 324

<210> 216
<211> 658
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (658)..(658)
<223> n can be TGC, GAATTC, or TGCGAATTC

<400> 216
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atcgatccgt ctgatagcca taccacttat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc agcgtcgacc 360

aaaggtccaa gcgtgtttcc gctggctccg agcagcaaaa gcaccagcgg cggcacggct 420

gccctgggct gcctggttaa agattatttc ccggaaccag tcaccgtgag ctggaacagc 480

ggggcgctga ccagcggcgt gcataccttt ccggcggtgc tgcaaagcag cggcctgtat 540

agcctgagca gcgttgtgac cgtgccgagc agcagcttag gcactcagac ctatatttgc 600

aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagtggaacc gaaaagcn 658

<210> 217
<211> 637
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (637)..(637)
<223> n can be TGCAGC or GCC

<400> 217
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttgg actgattctc ctaatactct tgtgtttggc 300

ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt 360

ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac 420

ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600

gggagcaccg tggaaaaaac cgttgcgccg actgagn 637

<210> 218
<211> 116
<212> PRT
<213> homo sapiens

<400> 218

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 219
<211> 106
<212> PRT
<213> homo sapiens

<400> 219

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Tyr Asp Ile Glu Ser Tyr Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 220
<211> 219
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (219)..(219)
<223> X can be C, EF, or CEF

<400> 220

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215

<210> 221
<211> 211
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (211)..(211)
<223> X can be CS or A

<400> 221

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Tyr Asp Ile Glu Ser Tyr Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125

Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140

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

Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175

Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190

Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205

Thr Glu Xaa
210

<210> 222
<211> 348
<212> DNA
<213> homo sapiens

<400> 222
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatc gatccggatg atagctatac cgttattct 180

ccgagctttc agggacaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 223
<211> 318

<212> DNA
<213> homo sapiens

<400> 223
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cggtacttat gatattgagt cttatgtgtt tggcggcggc 300

acgaagttaa ccgttctt 318

<210> 224
<211> 655
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (655)..(655)
<223> n can be TGC, GAATTC, or TGCGAATTC

<400> 224
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatc gatccggatg atagctatac ccgttattct 180

ccgagctttc agggacaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360

ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420

ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg 480

gcgctgacca gcggcgtgca taccttttcg gcggtgctgc aaagcagcgg cctgtatagc 540

ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600

gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagcn 655

<210> 225
<211> 631
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (631)..(631)
<223> n can be TGCAGC or GCC

<400> 225
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cggtacttat gatattgagt cttatgtgtt tggcggcggc 300

acgaagttaa ccgttcttgg ccagccgaaa gccgcaccga gtgtgacgct gtttccgccg 360

agcagcgaag aattgcaggc gaacaaagcg accctggtgt gcctgattag cgacttttat 420

ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag 480

accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg 540

acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaggggagc 600

accgtggaaa aaaccgttgc gccgactgag n 631

<210> 226
<211> 16
<212> PRT
<213> homo sapiens

<400> 226

His Ile Phe Ser Asp Asp Asp Lys Tyr Tyr Ser Thr Ser Leu Lys Thr
1 5 10 15

<210> 227
<211> 117
<212> PRT
<213> homo sapiens

<400> 227

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

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

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

Trp Leu Ala His Ile Phe Ser Asp Asp Asp Lys Tyr Tyr Ser Thr Ser
50 55 60

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr

85 90 95

Cys Ala Arg Gly Pro Tyr Gly Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 228
<211> 109
<212> PRT
<213> homo sapiens

<400> 228

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Thr Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Asp Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Gln
85 90 95

Ser Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 229
<211> 220
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (220)..(220)
<223> X can be C, EF, or CEF

<400> 229

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

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Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30

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

Trp Leu Ala His Ile Phe Ser Asp Asp Asp Lys Tyr Tyr Ser Thr Ser
    50                  55                  60

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Gly Pro Tyr Gly Phe Asp Ser Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
    210                 215                 220
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<210> 230
<211> 214
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (214)..(214)
<223> X can be CS or A

<400> 230

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Thr Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Asp Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Gln
85 90 95

Ser Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
100 105 110

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
115 120 125

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
165 170 175

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180 185 190

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
195 200 205

Val Ala Pro Thr Glu Xaa
210

<210> 231
<211> 351
<212> DNA
<213> homo sapiens

<400> 231
caggtgcaat tgaaagaaag cggcccggcc ctggtgaaac cgacccaaac cctgaccctg 60
acctgtacct tttccggatt tagcctgtct acttctggtg gtggtgtgtc ttggattcgc 120
cagccgcctg ggaaagccct cgagtggctg gctcatatct tttctgatga tgataagtat 180
tatagcacca gcctgaaaac gcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240
gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgtggt 300
ccttatggtt ttgattcttg gggccaaggc accctggtga cggttagctc a 351

<210> 232
<211> 327
<212> DNA
<213> homo sapiens

<400> 232
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60
tcgtgtacgg gtactagcag cgatattggt acttataatt atgtgtcttg gtaccagcag 120
catcccggga aggcgccgaa acttatgatt tatgatgatt ctaatcgtcc ctcaggcgtg 180
agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
caagcggaag acgaagcgga ttattattgc cagtcttatg attctcagtc tattgtgttt 300
ggcggcggca cgaagttaac cgttctt 327

<210> 233
<211> 658
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (658)..(658)
<223> n can be TGC, GAATTC, or TGCGAATTC

<400> 233
caggtgcaat tgaaagaaag cggcccggcc ctggtgaaac cgacccaaac cctgaccctg 60
acctgtacct tttccggatt tagcctgtct acttctggtg gtggtgtgtc ttggattcgc 120
cagccgcctg ggaaagccct cgagtggctg gctcatatct tttctgatga tgataagtat 180
tatagcacca gcctgaaaac gcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240
gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgtggt 300
ccttatggtt ttgattcttg gggccaaggc accctggtga cggttagctc agcgtcgacc 360
aaaggtccaa gcgtgttttc gctggctccg agcagcaaaa gcaccagcgg cggcacggct 420
gccctgggct gcctggttaa agattatttc ccggaaccag tcaccgtgag ctggaacagc 480
ggggcgctga ccagcggcgt gcataccttt ccggcggtgc tgcaaagcag cggcctgtat 540

agcctgagca gcgttgtgac cgtgccgagc agcagcttag gcactcagac ctatatttgc 600

aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagtggaacc gaaaagcn 658

<210> 234
<211> 640
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (640)..(640)
<223> n can be TGCAGC or GCC

<400> 234
gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatattggt acttataatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgatt ctaatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc cagtcttatg attctcagtc tattgtgttt 300

ggcggcggca cgaagttaac cgttcttggc cagccgaaag ccgcaccgag tgtgacgctg 360

tttccgccga gcagcgaaga attgcaggcg aacaaagcga ccctggtgtg cctgattagc 420

gacttttatc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg 480

ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540

ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat 600

gaggggagca ccgtggaaaa aaccgttgcg ccgactgagn 640

<210> 235
<211> 7
<212> PRT
<213> homo sapiens

<400> 235

Thr Ser Gly Met Ser Val Gly
1 5

<210> 236
<211> 16
<212> PRT
<213> homo sapiens

<400> 236

Leu Ile Asp Trp Asp Glu Asp Lys Ser Tyr Ser Thr Ser Leu Lys Thr
1 5 10 15

<210> 237

<211> 11
<212> PRT
<213> homo sapiens

<400> 237

Tyr Asn Trp Tyr Asn Pro Pro Gly Phe Asp Asn
1 5 10

<210> 238
<211> 13
<212> PRT
<213> homo sapiens

<400> 238

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Tyr Val Ser
1 5 10

<210> 239
<211> 7
<212> PRT
<213> homo sapiens

<400> 239

Arg Asn Asp Lys Arg Pro Ser
1 5

<210> 240
<211> 9
<212> PRT
<213> homo sapiens

<400> 240

Gln Ser Ala Asp Ser Ser Ser Met Val
1 5

<210> 241
<211> 121
<212> PRT
<213> homo sapiens

<400> 241

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

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

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

Trp Leu Ala Leu Ile Asp Trp Asp Glu Asp Lys Ser Tyr Ser Thr Ser

50 55 60

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Tyr Asn Trp Tyr Asn Pro Pro Gly Phe Asp Asn Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 242
<211> 108
<212> PRT
<213> homo sapiens

<400> 242

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

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Arg Asn Asp Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Ala Asp Ser Ser Ser
85 90 95

Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 243
<211> 224
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (224)..(224)

<223> X can be C, EF, or CEF

<400> 243

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

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

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

Trp Leu Ala Leu Ile Asp Trp Asp Glu Asp Lys Ser Tyr Ser Thr Ser
50 55 60

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Tyr Asn Trp Tyr Asn Pro Pro Gly Phe Asp Asn Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215 220

<210> 244
<211> 213
<212> PRT

<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (213)..(213)
<223> X can be CS or A

<400> 244

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

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Arg Asn Asp Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Ala Asp Ser Ser Ser
                85                  90                  95

Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
        115                 120                 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
    130                 135                 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145                 150                 155                 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
            180                 185                 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
        195                 200                 205

Ala Pro Thr Glu Xaa
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210

<210> 245
<211> 363
<212> DNA
<213> homo sapiens

<400> 245
caggtgcaat tgaaagaaag cggcccggcc ctggtgaaac cgacccaaac cctgaccctg 60

acctgtacct tttccggatt tagcctgtct acttctggta tgtctgtggg ttggattcgc 120

cagccgcctg ggaaagccct cgagtggctg gctcttatcg attgggatga ggataagtct 180

tatagcacca gcctgaaaac gcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240

gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgttat 300

aattggtata atcctcctgg ttttgataat tggggccaag gcaccctggt gacggttagc 360

tca 363

<210> 246
<211> 324
<212> DNA
<213> homo sapiens

<400> 246
gatatcgtgc tgacccagcc gccttcagtg agtggcgcac caggtcagcg tgtgaccatc 60

tcgtgtagcg gcagcagcag caacattggt tctaattatg tgtcttggta ccagcagttg 120

cccgggacgg cgccgaaact tctgatttat cgtaatgata agcgtccctc aggcgtgccg 180

gatcgtttta gcggatccaa aagcggcacc agcgcgagcc ttgcgattac gggcctgcaa 240

agcgaagacg aagcggatta ttattgccag tctgctgatt cttcttctat ggtgtttggc 300

ggcggcacga agttaaccgt tctt 324

<210> 247
<211> 670
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (670)..(670)
<223> n can be TGC, GAATTC, or TGCGAATTC

<400> 247
caggtgcaat tgaaagaaag cggcccggcc ctggtgaaac cgacccaaac cctgaccctg 60

acctgtacct tttccggatt tagcctgtct acttctggta tgtctgtggg ttggattcgc 120

cagccgcctg ggaaagccct cgagtggctg gctcttatcg attgggatga ggataagtct 180

tatagcacca gcctgaaaac gcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240

gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgttat 300

aattggtata atcctcctgg ttttgataat tggggccaag gcaccctggt gacggttagc 360

tcagcgtcga ccaaaggtcc aagcgtgttt ccgctggctc cgagcagcaa aagcaccagc 420

ggcggcacgg ctgccctggg ctgcctggtt aaagattatt tcccggaacc agtcaccgtg 480

agctggaaca gcggggcgct gaccagcggc gtgcatacct ttccggcggt gctgcaaagc 540

agcggcctgt atagcctgag cagcgttgtg accgtgccga gcagcagctt aggcactcag 600

acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660

ccgaaaagcn 670

<210> 248
<211> 637
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (637)..(637)
<223> n can be TGCAGC or GCC

<400> 248
gatatcgtgc tgacccagcc gccttcagtg agtggcgcac caggtcagcg tgtgaccatc 60

tcgtgtagcg gcagcagcag caacattggt tctaattatg tgtcttggta ccagcagttg 120

cccgggacgg cgccgaaact tctgatttat cgtaatgata agcgtccctc aggcgtgccg 180

gatcgtttta gcggatccaa aagcggcacc agcgcgagcc ttgcgattac gggcctgcaa 240

agcgaagacg aagcggatta ttattgccag tctgctgatt cttcttctat ggtgtttggc 300

ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt 360

ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac 420

ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600

gggagcaccg tggaaaaaac cgttgcgccg actgagn 637

<210> 249
<211> 219
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (219)..(219)
<223> X can be C, EF, or CEF

<400> 249

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

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

Gly Asn Ile Gly Pro Phe Phe Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215

<210> 250
<211> 655
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (655)..(655)
<223> n can be TGC, GAATTC, or TGCGAATTC

<400> 250
caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60

agctgcaaag cctccggagg cacttttttct tcttatgcca tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcaat atcggtccgt tttttggcat tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300

ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360

ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420

ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg 480

gcgctgacca gcggcgtgca taccttttccg gcggtgctgc aaagcagcgg cctgtatagc 540

ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600

gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagcn 655

<210> 251
<211> 213
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (213)..(213)
<223> X can be CS or A

<400> 251

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val
20 25 30

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

Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

eolf-seql

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Asp Asp Gly Ser Thr Ala
85 90 95

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Xaa
210

<210> 252
<211> 637
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (637)..(637)
<223> n can be TGCAGC or GCC

<400> 252
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctat tcctaattat tatgtttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttat gatgatggtt ctactgctga ggtgtttggc 300

ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt 360

ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac 420

ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600

gggagcaccg tggaaaaaac cgttgcgccg actgagn 637

<210> 253
<211> 117
<212> PRT
<213> homo sapiens

<400> 253

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Thr Asp Ser Gln Thr Ala Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 254
<211> 220
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (220)..(220)
<223> X can be C, EF, or CEF

<400> 254

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

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Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

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

Gly Ile Ile Asp Pro Thr Asp Ser Gln Thr Ala Tyr Ser Pro Ser Phe
    50                  55                  60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
    210                 215                 220
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<210> 255
<211> 351
<212> DNA
<213> homo sapiens

<400> 255
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt attgatccta ctgattctca gactgcttat 180

tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc a 351

<210> 256
<211> 658
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (658)..(658)
<223> n can be TGC, GAATTC, or TGCGAATTC

<400> 256
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt attgatccta ctgattctca gactgcttat 180

tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc agcgtcgacc 360

aaaggtccaa gcgtgtttcc gctggctccg agcagcaaaa gcaccagcgg cggcacggct 420

gccctgggct gcctggttaa agattatttc ccggaaccag tcaccgtgag ctggaacagc 480

ggggcgctga ccagcggcgt gcataccttt ccggcggtgc tgcaaagcag cggcctgtat 540

agcctgagca gcgttgtgac cgtgccgagc agcagcttag gcactcagac ctatatttgc 600

aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagtggaacc gaaaagcn 658

<210> 257
<211> 117
<212> PRT
<213> homo sapiens

<400> 257

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Thr Asp Ser Tyr Thr Val Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 258
<211> 220
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (220)..(220)
<223> X can be C, EF, or CEF

<400> 258

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Thr Asp Ser Tyr Thr Val Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215 220

<210> 259
<211> 351
<212> DNA
<213> homo sapiens

<400> 259
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt attgatccta ctgattctta tactgtttat 180

tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc a 351

<210> 260
<211> 658
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (658)..(658)
<223> n can be TGC, GAATTC, or TGCGAATTC

<400> 260
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt attgatccta ctgattctta tactgtttat 180

tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc agcgtcgacc 360

aaaggtccaa gcgtgtttcc gctggctccg agcagcaaaa gcaccagcgg cggcacggct 420

gccctgggct gcctggttaa agattatttc ccggaaccag tcaccgtgag ctggaacagc 480

ggggcgctga ccagcggcgt gcataccttt ccggcggtgc tgcaaagcag cggcctgtat 540

agcctgagca gcgttgtgac cgtgccgagc agcagcttag gcactcagac ctatatttgc 600

aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagtggaacc gaaaagcn 658

<210> 261
<211> 107
<212> PRT
<213> homo sapiens

<400> 261

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Thr Gly Glu Ser Gly
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 262
<211> 212
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (212)..(212)
<223> X can be CS or A

<400> 262

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Thr Gly Glu Ser Gly
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110

Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125

Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140

Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160

Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
165 170 175

Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
180 185 190

Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
195 200 205

Pro Thr Glu Xaa
210

<210> 263
<211> 321
<212> DNA
<213> homo sapiens

<400> 263
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttgg gatactggtg agtctggtgt gtttggcggc 300

ggcacgaagt taaccgttct t 321

<210> 264
<211> 634
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (634)..(634)
<223> n can be TGCAGC or GCC

<400> 264
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttgg gatactggtg agtctggtgt gtttggcggc 300

ggcacgaagt taaccgttct tggccagccg aaagccgcac cgagtgtgac gctgtttccg 360

ccgagcagcg aagaattgca ggcgaacaaa gcgaccctgg tgtgcctgat tagcgacttt 420

tatccgggag ccgtgacagt ggcctggaag gcagatagca gccccgtcaa ggcgggagtg 480

gagaccacca caccctccaa acaaagcaac aacaagtacg cggccagcag ctatctgagc 540

ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgagggg 600

agcaccgtgg aaaaaaccgt tgcgccgact gagn 634

<210> 265
<211> 108
<212> PRT
<213> homo sapiens

<400> 265

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Ile Leu Pro His Gly
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 266
<211> 213
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (213)..(213)
<223> X can be CS or A

<400> 266

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Ile Leu Pro His Gly
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln

115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Xaa
210

<210> 267
<211> 324
<212> DNA
<213> homo sapiens

<400> 267
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttgg gatattcttc ctcatggtct tgtgtttggc 300

ggcggcacga agttaaccgt tctt 324

<210> 268
<211> 637
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (637)..(637)
<223> n can be TGCAGC or GCC

<400> 268
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttgg gatattcttc ctcatggtct tgtgtttggc 300

ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt 360

ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac 420

ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600

gggagcaccg tggaaaaaac cgttgcgccg actgagn 637

<210> 269
<211> 108
<212> PRT
<213> homo sapiens

<400> 269

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Thr Asp Ser Pro Thr Gly
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 270
<211> 213
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (213)..(213)
<223> X can be CS or A

<400> 270

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Thr Asp Ser Pro Thr Gly
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Xaa
210

<210> 271
<211> 324
<212> DNA
<213> homo sapiens

<400> 271
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccaggcttgg actgattctc ctactggtct tgtgtttggc 300

ggcggcacga agttaaccgt tctt 324

<210> 272
<211> 637
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (637)..(637)
<223> n can be TGCAGC or GCC

<400> 272
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccaggcttgg actgattctc ctactggtct tgtgtttggc 300

ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt 360

ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac 420

ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600

gggagcaccg tggaaaaaac cgttgcgccg actgagn 637

<210> 273
<211> 116
<212> PRT
<213> homo sapiens

<400> 273

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 274
<211> 219
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (219)..(219)
<223> X can be C, EF, or CEF

<400> 274

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215

<210> 275
<211> 348
<212> DNA
<213> homo sapiens

<400> 275
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctgatg attcttatac tgagtattct 180

ccttcttttc agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 276
<211> 655
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (655)..(655)
<223> n can be TGC, GAATTC, or TGCGAATTC

<400> 276

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctgatg attcttatac tgagtattct 180

ccttcttttc agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360

ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420

ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg 480

gcgctgacca gcggcgtgca taccttttccg gcggtgctgc aaagcagcgg cctgtatagc 540

ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600

gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagcn 655

<210> 277
<211> 116
<212> PRT
<213> homo sapiens

<400> 277

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Gln Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 278

<211> 219
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (219)..(219)
<223> X can be C, EF, or CEF

<400> 278

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
            20                  25                  30

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

Ile Ile Asp Pro Gln Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
    50                  55                  60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65                  70                  75                  80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
                85                  90                  95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
            100                 105                 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115                 120                 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205
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Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215

<210> 279
<211> 348
<212> DNA
<213> homo sapiens

<400> 279
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctcagg attcttatac tgagtattct 180

ccttcttttc agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 280
<211> 655
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (655)..(655)
<223> n can be TGC, GAATTC, TGCGAATTC

<400> 280
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctcagg attcttatac tgagtattct 180

ccttcttttc agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360

ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420

ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg 480

gcgctgacca gcggcgtgca taccttttcg gcggtgctgc aaagcagcgg cctgtatagc 540

ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600

gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagcn 655

<210> 281
<211> 116
<212> PRT
<213> homo sapiens

<400> 281

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Glu Asp Ser His Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 282
<211> 219
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (219)..(219)
<223> X can be C, EF, or CEF

<400> 282

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Glu Asp Ser His Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215

<210> 283
<211> 348
<212> DNA
<213> homo sapiens

<400> 283
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctgagg attctcatac tgagtattct 180

ccttcttttc agggtcaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 284
<211> 655
<212> DNA

<213> homo sapiens

<220>
<221> misc_feature
<222> (655)..(655)
<223> n can be TGC, GAATTC, or TGCGAATTC

<400> 284
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctgagg attctcatac tgagtattct 180

ccttcttttc agggtcaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360

ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420

ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg 480

gcgctgacca gcggcgtgca taccttttccg gcggtgctgc aaagcagcgg cctgtatagc 540

ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600

gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagcn 655

<210> 285
<211> 106
<212> PRT
<213> homo sapiens

<400> 285

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Gly Ser Glu Asp Gln Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 286
<211> 211
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (211)..(211)
<223> X can be CS or A

<400> 286

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Gly Ser Glu Asp Gln Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125

Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140

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

Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175

Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190

Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205

Thr Glu Xaa
210

<210> 287
<211> 318
<212> DNA
<213> homo sapiens

<400> 287
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cgctacttgg ggttctgagg atcaggtgtt tggcggcggc 300

acgaagttaa ccgttctt 318

<210> 288
<211> 631
<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (631)..(631)
<223> n can be TGCAGC or GCC

<400> 288
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cgctacttgg ggttctgagg atcaggtgtt tggcggcggc 300

acgaagttaa ccgttcttgg ccagccgaaa gccgcaccga gtgtgacgct gtttccgccg 360

agcagcgaag aattgcaggc gaacaaagcg accctggtgt gcctgattag cgacttttat 420

ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag 480

accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg 540

acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaggggagc 600

accgtggaaa aaaccgttgc gccgactgag n 631

<210> 289
<211> 107
<212> PRT
<213> homo sapiens

<400> 289

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ser Thr Trp Asp Ile Glu Pro Thr Tyr
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 290
<211> 212
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<222> (212)..(212)
<223> X can be CS or A

<400> 290

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ser Thr Trp Asp Ile Glu Pro Thr Tyr
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110

Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125

Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140

Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160

Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
165 170 175

Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
180 185 190

Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
195 200 205

Pro Thr Glu Xaa
210

<210> 291
<211> 321
<212> DNA
<213> homo sapiens

<400> 291
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ctctacttgg gatattgagc ctacttatgt gtttggcggc 300

ggcacgaagt taaccgttct t 321

<210> 292
<211> 634

<212> DNA
<213> homo sapiens

<220>
<221> misc_feature
<222> (634)..(634)
<223> n can be TGCAGC or GCC

<400> 292
gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ctctacttgg gatattgagc ctacttatgt gtttggcggc 300

ggcacgaagt taaccgttct tggccagccg aaagccgcac cgagtgtgac gctgtttccg 360

ccgagcagcg aagaattgca ggcgaacaaa gcgacccctgg tgtgcctgat tagcgacttt 420

tatccgggag ccgtgacagt ggcctggaag gcagatagca gccccgtcaa ggcgggagtg 480

gagaccacca caccctccaa acaaagcaac aacaagtacg cggccagcag ctatctgagc 540

ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgagggg 600

agcaccgtgg aaaaaaccgt tgcgccgact gagn 634

<210> 293
<211> 228
<212> PRT
<213> homo sapiens

<400> 293

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
1 5 10 15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
35 40 45

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
50 55 60

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65 70 75 80

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
85 90 95

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
100 105 110

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125

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

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
145 150 155 160

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
165 170 175

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
180 185 190

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
195 200 205

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
210 215 220

Ser Pro Gly Lys
225

<210> 294
<211> 103
<212> PRT
<213> homo sapiens

<220>
<221> misc_feature
<222> (103)..(103)
<223> Xaa can be any naturally occurring amino acid

<400> 294

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser

50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Xaa
100

<210> 295
<211> 326
<212> PRT
<213> homo sapiens

<400> 295

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
100 105 110

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
115 120 125

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
130 135 140

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145 150 155 160

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn

165 170 175

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
180 185 190

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
195 200 205

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
210 215 220

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225 230 235 240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
245 250 255

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
260 265 270

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
275 280 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
290 295 300

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305 310 315 320

Ser Leu Ser Pro Gly Lys
325

<210> 296
<211> 1676
<212> PRT
<213> homo sapiens

<400> 296

Met Gly Leu Leu Gly Ile Leu Cys Phe Leu Ile Phe Leu Gly Lys Thr
1 5 10 15

Trp Gly Gln Glu Gln Thr Tyr Val Ile Ser Ala Pro Lys Ile Phe Arg
20 25 30

Val Gly Ala Ser Glu Asn Ile Val Ile Gln Val Tyr Gly Tyr Thr Glu
35 40 45

Ala Phe Asp Ala Thr Ile Ser Ile Lys Ser Tyr Pro Asp Lys Lys Phe

50 55 60

Ser Tyr Ser Ser Gly His Val His Leu Ser Ser Glu Asn Lys Phe Gln
65 70 75 80

Asn Ser Ala Ile Leu Thr Ile Gln Pro Lys Gln Leu Pro Gly Gly Gln
85 90 95

Asn Pro Val Ser Tyr Val Tyr Leu Glu Val Val Ser Lys His Phe Ser
100 105 110

Lys Ser Lys Arg Met Pro Ile Thr Tyr Asp Asn Gly Phe Leu Phe Ile
115 120 125

His Thr Asp Lys Pro Val Tyr Thr Pro Asp Gln Ser Val Lys Val Arg
130 135 140

Val Tyr Ser Leu Asn Asp Asp Leu Lys Pro Ala Lys Arg Glu Thr Val
145 150 155 160

Leu Thr Phe Ile Asp Pro Glu Gly Ser Glu Val Asp Met Val Glu Glu
165 170 175

Ile Asp His Ile Gly Ile Ile Ser Phe Pro Asp Phe Lys Ile Pro Ser
180 185 190

Asn Pro Arg Tyr Gly Met Trp Thr Ile Lys Ala Lys Tyr Lys Glu Asp
195 200 205

Phe Ser Thr Thr Gly Thr Ala Tyr Phe Glu Val Lys Glu Tyr Val Leu
210 215 220

Pro His Phe Ser Val Ser Ile Glu Pro Glu Tyr Asn Phe Ile Gly Tyr
225 230 235 240

Lys Asn Phe Lys Asn Phe Glu Ile Thr Ile Lys Ala Arg Tyr Phe Tyr
245 250 255

Asn Lys Val Val Thr Glu Ala Asp Val Tyr Ile Thr Phe Gly Ile Arg
260 265 270

Glu Asp Leu Lys Asp Asp Gln Lys Glu Met Met Gln Thr Ala Met Gln
275 280 285

Asn Thr Met Leu Ile Asn Gly Ile Ala Gln Val Thr Phe Asp Ser Glu
290 295 300

Thr Ala Val Lys Glu Leu Ser Tyr Tyr Ser Leu Glu Asp Leu Asn Asn
305 310 315 320

Lys Tyr Leu Tyr Ile Ala Val Thr Val Ile Glu Ser Thr Gly Gly Phe
325 330 335

Ser Glu Glu Ala Glu Ile Pro Gly Ile Lys Tyr Val Leu Ser Pro Tyr
340 345 350

Lys Leu Asn Leu Val Ala Thr Pro Leu Phe Leu Lys Pro Gly Ile Pro
355 360 365

Tyr Pro Ile Lys Val Gln Val Lys Asp Ser Leu Asp Gln Leu Val Gly
370 375 380

Gly Val Pro Val Thr Leu Asn Ala Gln Thr Ile Asp Val Asn Gln Glu
385 390 395 400

Thr Ser Asp Leu Asp Pro Ser Lys Ser Val Thr Arg Val Asp Asp Gly
405 410 415

Val Ala Ser Phe Val Leu Asn Leu Pro Ser Gly Val Thr Val Leu Glu
420 425 430

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

Arg Glu Gly Tyr Arg Ala Ile Ala Tyr Ser Ser Leu Ser Gln Ser Tyr
450 455 460

Leu Tyr Ile Asp Trp Thr Asp Asn His Lys Ala Leu Leu Val Gly Glu
465 470 475 480

His Leu Asn Ile Ile Val Thr Pro Lys Ser Pro Tyr Ile Asp Lys Ile
485 490 495

Thr His Tyr Asn Tyr Leu Ile Leu Ser Lys Gly Lys Ile Ile His Phe
500 505 510

Gly Thr Arg Glu Lys Phe Ser Asp Ala Ser Tyr Gln Ser Ile Asn Ile
515 520 525

Pro Val Thr Gln Asn Met Val Pro Ser Ser Arg Leu Leu Val Tyr Tyr
530 535 540

Ile Val Thr Gly Glu Gln Thr Ala Glu Leu Val Ser Asp Ser Val Trp
545 550 555 560

Leu Asn Ile Glu Glu Lys Cys Gly Asn Gln Leu Gln Val His Leu Ser
565 570 575

Pro Asp Ala Asp Ala Tyr Ser Pro Gly Gln Thr Val Ser Leu Asn Met
580 585 590

Ala Thr Gly Met Asp Ser Trp Val Ala Leu Ala Ala Val Asp Ser Ala
595 600 605

Val Tyr Gly Val Gln Arg Gly Ala Lys Lys Pro Leu Glu Arg Val Phe
610 615 620

Gln Phe Leu Glu Lys Ser Asp Leu Gly Cys Gly Ala Gly Gly Gly Leu
625 630 635 640

Asn Asn Ala Asn Val Phe His Leu Ala Gly Leu Thr Phe Leu Thr Asn
645 650 655

Ala Asn Ala Asp Asp Ser Gln Glu Asn Asp Glu Pro Cys Lys Glu Ile
660 665 670

Leu Arg Pro Arg Arg Thr Leu Gln Lys Lys Ile Glu Glu Ile Ala Ala
675 680 685

Lys Tyr Lys His Ser Val Val Lys Lys Cys Cys Tyr Asp Gly Ala Cys
690 695 700

Val Asn Asn Asp Glu Thr Cys Glu Gln Arg Ala Ala Arg Ile Ser Leu
705 710 715 720

Gly Pro Arg Cys Ile Lys Ala Phe Thr Glu Cys Cys Val Val Ala Ser
725 730 735

Gln Leu Arg Ala Asn Ile Ser His Lys Asp Met Gln Leu Gly Arg Leu
740 745 750

His Met Lys Thr Leu Leu Pro Val Ser Lys Pro Glu Ile Arg Ser Tyr
755 760 765

Phe Pro Glu Ser Trp Leu Trp Glu Val His Leu Val Pro Arg Arg Lys
770 775 780

Gln Leu Gln Phe Ala Leu Pro Asp Ser Leu Thr Thr Trp Glu Ile Gln
785 790 795 800

Gly Val Gly Ile Ser Asn Thr Gly Ile Cys Val Ala Asp Thr Val Lys
805 810 815

Ala Lys Val Phe Lys Asp Val Phe Leu Glu Met Asn Ile Pro Tyr Ser
820 825 830

Val Val Arg Gly Glu Gln Ile Gln Leu Lys Gly Thr Val Tyr Asn Tyr
835 840 845

Arg Thr Ser Gly Met Gln Phe Cys Val Lys Met Ser Ala Val Glu Gly
850 855 860

Ile Cys Thr Ser Glu Ser Pro Val Ile Asp His Gln Gly Thr Lys Ser
865 870 875 880

Ser Lys Cys Val Arg Gln Lys Val Glu Gly Ser Ser Ser His Leu Val
885 890 895

Thr Phe Thr Val Leu Pro Leu Glu Ile Gly Leu His Asn Ile Asn Phe
900 905 910

Ser Leu Glu Thr Trp Phe Gly Lys Glu Ile Leu Val Lys Thr Leu Arg
915 920 925

Val Val Pro Glu Gly Val Lys Arg Glu Ser Tyr Ser Gly Val Thr Leu
930 935 940

Asp Pro Arg Gly Ile Tyr Gly Thr Ile Ser Arg Arg Lys Glu Phe Pro
945 950 955 960

Tyr Arg Ile Pro Leu Asp Leu Val Pro Lys Thr Glu Ile Lys Arg Ile
965 970 975

Leu Ser Val Lys Gly Leu Leu Val Gly Glu Ile Leu Ser Ala Val Leu
980 985 990

Ser Gln Glu Gly Ile Asn Ile Leu Thr His Leu Pro Lys Gly Ser Ala
995 1000 1005

Glu Ala Glu Leu Met Ser Val Val Pro Val Phe Tyr Val Phe His
1010 1015 1020

Tyr Leu Glu Thr Gly Asn His Trp Asn Ile Phe His Ser Asp Pro
1025 1030 1035

Leu Ile Glu Lys Gln Lys Leu Lys Lys Lys Leu Lys Glu Gly Met
1040 1045 1050

Leu Ser Ile Met Ser Tyr Arg Asn Ala Asp Tyr Ser Tyr Ser Val

1055 1060 1065

Trp Lys Gly Gly Ser Ala Ser Thr Trp Leu Thr Ala Phe Ala Leu
1070 1075 1080

Arg Val Leu Gly Gln Val Asn Lys Tyr Val Glu Gln Asn Gln Asn
1085 1090 1095

Ser Ile Cys Asn Ser Leu Leu Trp Leu Val Glu Asn Tyr Gln Leu
1100 1105 1110

Asp Asn Gly Ser Phe Lys Glu Asn Ser Gln Tyr Gln Pro Ile Lys
1115 1120 1125

Leu Gln Gly Thr Leu Pro Val Glu Ala Arg Glu Asn Ser Leu Tyr
1130 1135 1140

Leu Thr Ala Phe Thr Val Ile Gly Ile Arg Lys Ala Phe Asp Ile
1145 1150 1155

Cys Pro Leu Val Lys Ile Asp Thr Ala Leu Ile Lys Ala Asp Asn
1160 1165 1170

Phe Leu Leu Glu Asn Thr Leu Pro Ala Gln Ser Thr Phe Thr Leu
1175 1180 1185

Ala Ile Ser Ala Tyr Ala Leu Ser Leu Gly Asp Lys Thr His Pro
1190 1195 1200

Gln Phe Arg Ser Ile Val Ser Ala Leu Lys Arg Glu Ala Leu Val
1205 1210 1215

Lys Gly Asn Pro Pro Ile Tyr Arg Phe Trp Lys Asp Asn Leu Gln
1220 1225 1230

His Lys Asp Ser Ser Val Pro Asn Thr Gly Thr Ala Arg Met Val
1235 1240 1245

Glu Thr Thr Ala Tyr Ala Leu Leu Thr Ser Leu Asn Leu Lys Asp
1250 1255 1260

Ile Asn Tyr Val Asn Pro Val Ile Lys Trp Leu Ser Glu Glu Gln
1265 1270 1275

Arg Tyr Gly Gly Gly Phe Tyr Ser Thr Gln Asp Thr Ile Asn Ala
1280 1285 1290

Ile Glu Gly Leu Thr Glu Tyr Ser Leu Leu Val Lys Gln Leu Arg
1295 1300 1305

Leu Ser Met Asp Ile Asp Val Ser Tyr Lys His Lys Gly Ala Leu
1310 1315 1320

His Asn Tyr Lys Met Thr Asp Lys Asn Phe Leu Gly Arg Pro Val
1325 1330 1335

Glu Val Leu Leu Asn Asp Asp Leu Ile Val Ser Thr Gly Phe Gly
1340 1345 1350

Ser Gly Leu Ala Thr Val His Val Thr Thr Val Val His Lys Thr
1355 1360 1365

Ser Thr Ser Glu Glu Val Cys Ser Phe Tyr Leu Lys Ile Asp Thr
1370 1375 1380

Gln Asp Ile Glu Ala Ser His Tyr Arg Gly Tyr Gly Asn Ser Asp
1385 1390 1395

Tyr Lys Arg Ile Val Ala Cys Ala Ser Tyr Lys Pro Ser Arg Glu
1400 1405 1410

Glu Ser Ser Ser Gly Ser Ser His Ala Val Met Asp Ile Ser Leu
1415 1420 1425

Pro Thr Gly Ile Ser Ala Asn Glu Glu Asp Leu Lys Ala Leu Val
1430 1435 1440

Glu Gly Val Asp Gln Leu Phe Thr Asp Tyr Gln Ile Lys Asp Gly
1445 1450 1455

His Val Ile Leu Gln Leu Asn Ser Ile Pro Ser Ser Asp Phe Leu
1460 1465 1470

Cys Val Arg Phe Arg Ile Phe Glu Leu Phe Glu Val Gly Phe Leu
1475 1480 1485

Ser Pro Ala Thr Phe Thr Val Tyr Glu Tyr His Arg Pro Asp Lys
1490 1495 1500

Gln Cys Thr Met Phe Tyr Ser Thr Ser Asn Ile Lys Ile Gln Lys
1505 1510 1515

Val Cys Glu Gly Ala Ala Cys Lys Cys Val Glu Ala Asp Cys Gly
1520 1525 1530

Gln Met Gln Glu Glu Leu Asp Leu Thr Ile Ser Ala Glu Thr Arg
1535 1540 1545

Lys Gln Thr Ala Cys Lys Pro Glu Ile Ala Tyr Ala Tyr Lys Val
1550 1555 1560

Ser Ile Thr Ser Ile Thr Val Glu Asn Val Phe Val Lys Tyr Lys
1565 1570 1575

Ala Thr Leu Leu Asp Ile Tyr Lys Thr Gly Glu Ala Val Ala Glu
1580 1585 1590

Lys Asp Ser Glu Ile Thr Phe Ile Lys Lys Val Thr Cys Thr Asn
1595 1600 1605

Ala Glu Leu Val Lys Gly Arg Gln Tyr Leu Ile Met Gly Lys Glu
1610 1615 1620

Ala Leu Gln Ile Lys Tyr Asn Phe Ser Phe Arg Tyr Ile Tyr Pro
1625 1630 1635

Leu Asp Ser Leu Thr Trp Ile Glu Tyr Trp Pro Arg Asp Thr Thr
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Cys Ser Ser Cys Gln Ala Phe Leu Ala Asn Leu Asp Glu Phe Ala
1655 1660 1665

Glu Asp Ile Phe Leu Asn Gly Cys
1670 1675

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<211> 1676
<212> PRT
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<400> 297

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20 25 30

Val Gly Ala Ser Glu Asn Ile Val Ile Gln Val Tyr Gly Tyr Thr Glu
35 40 45

Ala Phe Asp Ala Thr Ile Ser Ile Lys Ser Tyr Pro Asp Lys Lys Phe
50 55 60

Ser Tyr Ser Ser Gly His Val His Leu Ser Ser Glu Asn Lys Phe Gln
65 70 75 80

Asn Ser Ala Val Leu Thr Ile Gln Pro Lys Gln Leu Pro Gly Gly Gln
85 90 95

Asn Gln Val Ser Tyr Val Tyr Leu Glu Val Val Ser Lys His Phe Ser
100 105 110

Lys Ser Lys Lys Ile Pro Ile Thr Tyr Asp Asn Gly Phe Leu Phe Ile
115 120 125

His Thr Asp Lys Pro Val Tyr Thr Pro Asp Gln Ser Val Lys Val Arg
130 135 140

Val Tyr Ser Leu Asn Asp Asp Leu Lys Pro Ala Lys Arg Glu Thr Val
145 150 155 160

Leu Thr Phe Ile Asp Pro Glu Gly Ser Glu Ile Asp Met Val Glu Glu
165 170 175

Ile Asp His Ile Gly Ile Ile Ser Phe Pro Asp Phe Lys Ile Pro Ser
180 185 190

Asn Pro Arg Tyr Gly Met Trp Thr Ile Gln Ala Lys Tyr Lys Glu Asp
195 200 205

Phe Ser Thr Thr Gly Thr Ala Phe Phe Glu Val Lys Glu Tyr Val Leu
210 215 220

Pro His Phe Ser Val Ser Val Glu Pro Glu Ser Asn Phe Ile Gly Tyr
225 230 235 240

Lys Asn Phe Lys Asn Phe Glu Ile Thr Ile Lys Ala Arg Tyr Phe Tyr
245 250 255

Asn Lys Val Val Thr Glu Ala Asp Val Tyr Ile Thr Phe Gly Ile Arg
260 265 270

Glu Asp Leu Lys Asp Asp Gln Lys Glu Met Met Gln Thr Ala Met Gln
275 280 285

Asn Thr Met Leu Ile Asn Gly Ile Ala Gln Val Thr Phe Asp Ser Glu
290 295 300

Thr Ala Val Lys Glu Leu Ser Tyr Tyr Ser Leu Glu Asp Leu Asn Asn
305 310 315 320

Lys Tyr Leu Tyr Ile Ala Val Thr Val Ile Glu Ser Thr Gly Gly Phe
325 330 335

Ser Glu Glu Ala Glu Ile Pro Gly Ile Lys Tyr Val Leu Ser Pro Tyr
340 345 350

Lys Leu Asn Leu Val Ala Thr Pro Leu Phe Leu Lys Pro Gly Ile Pro
355 360 365

Tyr Ser Ile Lys Val Gln Val Lys Asp Ala Leu Asp Gln Leu Val Gly
370 375 380

Gly Val Pro Val Thr Leu Asn Ala Gln Thr Ile Asp Val Asn Gln Glu
385 390 395 400

Thr Ser Asp Leu Glu Pro Arg Lys Ser Val Thr Arg Val Asp Asp Gly
405 410 415

Val Ala Ser Phe Val Val Asn Leu Pro Ser Gly Val Thr Val Leu Glu
420 425 430

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

Arg Glu Gly Tyr Arg Ala Ile Ala Tyr Ser Ser Leu Ser Gln Ser Tyr
450 455 460

Leu Tyr Ile Asp Trp Thr Asp Asn His Lys Ala Leu Leu Val Gly Glu
465 470 475 480

Tyr Leu Asn Ile Ile Val Thr Pro Lys Ser Pro Tyr Ile Asp Lys Ile
485 490 495

Thr His Tyr Asn Tyr Leu Ile Leu Ser Lys Gly Lys Ile Ile His Phe
500 505 510

Gly Thr Arg Glu Lys Leu Ser Asp Ala Ser Tyr Gln Ser Ile Asn Ile
515 520 525

Pro Val Thr Gln Asn Met Val Pro Ser Ser Arg Leu Leu Val Tyr Tyr
530 535 540

Ile Val Thr Gly Glu Gln Thr Ala Glu Leu Val Ser Asp Ser Val Trp
545 550 555 560

Leu Asn Ile Glu Glu Lys Cys Gly Asn Gln Leu Gln Val His Leu Ser

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                565                 570                 575

Pro Asp Ala Asp Thr Tyr Ser Pro Gly Gln Thr Val Ser Leu Asn Met
            580                 585                 590

Val Thr Gly Met Asp Ser Trp Val Ala Leu Thr Ala Val Asp Ser Ala
        595                 600                 605

Val Tyr Gly Val Gln Arg Arg Ala Lys Lys Pro Leu Glu Arg Val Phe
    610                 615                 620

Gln Phe Leu Glu Lys Ser Asp Leu Gly Cys Gly Ala Gly Gly Gly Leu
625                 630                 635                 640

Asn Asn Ala Asn Val Phe His Leu Ala Gly Leu Thr Phe Leu Thr Asn
                645                 650                 655

Ala Asn Ala Asp Asp Ser Gln Glu Asn Asp Glu Pro Cys Lys Glu Ile
            660                 665                 670

Ile Arg Pro Arg Arg Met Leu Gln Glu Lys Ile Glu Glu Ile Ala Ala
        675                 680                 685

Lys Tyr Lys His Leu Val Val Lys Lys Cys Cys Tyr Asp Gly Val Arg
    690                 695                 700

Ile Asn His Asp Glu Thr Cys Glu Gln Arg Ala Ala Arg Ile Ser Val
705                 710                 715                 720

Gly Pro Arg Cys Val Lys Ala Phe Thr Glu Cys Cys Val Val Ala Ser
                725                 730                 735

Gln Leu Arg Ala Asn Asn Ser His Lys Asp Leu Gln Leu Gly Arg Leu
            740                 745                 750

His Met Lys Thr Leu Leu Pro Val Ser Lys Pro Glu Ile Arg Ser Tyr
        755                 760                 765

Phe Pro Glu Ser Trp Leu Trp Glu Val His Leu Val Pro Arg Arg Lys
    770                 775                 780

Gln Leu Gln Phe Ala Leu Pro Asp Ser Val Thr Thr Trp Glu Ile Gln
785                 790                 795                 800

Gly Val Gly Ile Ser Asn Ser Gly Ile Cys Val Ala Asp Thr Ile Lys
                805                 810                 815
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Ala Lys Val Phe Lys Asp Val Phe Leu Glu Met Asn Ile Pro Tyr Ser
820 825 830

Val Val Arg Gly Glu Gln Val Gln Leu Lys Gly Thr Val Tyr Asn Tyr
835 840 845

Arg Thr Ser Gly Met Gln Phe Cys Val Lys Met Ser Ala Val Glu Gly
850 855 860

Ile Cys Thr Ser Glu Ser Pro Val Ile Asp His Gln Gly Thr Lys Ser
865 870 875 880

Ser Lys Cys Val Arg Gln Lys Val Glu Gly Ser Ser Asn His Leu Val
885 890 895

Thr Phe Thr Val Leu Pro Leu Glu Ile Gly Leu Gln Asn Ile Asn Phe
900 905 910

Ser Leu Glu Thr Ser Phe Gly Lys Glu Ile Leu Val Lys Ser Leu Arg
915 920 925

Val Val Pro Glu Gly Val Lys Arg Glu Ser Tyr Ser Gly Ile Thr Leu
930 935 940

Asp Pro Arg Gly Ile Tyr Gly Thr Ile Ser Arg Arg Lys Glu Phe Pro
945 950 955 960

Tyr Arg Ile Pro Leu Asp Leu Val Pro Lys Thr Glu Ile Lys Arg Ile
965 970 975

Leu Ser Val Lys Gly Leu Leu Val Gly Glu Ile Leu Ser Ala Val Leu
980 985 990

Ser Arg Glu Gly Ile Asn Ile Leu Thr His Leu Pro Lys Gly Ser Ala
995 1000 1005

Glu Ala Glu Leu Met Ser Val Val Pro Val Phe Tyr Val Phe His
1010 1015 1020

Tyr Leu Glu Thr Gly Asn His Trp Asn Ile Phe His Ser Asp Pro
1025 1030 1035

Leu Ile Glu Lys Arg Asn Leu Glu Lys Lys Leu Lys Glu Gly Met
1040 1045 1050

Val Ser Ile Met Ser Tyr Arg Asn Ala Asp Tyr Ser Tyr Ser Val
1055 1060 1065

Trp Lys Gly Gly Ser Ala Ser Thr Trp Leu Thr Ala Phe Ala Leu
1070 1075 1080

Arg Val Leu Gly Gln Val His Lys Tyr Val Glu Gln Asn Gln Asn
1085 1090 1095

Ser Ile Cys Asn Ser Leu Leu Trp Leu Val Glu Asn Tyr Gln Leu
1100 1105 1110

Asp Asn Gly Ser Phe Lys Glu Asn Ser Gln Tyr Gln Pro Ile Lys
1115 1120 1125

Leu Gln Gly Thr Leu Pro Val Glu Ala Arg Glu Asn Ser Leu Tyr
1130 1135 1140

Leu Thr Ala Phe Thr Val Ile Gly Ile Arg Lys Ala Phe Asp Ile
1145 1150 1155

Cys Pro Leu Val Lys Ile Asn Thr Ala Leu Ile Lys Ala Asp Thr
1160 1165 1170

Phe Leu Leu Glu Asn Thr Leu Pro Ala Gln Ser Thr Phe Thr Leu
1175 1180 1185

Ala Ile Ser Ala Tyr Ala Leu Ser Leu Gly Asp Lys Thr His Pro
1190 1195 1200

Gln Phe Arg Ser Ile Val Ser Ala Leu Lys Arg Glu Ala Leu Val
1205 1210 1215

Lys Gly Asn Pro Pro Ile Tyr Arg Phe Trp Lys Asp Ser Leu Gln
1220 1225 1230

His Lys Asp Ser Ser Val Pro Asn Thr Gly Thr Ala Arg Met Val
1235 1240 1245

Glu Thr Thr Ala Tyr Ala Leu Leu Thr Ser Leu Asn Leu Lys Asp
1250 1255 1260

Ile Asn Tyr Val Asn Pro Ile Ile Lys Trp Leu Ser Glu Glu Gln
1265 1270 1275

Arg Tyr Gly Gly Gly Phe Tyr Ser Thr Gln Asp Thr Ile Asn Ala
1280 1285 1290

Ile Glu Gly Leu Thr Glu Tyr Ser Leu Leu Val Lys Gln Leu Arg
1295 1300 1305

Leu Asn Met Asp Ile Asp Val Ala Tyr Lys His Lys Gly Pro Leu
1310 1315 1320

His Asn Tyr Lys Met Thr Asp Lys Asn Phe Leu Gly Arg Pro Val
1325 1330 1335

Glu Val Leu Leu Asn Asp Asp Leu Val Val Ser Thr Gly Phe Gly
1340 1345 1350

Ser Gly Leu Ala Thr Val His Val Thr Thr Val Val His Lys Thr
1355 1360 1365

Ser Thr Ser Glu Glu Val Cys Ser Phe Tyr Leu Lys Ile Asp Thr
1370 1375 1380

Gln Asp Ile Glu Ala Ser His Tyr Arg Gly Tyr Gly Asn Ser Asp
1385 1390 1395

Tyr Lys Arg Ile Val Ala Cys Ala Ser Tyr Lys Pro Ser Lys Glu
1400 1405 1410

Glu Ser Ser Ser Gly Ser Ser His Ala Val Met Asp Ile Ser Leu
1415 1420 1425

Pro Thr Gly Ile Asn Ala Asn Glu Glu Asp Leu Lys Ala Leu Val
1430 1435 1440

Glu Gly Val Asp Gln Leu Phe Thr Asp Tyr Gln Ile Lys Asp Gly
1445 1450 1455

His Val Ile Leu Gln Leu Asn Ser Ile Pro Ser Ser Asp Phe Leu
1460 1465 1470

Cys Val Arg Phe Arg Ile Phe Glu Leu Phe Glu Val Gly Phe Leu
1475 1480 1485

Ser Pro Ala Thr Phe Thr Val Tyr Glu Tyr His Arg Pro Asp Lys
1490 1495 1500

Gln Cys Thr Met Phe Tyr Ser Thr Ser Asn Ile Lys Ile Gln Lys
1505 1510 1515

Val Cys Glu Gly Ala Thr Cys Lys Cys Ile Glu Ala Asp Cys Gly
1520 1525 1530

Gln Met Gln Lys Glu Leu Asp Leu Thr Ile Ser Ala Glu Thr Arg

1535 1540 1545

Lys Gln Thr Ala Cys Asn Pro Glu Ile Ala Tyr Ala Tyr Lys Val
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Ile Ile Thr Ser Ile Thr Thr Glu Asn Val Phe Val Lys Tyr Lys
1565 1570 1575

Ala Thr Leu Leu Asp Ile Tyr Lys Thr Gly Glu Ala Val Ala Glu
1580 1585 1590

Lys Asp Ser Glu Ile Thr Phe Ile Lys Lys Val Thr Cys Thr Asn
1595 1600 1605

Ala Glu Leu Val Lys Gly Arg Gln Tyr Leu Ile Met Gly Lys Glu
1610 1615 1620

Ala Leu Gln Ile Lys Tyr Asn Phe Thr Phe Arg Tyr Ile Tyr Pro
1625 1630 1635

Leu Asp Ser Leu Thr Trp Ile Glu Tyr Trp Pro Arg Asp Thr Thr
1640 1645 1650

Cys Ser Ser Cys Gln Ala Phe Leu Ala Asn Leu Asp Glu Phe Ala
1655 1660 1665

Glu Asp Ile Phe Leu Asn Gly Cys
1670 1675

COMPOSICIONES Y MÉTODOS PARA ANTICUERPOS QUE SE DIRIGEN A LA PROTEÍNA DE COMPLEMENTO C5

1. INTRODUCCIÓN

La presente invención se refiere a anticuerpos que se dirigen a la proteína de complemento C5, y a composiciones y métodos de uso de los mismos.

2. ANTECEDENTES DE LA INVENCIÓN.

El papel normal del complemento, que es parte del sistema inmunitario innato, está en la defensa del huésped. El complemento defiende contra la infección bacteriana, se liga a la inmunidad adaptable e innata, y dispone de los complejos inmunes y de los productos de las lesiones inflamatorias.

Las funciones de defensa se llevan a cabo mediante productos biológicamente activos generados en el transcurso de la activación del complemento, los cuales opsonizan a los agentes infecciosos, promueven la inflamación, o lisan los objetivos susceptibles (Marzari y colaboradores, Eur. J. Immunol. 32:2773-2782 (2002)). El sistema de complemento consiste en aproximadamente 25 a 30 proteínas de plasma que tienen un papel en el sistema inmunitario. La cascada del complemento se activa mediante cuando menos tres sendas principales. La senda clásica típicamente es activada por los complejos inmunes, la senda alternativa puede ser activada por las superficies celulares no protegidas, y la senda de lectina de enlace de manosa (MBL) es iniciada por el enlace de MBL a los

carbohidratos de superficie celular (Trendelenburg, Swiss Med Wkly 137:413-417 (2007)).

Las tres sendas conducen a la disociación de C5 mediante la convertasa de C5. El resultado de esta disociación es la liberación de un fragmento C5a, una potente molécula inflamatoria, y C5b, que inicia el complejo de ataque de membrana (MAC). Los productos de complemento, una vez liberados, no diferencian entre los objetivos extraños y propios, y, si no se regulan estrechamente, con frecuencia provocan un daño extenso de las células y tejidos en espera en condiciones clínicas asociadas con la activación del complemento sin restricciones (Marzari y colaboradores, 2002).

C5 se expresa intracelularmente como un solo péptido pro-C5 de 1,676 aminoácidos, que consiste en una secuencia de señal de 18 residuos y una secuencia enlazadora rica en Arg (RPRR) situada entre la cadena-β N-terminal madura y la cadena-α C-terminal. El C5 maduro tiene un peso molecular de aproximadamente 190 kDa, y consiste en dos cadenas de polipéptido (α, de 115 kDa, y β, de 75 kDa), que están conectadas mediante enlaces de disulfuro. La convertasa de C5 disocia a C5 entre los residuos 74 y 75 de la cadena alfa para liberar el péptido C5a de 74 aminoácidos y el fragmento C5b que subsiguientemente se incorpora en el complejo de ataque de membrana (MAC).

La degeneración macular es una condición médica que se encuentra predominantemente en la ancianidad, en donde el centro del revestimiento interno del ojo, conocido como el área de la mácula

de la retina, sufre adelgazamiento, atrofia, y en algunos casos, hemorragia. Esto puede dar como resultado la pérdida de la visión central, lo cual implica una incapacidad para ver los detalles finos, para leer, o para reconocer las caras. La patogénesis de la nueva formación de vasos coroidales es pobremente entendida, pero se piensa que son importantes factores tales como la inflamación, la isquemia, y la producción local de factores angiogénicos.

A pesar de las opciones de tratamiento actuales para tratar las enfermedades y trastornos asociados con la sendas de componentes clásicas o alternativas, en particular la degeneración macular relacionada con la edad, sigue existiendo una necesidad de encontrar agentes específicos que conduzcan a tratamientos que sean efectivos y bien tolerados.

3. BREVE DESCRIPCIÓN DE LA INVENCIÓN.

La presente invención proporciona moléculas de enlace del complemento C5 aisladas (por ejemplo, anticuerpos de enlace de C5 o fragmentos de enlace de antígeno de los mismos), composiciones farmacéuticas que comprenden estas moléculas, métodos para la elaboración de tales moléculas y composiciones, y métodos de uso de las mismas.

En algunas modalidades, la presente invención proporciona anticuerpos aislados o fragmentos de enlace de antígeno de los mismos que se enlazan específicamente a una proteína C5, en donde este anticuerpo tiene una constante de afinidad (K_A) de cuando menos 1 x 10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, ó 10^{11} M^{-1}.

En algunas modalidades, la presente invención proporciona anticuerpos aislados o fragmentos de enlace de antígeno de los mismos, que se enlazan específicamente a una proteína C5, y que inhiben la senda de complemento alternativa, como se mide mediante un ensayo hemolítico *in vitro*, con un intervalo de IC_{50} de aproximadamente 20 pM a aproximadamente 200 pM.

En algunas modalidades, la presente invención proporciona anticuerpos aislados o fragmentos de enlace de antígeno de los mismos, que se enlazan específicamente a una proteína C5, y compiten cruzadamente con un anticuerpo descrito en la Tabla 1 que se encuentra más adelante. En algunas modalidades, la presente invención proporciona anticuerpos aislados o fragmentos de enlace de antígeno de los mismos, que se enlazan al mismo epítopo de la proteína C5 que un anticuerpo descrito en la Tabla 1 que se encuentra más adelante.

En algunas modalidades, los anticuerpos de la invención son anticuerpos monoclonales aislados que se enlazan específicamente a una proteína C5. En algunas modalidades, los anticuerpos de la invención son anticuerpos monoclonales humanos o humanizados aislados que se enlazan específicamente a una proteína C5. En algunas modalidades, los anticuerpos de la invención son anticuerpos quiméricos aislados que se enlazan específicamente a una proteína C5. En algunas modalidades, los anticuerpos de la invención comprenden una región constante de cadena pesada humana y una región constante de cadena ligera humana.

En algunas modalidades, la presente invención proporciona anticuerpos aislados o fragmentos de enlace de antígeno de los mismos, que se enlazan específicamente a una proteína C5, en donde estos anticuerpos son anticuerpos de una sola cadena. En algunas modalidades, los anticuerpos de la invención son fragmentos Fab. En algunas modalidades, los anticuerpos de la invención son scFv.

En algunas modalidades, la presente invención proporciona anticuerpos aislados o fragmentos de enlace de antígeno de los mismos, que se enlazan específicamente tanto a la C5 humana como a la C5 de cinomolgo. En algunas modalidades, los anticuerpos de la invención son un isotipo de IgG1.

En algunas modalidades, la presente invención proporciona anticuerpos aislados o fragmentos de enlace de antígeno de los mismos, los cuales comprenden una estructura en donde se han sustituido aminoácidos en la estructura del anticuerpo a partir de secuencias de la línea germinal V_H o V_L humanas respectivas.

En algunas modalidades, la presente invención proporciona anticuerpos monoclonales aislados o fragmentos de enlace de antígeno de los mismos, que se enlazan específicamente a una proteína C5, en donde estos anticuerpos comprenden cuando menos una secuencia de región determinante de complementariedad (CDR) que tiene una identidad de secuencia de cuando menos el 90 por ciento, el 95 por ciento, el 97 por ciento, el 98 por ciento, o cuando menos el 99 por ciento con las SEQ ID NOs: 1, 2, 3, 4, 5, 6, 17, 18,

19, 20, 21, 22, 33, 34, 35, 36, 37, 38, 49, 50, 61, 62, 63, 64, 65, 66, 77, 78, 89, 95, 101, 107, 113, 119, 120, 131, 132, 133, 134, 135, 136, 145, 146, 147, 148, 149, 150, 159, 160, 161, 162, 163, 164, 173, 174, 175, 176, 177, 178, 195, 196, 197, 198, 199, 200, 209, 226, 235, 236, 237, 238, 239, ó 240.

En algunas modalidades, la presente invención proporciona anticuerpos monoclonales aislados o fragmentos de enlace de antígeno de los mismos, que se enlazan específicamente a una proteína C5, en donde estos anticuerpos comprenden cuando menos una secuencia de la región determinante de complementariedad de cadena pesada que es idéntica a las SEQ ID NOs: 1, 2, 3, 17, 18, 19, 33, 34, 35, 49, 61, 62, 63, 77, 77, 95, 107, 113, 119, 132, 131, 133, 145, 146, 147, 159, 160, 161, 173, 174, 175, 195, 196, 197, 226, 235, 236, ó 237.

En algunas modalidades, la presente invención proporciona anticuerpos monoclonales aislados o fragmentos de enlace de antígeno de los mismos, que se enlazan específicamente a una proteína C5, en donde estos anticuerpos comprenden cuando menos una secuencia de la región determinante de complementariedad de cadena ligera que es idéntica a las SEQ ID NOs: 4, 5, 6, 20, 21, 22, 36, 37, 38, 50, 64, 65, 66, 78, 89, 101, 120, 134, 135, 136, 148, 149, 150, 162, 163, 164, 176, 177, 178, 198, 199, 200, 209, 238, 239, ó 240.

En algunas modalidades, la presente invención proporciona anticuerpos monoclonales aislados o fragmentos de enlace de

antígeno de los mismos, que se enlazan específicamente a una proteína C5, en donde estos anticuerpos comprenden una CDR1 de cadena pesada seleccionada a partir del grupo que consiste en las SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, y 235; una CDR2 de cadena pesada seleccionada a partir del grupo que consiste en las SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, y 236; y una CDR3 de cadena pesada seleccionada a partir del grupo que consiste en las SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, y 237. En algunas modalidades, estos anticuerpos o fragmentos de enlace de antígeno de los mismos, comprenden además una CDR1 de cadena ligera seleccionada a partir del grupo que consiste en las SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, y 238; una CDR2 de cadena ligera seleccionada a partir del grupo que consiste en las SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, y 239; y una CDR3 de cadena ligera seleccionada a partir del grupo que consiste en las SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, y 240.

En algunas modalidades, la presente invención proporciona anticuerpos monoclonales aislados o fragmentos de enlace de antígeno de los mismos, que se enlazan específicamente a una proteína C5, en donde estos anticuerpos comprenden una CDR1 de cadena ligera seleccionada a partir del grupo que consiste en las SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, y 238; una CDR2 de cadena ligera seleccionada a partir del grupo que consiste

en las SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, y 239; y una CDR3 de cadena ligera seleccionada a partir del grupo que consiste en las SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, y 240.

BA En algunas modalidades, la presente invención proporciona anticuerpos monoclonales aislados o fragmentos de enlace de antígeno de los mismos, que se enlazan específicamente a una proteína C5, en donde **BA** estos anticuerpos comprenden una región variable de cadena pesada que tiene una identidad de secuencia de cuando menos el 90 por ciento, el 95 por ciento, el 97 por ciento, el 98 por ciento, o cuando menos el 99 por ciento con las SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, ó 281. En algunas modalidades, estos anticuerpos o fragmentos de enlace de antígeno de los mismos, comprenden además una región variable de cadena ligera que tiene una identidad de secuencia de cuando menos el 90 por ciento, el 95 por ciento, el 97 por ciento, el 98 por ciento, o cuando menos el 99 por ciento con las SEQ ID NOs: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, y 289.

En algunas modalidades, la presente invención proporciona anticuerpos monoclonales aislados o fragmentos de enlace de antígeno de los mismos, que se enlazan específicamente a una proteína C5, en donde estos anticuerpos comprenden una región variable de cadena ligera que tiene una identidad de secuencia de

cuando menos el 90 por ciento, el 95 por ciento, el 97 por ciento, el 98 por ciento, o cuando menos el 99 por ciento con las SEQ ID NOs: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, y 289.

En algunas modalidades, la presente invención proporciona anticuerpos monoclonales aislados o fragmentos de enlace de antígeno de los mismos, que se enlazan específicamente a una proteína C5, en donde estos anticuerpos comprenden una cadena pesada que tiene una identidad de secuencia de cuando menos el 90 por ciento, el 95 por ciento, el 97 por ciento, el 98 por ciento, o cuando menos el 99 por ciento con las SEQ ID NOs: 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, ó 282. En algunas modalidades, estos anticuerpos comprenden además una cadena ligera que tiene una identidad de secuencia de cuando menos el 90 por ciento, el 95 por ciento, el 97 por ciento, el 98 por ciento, o cuando menos el 99 por ciento con las SEQ ID NOs: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, ó 290.

En algunas modalidades, la presente invención proporciona anticuerpos monoclonales aislados o fragmentos de enlace de antígeno de los mismos, que se enlazan específicamente a una proteína C5, en donde estos anticuerpos comprenden una cadena ligera que tiene una identidad de secuencia de cuando menos el 90 por ciento, el 95 por ciento, el 97 por ciento, el 98 por ciento, o

cuando menos el 99 por ciento con las SEQ ID NOs: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, ó 290.

La presente invención también comprende composiciones farmacéuticas que comprenden una o más moléculas de enlace de C5 de la invención (por ejemplo, anticuerpos de enlace de C5 o fragmentos de enlace de antígeno de los mismos), y un vehículo farmacéuticamente aceptable.

En algunas modalidades, la presente invención proporciona ácidos nucleicos que comprenden una secuencia de nucleótidos que codifica un polipéptido que comprende una región variable de cadena pesada que tiene una identidad de secuencia de cuando menos el 90 por ciento, el 95 por ciento, el 97 por ciento, el 98 por ciento, o cuando menos el 99 por ciento con las SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, ó 281.

En algunas modalidades, la presente invención proporciona ácidos nucleicos que comprenden una secuencia de nucleótidos que codifica un polipéptido que comprende una región variable de cadena ligera que tiene una identidad de secuencia de cuando menos el 90 por ciento, el 95 por ciento, el 97 por ciento, el 98 por ciento, o cuando menos el 99 por ciento con las SEQ ID NOs: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, y 289.

La presente invención también proporciona vectores y células

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huésped que comprenden estos ácidos nucleicos. En una modalidad, la presente invención proporciona células huésped aisladas que comprenden: (1) un segmento de ADN recombinante que codifica una cadena pesada de los anticuerpos de la invención, y (2) un segundo segmento de ADN recombinante que codifica una cadena ligera de los anticuerpos de la invención; en donde estos segmentos de ADN se enlazan respectivamente de una manera operable con un primero y un segundo promotor, y son capaces de expresarse en esta célula huésped. En otra modalidad, la presente invención proporciona células huésped aisladas que comprenden un segmento de ADN recombinante que codifica una cadena pesada, y una cadena ligera de los anticuerpos de la invención, respectivamente, en donde este segmento de ADN se enlaza operablemente a un promotor, y es capaz de expresarse en estas células huésped. En algunas modalidades, las células huésped son una línea celular de mamífero no humano. En algunas modalidades, los anticuerpos o fragmentos de enlace de antígeno de los mismos son un anticuerpo monoclonal humano, o un fragmento de enlace de antígeno del mismo.

La presente invención proporciona además métodos de tratamiento o de diagnóstico que utilizan las moléculas de enlace de C5 (por ejemplo, anticuerpos de enlace de C5 o fragmentos de enlace de antígeno de los mismos) de la invención. En una modalidad, la presente invención proporciona métodos para el tratamiento de la degeneración macular relacionada con la edad, los cuales comprenden administrar a un sujeto que lo necesite, una

cantidad efectiva de una composición que comprende un anticuerpo o un fragmento de enlace de antígeno del mismo de la invención.

En otra modalidad, la presente invención proporciona métodos para el tratamiento de una enfermedad, los cuales comprenden administrar a un sujeto que lo necesite, una cantidad efectiva de una composición que comprende un anticuerpo o un fragmento de enlace de antígeno del mismo de la invención, en donde esta enfermedad es asma, artritis, enfermedad cardíaca autoinmune, esclerosis múltiple, enfermedad inflamatoria del intestino, lesiones por isquemia-reperfusión, síndrome de Barraquer-Simons, hemodiálisis, lupus sistémico, lupus eritematoso, soriasis, esclerosis múltiple, trasplante, enfermedad de Alzheimer, glomerulonefritis, ó MPGN II.

La presente invención también proporciona métodos para el tratamiento de hemoglobinuria nocturna paroxismal (PNH), los cuales comprenden administrar a un sujeto que lo necesite, una cantidad efectiva de una composición que comprende un anticuerpo o un fragmento de enlace de antígeno del mismo de la invención.

La presente invención proporciona además métodos para aminorar un síntoma asociado con la circulación extracorpórea, los cuales comprenden administrar a un sujeto que lo necesite, una cantidad efectiva de una composición que comprende un anticuerpo o un fragmento de enlace de antígeno del mismo de la invención.

3.1 Definiciones

A menos que se definan de otra manera, los términos técnicos

y científicos utilizados en la presente tienen el mismo significado que es entendido comúnmente por los expertos ordinarios en la materia a la que pertenece esta invención.

El término "anticuerpo", como se utiliza en la presente, incluye anticuerpos enteros y cualquier fragmento de enlace de antígeno (es decir, "porción de enlace de antígeno") o cadenas individuales de los mismos. Un "anticuerpo" que se presenta naturalmente es una glicoproteína que comprende cuando menos dos cadenas pesadas (H) y dos cadenas ligeras (L) interconectadas por enlaces de disulfuro. Cada cadena pesada está comprendida de una región variable de cadena pesada (abreviada en la presente como VH), y una región constante de cadena pesada. La región constante de cadena pesada está comprendida de tres dominios, CH1 CH2, y CH3. Cada cadena ligera está comprendida de una región variable de cadena ligera (abreviada en la presente como VL), y una región constante de cadena ligera. La región constante de cadena ligera está comprendida de un dominio, CL. Las regiones VH y VL se pueden subdividir adicionalmente en regiones de hipervariabilidad, denominadas como regiones determinantes de complementariedad (CDR), intercaladas con regiones que están más conservadas, denominadas como regiones de estructura (FR). Cada VH y VL está compuesta de tres regiones determinantes de complementariedad y cuatro regiones de estructura configuradas desde el término amino hasta el término carboxilo en el siguiente orden: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Las regiones variables de las cadenas

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pesada y ligera contienen un dominio de enlace que interactúa con un antígeno. Las regiones constantes de los anticuerpos pueden mediar el enlace de la inmunoglobulina a los tejidos o factores del huésped, incluyendo diferentes células del sistema inmunitario (por ejemplo, las células efectoras), y el primer componente (C1q) del sistema de complemento clásico.

El término "porción de enlace de antígeno" de un anticuerpo, como se utiliza en la presente, se refiere a uno o más fragmentos de un anticuerpo intacto, que retienen la capacidad para enlazarse específicamente a un antígeno dado (por ejemplo, C5). Las funciones de enlace de antígeno de un anticuerpo se pueden llevar a cabo mediante los fragmentos de un anticuerpo intacto. Los ejemplos de los fragmentos de enlace abarcados dentro del término "porción de enlace de antígeno" de un anticuerpo incluyen un fragmento Fab, un fragmento monovalente que consiste en los dominios VL, VH, CL, y CH1; un fragmento $F(ab)_2$, un fragmento bivalente que comprende dos fragmentos Fab enlazados por un puente de bisulfuro en la región de articulación; un fragmento Fd que consiste en los dominios VH y CH1; un fragmento Fv que consiste en los dominios VL y VH de un solo brazo de un anticuerpo; un fragmento de anticuerpo de un solo dominio (DAB) (Ward y colaboradores, 1989 Nature 341:544-546), que consiste en un dominio VH; y una región determinante de complementariedad aislada (CDR).

Adicionalmente, aunque los dos dominios del fragmento Fv, VL y VH, son codificados por genes separados, se pueden unir,

empleando métodos recombinantes, mediante un enlazador peptídico artificial, que les hace posible formarse como una sola cadena de proteína, en donde se emparejan las regiones VL y VH para formar moléculas monovalentes (conocidas como Fv de una sola cadena (scFv); véanse, por ejemplo, Bird y colaboradores, 1988 Science 242:423-426; y Huston y colaboradores, 1988 Proc. Natl. Acad. Sci. 85:5879-5883). Estos anticuerpos de una sola cadena incluyen una o más "porciones de enlace de antígeno" de un anticuerpo. Estos fragmentos de anticuerpo se obtienen empleando las técnicas convencionales conocidas por los expertos en este campo, y los fragmentos se rastrean para determinar su utilidad de la misma manera que los anticuerpos intactos.

Las porciones de enlace de antígeno también se pueden incorporar en anticuerpos de un solo dominio, maxicuerpos, minicuerpos, intracuerpos, diacuerpos, triacuerpos, tetracuerpos, v-NAR y bis-scFv (véase, por ejemplo, Hollinger y Hudson, 2005, Nature Biotechnology, 23, 9, 1126-1136). Las porciones de enlace de antígeno de los anticuerpos se pueden injertar en andamiajes basados en polipéptidos, tales como fibronectina tipo III (Fn3) (véase la Patente de los Estados Unidos de Norteamérica Número 6,703,199, la cual describe monocuerpos de polipéptido de fibronectina).

Las porciones de enlace de antígeno se pueden incorporar en las moléculas de una sola cadena que comprenden un par de segmentos Fv en fila (VH-CH1-VH-CH1) que, junto con los

polipéptidos de cadena ligera complementarios, forman un par de regiones de enlace de antígeno (Zapata y colaboradores, 1995 Protein Eng. 8(10):1057-1062; y Patente de los Estados Unidos de Norteamérica Número 5,641,870).

Como se utiliza en la presente, el término "afinidad" se refiere a la fuerza de interacción entre el anticuerpo y el antígeno en los sitios antigénicos individuales. Dentro de cada sitio antigénico, la región variable el "brazo" del anticuerpo interactúa a través de las fuerzas no covalentes débiles con el antígeno en numerosos sitios; mientras más interacciones haya, más fuerte será la afinidad.

Como se utiliza en la presente, el término "Avidez" se refiere a una medida informativa de la estabilidad o fuerza global del complejo de anticuerpo-antígeno. Se controla mediante tres factores principales: afinidad de epítopo del anticuerpo; la valencia de tanto el antígeno como del anticuerpo; y la configuración estructural de las partes que interactúan. Finalmente, estos factores definen la especificidad del anticuerpo, es decir, la probabilidad de que el anticuerpo particular se enlace a un epítopo de antígeno preciso.

El término "aminoácido" se refiere a los aminoácidos que se presentan naturalmente y sintéticos, así como a los análogos de aminoácidos y a los miméticos de aminoácidos que funcionan de una manera similar a los aminoácidos que se presentan naturalmente. Los aminoácidos que se presentan naturalmente son aquéllos codificados por el código genético, así como los aminoácidos que son modificados posteriormente, por ejemplo, hidroxi-prolina, γ-

carboxi-glutamato, y o-fosfoserina. Los análogos de aminoácidos se refieren a los compuestos que tienen la misma estructura química básica que un aminoácido que se presente naturalmente, es decir, un carbono-alfa que se enlaza a un hidrógeno, un grupo carboxilo, un grupo amino, y un grupo R, por ejemplo, homoserina, norleucina, sulfóxido de metionina, metionina-metil-sulfonio. Estos análogos tienen grupos R modificados (por ejemplo, norleucina), o estructuras base peptídicas modificadas, pero retienen la misma estructura química básica que un aminoácido que se presente naturalmente. Los miméticos de aminoácidos se refieren a los compuestos químicos que tienen una estructura que es diferente de la estructura química general de un aminoácido, pero que funcionan de una manera similar a un aminoácido que se presente naturalmente.

El término "especificidad de enlace", como se utiliza en la presente, se refiere a la capacidad de un sitio de combinación de anticuerpo individual para reaccionar solamente con un determinante antigénico. El sitio de combinación del anticuerpo se localiza en la porción Fab de la molécula, y se construye a partir de las regiones hipervariables de las cadenas pesada y ligera. La afinidad de enlace de un anticuerpo es la fuerza de la reacción entre un solo determinante antigénico y un solo sitio de combinación sobre el anticuerpo. Es la suma de las fuerzas de atracción y de repulsión que operan entre el determinante antigénico y el sitio de combinación del anticuerpo.

El enlace específico entre dos entidades significa un enlace

con una constante en equilibrio (K_A) de cuando menos 1 x 10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, ó 10^{11} M^{-1}. La frase "se enlaza específicamente (o selectivamente)" a un anticuerpo (por ejemplo, un anticuerpo de enlace de C5), se refiere a una reacción de enlace que determina la presencia de un antígeno cognado (por ejemplo, un C5 humano o un C5 de cinomolgo) en una población heterogénea de proteínas y otros productos biológicos. En adición a la constante en equilibrio (K_A) mencionada anteriormente, un anticuerpo de enlace de C5 de la invención típicamente también tiene una constante de índice de disociación (Kd) de aproximadamente 1 x 10^{-2} s^{-1}, 1 x 10^{-3} s^{-1}, 1 x 10^{-4} s^{-1}, 1 x 10^{-4} s^{-1}, o más baja, y se enlaza a C5 con una afinidad que es cuando menos dos veces mayor que su afinidad para el enlace con un antígeno no específico (por ejemplo, C3, C4, BSA). Las frases "un anticuerpo que reconoce un antígeno" y "un anticuerpo específico para un antígeno" se utilizan de una manera intercambiable en la presente con el término "un anticuerpo que se enlace específicamente a un antígeno".

El término "anticuerpo quimérico" es una molécula de anticuerpo en donde: (a) la región constante, o una porción de la misma, es alterada, reemplazada, o intercambiada, de tal manera que el sitio de enlace de antígeno (región variable) se enlaza a una región constante de una clase, función efectora, y/o especie diferente o alterada, o una molécula enteramente diferente que confiere nuevas propiedades al anticuerpo quimérico, por ejemplo, una enzima, toxina, hormona, factor de crecimiento, fármaco, etc.; o

(b) la región variable, o una porción de la misma, es alterada, reemplazada, o intercambiada con una región variable que tiene una especificidad de antígeno diferente o alterada. Por ejemplo, un anticuerpo de ratón se puede modificar reemplazando su región constante con la región constante de una inmunoglobulina humana. Debido al reemplazo con una región constante humana, el anticuerpo quimérico puede retener su especificidad en el reconocimiento del antígeno, mientras que puede tener una antigenicidad reducida en el ser humano, comparándose con el anticuerpo de ratón original.

Los términos "proteína de complemento C5" o "C5" se utilizan de una manera intercambiable, y se refieren a la proteína C5 en diferentes especies. Por ejemplo, la C5 humana tiene la secuencia como se estipula en la SEQ ID NO: 296, la C5 de cinomolgo tiene la secuencia como se estipula en la SEQ ID NO: 297 (*Macaca fascicularis*) (véase la Tabla 1). La C5 humana se puede obtener a partir de Quidel (Número de Catálogo A403). La C5 de cinomolgo se puede producir como se ilustra en la sección de Ejemplos más adelante.

El término "variante conservadoramente modificada" se aplica a las secuencias tanto de aminoácidos como se ácidos nucleicos. Con respecto a las secuencias de ácidos nucleicos particulares, las variantes conservadoramente modificadas se refieren a los ácidos nucleicos que codifican secuencias de aminoácidos idénticas o esencialmente idénticas, o en donde el ácido nucleico no codifica una secuencia de aminoácidos, hasta secuencias esencialmente

idénticas. Debido a la degeneración del código genético, un gran número de ácidos nucleicos funcionalmente idénticos codifican cualquier proteína dada. Por ejemplo, los codones GCA, GCC, GCG y GCU codifican todos al aminoácido alanina. Por consiguiente, en cada posición en donde un codón especifique una alanina, el codón se puede alterar hasta cualquiera de los codones correspondientes descritos, sin alterar el polipéptido codificado. Estas variaciones de ácidos nucleicos son "variaciones silencionadas", las cuales son una especie de variaciones conservadoramente modificadas. Cada secuencia de ácido nucleico de la presente que codifique un polipéptido, también describe cada posible variación silenciosa del ácido nucleico. Un experto reconocerá que cada codón de un ácido nucleico (con la excepción de AUG, que ordinariamente es el único codón para metionina, y TGG, que ordinariamente es el único codón para triptófano), se puede modificar para proporcionar una molécula funcionalmente idéntica. De conformidad con lo anterior, cada variación silenciosa de un ácido nucleico que codifique un polipéptido está implícita en cada secuencia descrita.

Para las secuencias de polipéptidos, las "variantes conservadoramente modificadas" incluyen sustituciones, supresiones, o adiciones individuales a una secuencia de polipéptido, que dan como resultado la sustitución de un aminoácido con un aminoácido químicamente similar. Las tablas de sustitución conservadora que proporcionan aminoácidos funcionalmente similares son bien conocidas en este campo. Estas variantes

conservadoramente modificadas son en adición a, y no excluyen, las variantes polimórficas, los homólogos inter-especies, y los alelos de la invención. Los siguientes ocho grupos contienen los aminoácidos que son sustituciones conservadoras unas por otras: (1) Alanina (A), Glicina (G); 2) ácido aspártico (D), ácido glutámico (E); 3) Asparagina (N), Glutamina (Q); 4) Arginina (R), Lisina (K); 5) Isoleucina (I), Leucina (L), Metionina (M), Valina (V); 6) Fenilalanina (F), Tirosina (Y), Triptófano (W); 7) Serina (S), Treonina (T); y 8) Cisteína (C), Metionina (M) (véase, pro ejemplo, Creighton, Proteins (1984)). En algunas modalidades, el término "modificaciones de secuencia conservadoras", se utiliza para referirse a las modificaciones de aminoácidos que no afectan o alteran de una manera significativa las características de enlace del anticuerpo que contiene la secuencia de aminoácidos.

Los términos "bloqueo cruzado", "cruzadamente bloqueado", y "bloquear cruzadamente", se utilizan una manera intercambiable en la presente, para significar la capacidad de un anticuerpo u otro agente de enlace para interferir con el enlace de otros anticuerpos o agentes de enlace para C5, en un ensayo de enlace competitivo convencional.

La capacidad o el grado hasta el cual un anticuerpo u otro agente de enlace es capaz de interferir con el enlace de otro anticuerpo o molécula de enlace con C5, y por consiguiente, si se puede decir que se bloquea cruzadamente de acuerdo con la invención, se puede determinar empleando ensayos de enlace de

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competencia convencionales. Un ensayo adecuado involucra el uso de la tecnología Biacore (por ejemplo, utilizando el instrumento Biacore 300 (Biacore, Uppsala, Suecia)), que puede medir la extensión de las interacciones utilizando la tecnología de resonancia de plasmón superficial. Otro ensayo para medir el bloqueo cruzado utiliza un planteamiento basado en ELISA.

El término "epítopo" significa un determinante de proteína capaz de enlazarse específicamente a un anticuerpo. Los epítopos normalmente consisten en agrupaciones superficiales químicamente activas de moléculas, tales como aminoácidos o cadenas laterales de azúcar, y usualmente tienen características estructurales tridimensionales específicas, así como características de carga específicas. Los epítopos de conformación y no de conformación se distinguen porque se pierde el enlace con el primero pero no con el último en la presencia de solventes desnaturalizantes.

Como se utiliza en la presente, el término "alta afinidad" por un anticuerpo de IgG, se refiere a un anticuerpo que tiene una KD de 10^{8} M o menos, de 10^{-9} o menos, o de 10^{10} M, o de 10^{-11} o menos, por un antígeno objetivo. Sin embargo, el enlace de "alta afinidad" puede variar para otros isotipos de anticuerpos. Por ejemplo, el enlace de "alta afinidad" por un isotipo de IgM se refiere a un anticuerpo que tiene una KD de 10^{-7} M o menos, o de 10^{-8} M o menos.

El término "anticuerpo humano", como se utiliza en la presente, pretende incluir los anticuerpos que tienen regiones variables en

donde tanto la región de estructura como las regiones determinantes de complementariedad se derivan a partir de secuencias de origen humano. Adicionalmente, si el anticuerpo contiene una región constante, la región constante también se deriva a partir de estas secuencias humanas, por ejemplo, las secuencias de la línea germinal humana, o las versiones mutadas de las secuencias de la línea germinal humana. Los anticuerpos humanos de la invención pueden incluir residuos de aminoácidos no codificados por las secuencias humanas (por ejemplo, mutaciones introducidas mediante mutagénesis aleatoria o específica del sitio *in vitro*, o mediante mutación somática *in vivo*).

El término "anticuerpo monoclonal humano" se refiere a los anticuerpos que exhiben una sola especificidad de enlace, que tienen regiones variables en donde tanto las regiones de estructura como las regiones determinantes de complementariedad se derivan a partir de secuencias humanas. En una modalidad, los anticuerpos monoclonales humanos son producidos por un hibridoma, el cual incluye una célula-B obtenida a partir de un animal no humano transgénico, por ejemplo, un ratón transgénico, que tenga un genoma que comprenda un transgén de cadena pesada humano, y un transgén de cadena ligera fusionados a una célula inmortalizada.

Un anticuerpo "humanizado" es un anticuerpo que retiene la reactividad de un anticuerpo no humano, mientras que es menos inmunogénico en los seres humanos. Esto se puede lograr, por ejemplo, mediante la retención de las regiones determinantes de

complementariedad no humanas, y reemplazando las partes restantes del anticuerpo con sus contrapartes humanas (es decir, la región constante así como las porciones de estructura de la región variable). Véanse, por ejemplo, Morrison y colaboradores, Proc. Natl. Acad. Sci. EUA, 81:6851-6855, 1984; Morrison y Oi, Adv. Immunol., 44:65-92, 1988; Verhoeyen y colaboradores, Science, 239:1534-1536, 1988; Padlan, Molec. Immun., 28:489-498, 1991; y Padlan, Molec. Immun., 31:169-217, 1994. Otros ejemplos de la tecnología de ingeniería humana incluyen, pero no se limitan a, la tecnología Xoma que se da a conocer en la Patente de los Estados Unidos de Norteamérica Número US 5,766,886.

Los términos "idéntica" o porcentaje de "identidad", en el contexto de dos o más secuencias de ácidos nucleicos o de polipéptido, se refieren a dos o más secuencias o subsecuencias que son iguales. Dos secuencias son "sustancialmente idénticas" si las dos secuencias tienen un porcentaje especificado de residuos de aminoácidos o nucleótidos que son iguales (es decir, identidad del 60 por ciento, y opcionalmente identidad del 65 por ciento, del 70 por ciento, del 75 por ciento, 80 por ciento, 85 por ciento, 90 por ciento, 95 por ciento, o del 99 por ciento sobre una región especificada, o, cuando no se especifique, sobre toda la secuencia), al compararse y alinearse para una máxima correspondencia sobre una ventana de comparación, o la región designada medida utilizando uno de los siguientes algoritmos de comparación de secuencias, o mediante alineación manual e inspección visual. Opcionalmente, la identidad

existe sobre una región que es de cuando menos aproximadamente 50 nucleótidos (o 10 aminoácidos) de longitud, o más preferiblemente, sobre una región que es de 100 a 500 ó 1,000 o más nucleótidos (o 20, 50, 200 o más aminoácidos) de longitud.

Para la comparación de secuencias, típicamente una secuencia actúa como una secuencia de referencia, con la cual se comparan las secuencias de prueba. Cuando se utiliza un algoritmo de comparación de secuencias, se introducen las secuencias de prueba y de referencia en una computadora, se designan las coordenadas de las subsecuencias, si es necesario, y se designan los parámetros del programa de algoritmo de secuencias. Se pueden utilizar los parámetros del programa por omisión, o se pueden designar parámetros alternativos. El algoritmo de comparación de secuencias calcula entonces el porcentaje de identidad de secuencia para las secuencias de prueba en relación con la secuencia de referencia, basándose en los parámetros del programa.

Una "ventana de comparación", como se utiliza en la presente, incluye la referencia a un segmento de cualquiera del número de posiciones contiguas seleccionadas a partir del grupo que consiste en de 20 a 600, usualmente de aproximadamente 50 a aproximadamente 200, más usualmente de aproximadamente 100 a aproximadamente 150, en donde se puede comparar una secuencia con una secuencia de referencia del mismo número de posiciones contiguas después de que se alinean óptimamente las dos secuencias. Los métodos de alineación de secuencias para

comparación son bien conocidos en este campo. La alineación óptima de las secuencias para comparación se puede conducir, por ejemplo, mediante el algoritmo de homología local de Smith y Waterman (1970) Adv. Appl. Math. 2:482c, mediante el algoritmo de alineación de homología de Needleman y Wunsch, J. Mol. Biol. 48:443, 1970, mediante el método de búsqueda de similitudes de Pearson y Lipman, Proc. Nat'l. Acad. Sci. EUA 85:2444, 1988, mediante implementaciones computarizadas de estos algoritmos (GAP, BESTFIT, FASTA, y TFASTA en el Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), o mediante alineación manual e inspección visual (véase, por ejemplo, Brent y colaboradores, Current Protocols in Molecular Biology, John Wiley & Sons, Inc. (Ringbou, Editor, 2003)).

Dos ejemplos de algoritmos que son adecuados para determinar el porcentaje de identidad de secuencias y de similitud de secuencias son los algoritmos BLAST y BLAS 2.0, los cuales se describen en Altschul y colaboradores, Nuc. Acids Res. 25:3389-3402, 1977; y Altschul y colaboradores, J. Mol. Biol. 215:403-410, 1990, respectivamente. El software para llevar a cabo los análisis BLAST está públicamente disponible a través del National Center for Biotechnology Information. Este algoritmo involucra identificar primero los pares de secuencias de alto puntaje (HSPs), mediante la identificación de las palabras cortas de longitud W en la secuencia pedida, las cuales concuerdan o satisfacen algún puntaje umbral T de valor positivo cuando se alinean con una palabra de la misma

longitud en una secuencia de la base de datos. T es referido como el umbral de puntaje de palabra vecina (Altschul y colaboradores, *supra*). Estos impactos de palabra vecina iniciales actúan como siembras para iniciar las búsquedas con el fin de encontrar pares de secuencias de alto puntaje más largos que las contengan. Los impactos de palabras se extienden en ambas direcciones a lo largo de cada secuencia por tanto como se pueda aumentar el puntaje de alineación acumulativo. Los puntajes acumulativos se calculan utilizando, para las secuencias de nucleótidos, los parámetros M (puntaje de recompensa para un par de residuos emparejados; siempre >0), y N (puntaje de multa para los residuos mal emparejados; siempre <0). Para las secuencias de aminoácidos, se utiliza una matriz de puntaje para calcular el puntaje acumulativo. La extensión de los impactos de palabras en cada dirección se detienen cuando: el puntaje de alineación acumulativo cae fuera por la cantidad X desde su máximo valor alcanzado; el puntaje acumulativo llega a cero o menos, debido a la acumulación de una o más alineaciones de residuos de puntaje negativo; o se llega al final de cualquiera de las secuencias. Los parámetros W, T, y X del algoritmo BLAST determinan la sensibilidad y velocidad de la alineación. El programa BLASTN (para secuencias de nucleótidos) utiliza como omisión una longitud de palabra (W) de 11, una expectativa (E) de 10, M=5, N=-4, y una comparación de ambas cadenas. Para las secuencias de aminoácidos, el programa BLASTP utiliza por omisión una longitud de palabra de 3, y una expectativa (C) de 10, y la matriz

de puntaje BLOSUM62 (véase Henikoff y Henikoff, Proc. Natl. Acad. Sci. EUA 89:10915, 1989) alineaciones (B) de 50, expectativa (E) de 10, M=5, N=-4, y una comparación de ambas cadenas.

El algoritmo BLAST también lleva a cabo un análisis estadístico de la similitud entre dos secuencias (véase, por ejemplo, Karlin y Altschul, Proc. Natl. Acad. Sci. EUA 90:5873-5787, 1993). Una medida de similitud proporcionada por el algoritmo BLAST es la probabilidad de suma más pequeña (P(N)), que proporciona una indicación de la probabilidad por la cual se presentaría un emparejamiento entre dos secuencias de nucleótidos o de aminoácidos por azar. Por ejemplo, un ácido nucleico se considera similar a una secuencia de referencia si la probabilidad de suma más pequeña en una comparación del ácido nucleico de prueba con el ácido nucleico de referencia es menor de aproximadamente 0.2, más preferiblemente menor de aproximadamente 0.01, y de una manera muy preferible menor de aproximadamente 0.001.

El porcentaje de identidad entre dos secuencias de aminoácidos también se puede determinar utilizando el algoritmo de E. Meyers y W. Miller (Comput. Appl. Biosci., 4:11-17, 1988), el cual se ha incorporado en el programa ALIGN (Versión 2.0), utilizando una tabla de residuos ponderados PAM120, una multa por longitud de hueco de 12, y una multa por hueco de 4. En adición, el porcentaje de identidad entre dos secuencias de aminoácidos se puede determinar utilizando el algoritmo de Needleman y Wunsch (J. Mol, Biol. 48:444-453, 1970), el cual se ha incorporado en el

programa GAP en el paquete de software GCG (disponible en www.gcg.com), utilizando ya sea una matriz BLOSUM62 o bien una matriz PAM250, y un peso de hueco de 16, 14, 12, 10, 8, 6, ó 4, y un peso por longitud de 1, 2, 3, 4, 5, ó 6.

De otra manera que no sea el porcentaje de identidad de secuencias observado anteriormente, otra indicación de que dos secuencias de ácidos nucleicos o polipéptidos son sustancialmente idénticas, es que el polipéptido codificado por el primer ácido nucleico reacciona cruzadamente inmunológicamente con los anticuerpos reproducidos contra el polipéptido codificado por el segundo ácido nucleico, como se describe más adelante. Por consiguiente, un polipéptido típicamente es sustancialmente idéntico a un segundo polipéptido, por ejemplo, cuando los dos polipéptidos difieren solamente por sustituciones conservadoras. Otra indicación de que dos secuencias de ácidos nucleicos son sustancialmente idénticas, es que las dos moléculas o sus complementos se hibridan una a la otra bajo condiciones restringentes, como se describe más adelante. Todavía otra indicación de que dos secuencias de ácidos nucleicos son sustancialmente idénticas, es que se pueden utilizar los mismos cebadores para amplificar la secuencia.

El término "anticuerpo aislado" se refiere a un anticuerpo que está sustancialmente libre de otros anticuerpos que tengan diferentes especificidades antigénicas (por ejemplo, un anticuerpo aislado que se enlaza específicamente a C5 está sustancialmente libre de anticuerpos que se enlacen específicamente con antígenos

diferentes de C5). Un anticuerpo aislado que se enlaza específicamente a C5, sin embargo, puede tener reactividad cruzada con otros antígenos. Más aún, un anticuerpo aislado puede estar sustancialmente libre de otro material celular y/o de productos químicos.

El término "isotipo" se refiere a la clase de anticuerpos (por ejemplo, IgM, IgE, IgG, tal como IgG1 ó IgG4), que es proporcionada por los genes de región constante de cadena pesada. El isotipo también incluye las versiones modificadas de una de estas clases, en donde las modificaciones se han hecho para alterar la función de Fc, por ejemplo, para mejorar o reducir las funciones efectoras o el enlace con los receptores de Fc.

El término "Kasoc" o "Ka", como se utiliza en la presente, pretende referirse al índice de asociación de una interacción particular de anticuerpo-antígeno, mientras que el término "Kdis" o "Kd" como se utiliza en la presente, pretende referirse al índice de disociación de una interacción particular de anticuerpo-antígeno. El término "K_D", como se utiliza en la presente, pretende referirse a la constante de disociación, la cual se obtiene a partir de la proporción de Kd a Ka (es decir, Kd/Ka), y se expresa como una concentración molar (M). Los valores K_D para los anticuerpos se pueden determinar empleando los métodos bien establecidos en este campo. Un método para determinar la K_D de un anticuerpo, es mediante la utilización de resonancia de plasmón superficial, o mediante la utilización de un sistema biosensor, tal como un sistema Biacore®.

Los términos "anticuerpo monoclonal" o composición de anticuerpo monoclonal", como se utilizan en la presente, se refieren a una preparación de moléculas de anticuerpo de una sola composición molecular. Una composición de anticuerpo monoclonal exhibe una sola especificidad de enlace y afinidad por un epítopo particular.

El término "ácido nucleico" se utiliza en la presente de una manera intercambiable con el término "polinucleótido", y se refiere a los desoxirribonucleótidos a o los ribonucleótidos y polímeros de los mismos, ya sea en la forma de una sola cadena o de doble cadena. El término abarca los ácidos nucleicos que contienen análogos de nucleótidos conocidos, o residuos de estructura o enlaces modificados, que son sintéticos, que se presentan naturalmente, y que no se presentan naturalmente, los cuales tienen propiedades de enlace similares a las del ácido nucleico de referencia, y los cuales se metabolizan de una manera similar a los nucleótidos de referencia. Los ejemplos de estos análogos incluyen, sin limitación, fosforotioatos, fosforamidatos, fosfonatos de metilo, fosfonatos de metilo quirales, 2-O-metil-ribonucleótidos, ácidos nucleicos peptídicos (PNAs).

A menos que se indique de otra manera, una secuencia de ácido nucleico particular también abarca implícitamente variantes conservadoramente modificadas de la misma (por ejemplo, sustituciones de codones degenerados), y secuencias complementarias, así como la secuencia explícitamente indicada. De

una manera más específica, como se detalla más adelante, se pueden lograr sustituciones de codones degenerados mediante la generación de secuencias en donde la tercera posición de uno o más (o todos) codones seleccionados, es sustituida con residuos de base mixta y/o de desoxi-inosina (Batzer y colaboradores, Nucleic Acid Res. 19:5081, 1991; Ohtsuka y colaboradores, J. Biol. Chem. 260:2605-2608, 1985; y Rossolini y colaboradores, Mol. Cell. Probes 8:91-98, 1994).

El término "operablemente enlazado" se refiere a una relación funcional entre dos o más segmentos de polinucleótido (por ejemplo, ADN). Típicamente, se refiere a la relación funcional de una secuencia reguladora de transcripción con una secuencia transcrita. Por ejemplo, una secuencia promotora o potenciadora se enlaza operablemente a una secuencia de codificación si estimula o modula la transcripción de la secuencia de codificación en una célula huésped apropiada o en otro sistema de expresión. En términos generales, las secuencias reguladoras de transcripción del promotor que se enlazan operablemente a una secuencia transcrita, están físicamente contiguas a la secuencia transcrita, es decir, son de acción-*cis*. Sin embargo, algunas secuencias reguladoras de transcripción, tales como las potenciadoras, no necesitan estar físicamente contiguas o localizadas en estrecha proximidad a las secuencias de codificación cuya transcripción potencian.

Como se utiliza en la presente, el término "optimizada" significa una secuencia de nucleótidos que se ha alterado para

codificar una secuencia de aminoácidos, utilizando los codones que son preferidos en la célula u organismo de producción, en general una célula eucariótica, por ejemplo, una célula de *Pichia*, una célula de ovario de hámster chino (CHO), o una célula humana. La secuencia de nucleótidos optimizada se diseña para retener completamente o tanto como sea posible la secuencia de aminoácidos originalmente codificada por la secuencia de nucleótidos de partida, que también se conoce como la secuencia "progenitora". Las secuencias optimizadas de la presente se han diseñado para tener codones que son preferidos en las células de mamífero. Sin embargo, también se prevé en la presente la expresión optimizada de estas secuencias en otras células eucarióticas o células procarióticas. Las secuencias de aminoácidos codificadas por las secuencias de nucleótidos optimizadas también son referidas como optimizadas.

Los términos "polipéptido" y "proteína" se utilizan de una manera intercambiable en la presente para referirse a un polímero de residuos de aminoácidos. Los términos se aplican a los polímeros de aminoácidos en donde uno o más residuos de aminoácidos son un mimético químico artificial de un aminoácido que se presente naturalmente correspondiente, así como a los polímeros de aminoácidos que se presentan naturalmente y a los polímeros de aminoácidos que no se presentan naturalmente. A menos que se indique de otra manera, una secuencia de polipéptido particular también abarca implícitamente variantes conservadoramente

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modificadas del mismo.

El término "anticuerpo humano recombinante", como se utiliza en la presente, incluye todos los anticuerpos humanos que se preparan, se expresan, se crean, o se aíslan por medios recombinantes, tales como los anticuerpos aislados a partir de un animal (por ejemplo, un ratón) que sea transgénico o transcromosómico para los genes de inmunoglobulina humana, o para un hibridoma preparado a partir de los mismos, los anticuerpos aislados a partir de una célula huésped transformada para expresar el anticuerpo humano, por ejemplo, a partir de un transfectoma, los anticuerpos aislados a partir de una biblioteca de anticuerpos humanos de combinación recombinantes, y los anticuerpos preparados, expresados, creados, o aislados por cualquier otro medio que involucre el empalme de todo o una porción de un gen de inmunoglobulina humana, y las secuencias para otras secuencias de ADN. Estos anticuerpos humanos recombinantes tienen regiones variables en donde las regiones de estructura y las regiones determinantes de complementariedad se derivan a partir de las secuencias de inmunoglobulina de la línea germinal humana. Sin embargo, en ciertas modalidades, estos anticuerpos humanos recombinantes se pueden someter a mutagénesis *in vitro* (o, cuando se utiliza un animal transgénico para las secuencias de Ig humana, mutagénesis somática *in vivo*), y por lo tanto, las secuencias de aminoácidos de las regiones VH y VL de los anticuerpos recombinantes son secuencias que, aunque se derivan a partir de, y

se relacionan con, las secuencias VH y VL de la línea germinal humana, pueden no existir naturalmente dentro del repertorio de la línea germinal de anticuerpos humanos *in vivo*.

El término "célula huésped recombinante" (o simplemente "célula huésped") se refiere a una célula en donde se ha introducido un vector de expresión recombinante. Se debe entender que estos términos pretenden referirse no solamente a la célula objeto particular, sino también a la progenie de esta célula. Debido a que se pueden presentar ciertas modificaciones en las siguientes generaciones debido ya sea a mutación o a influencias del medio ambiente, esta progenie, de hecho, puede no ser idéntica a la célula progenitora, pero todavía se puede incluir dentro del alcance del término "célula huésped" como se utiliza en la presente.

El término "sujeto" incluye los animales humanos y no humanos. Los animales no humanos incluyen a todos los vertebrados, por ejemplo, mamíferos y no mamíferos, tales como primates no humanos, ovejas, perros, vacas, pollos, anfibios, y reptiles. Excepto cuando se observe, los términos "paciente" o "sujeto" se utilizan en la presente de una manera intercambiable.

El término "tratamiento" incluye la administración de las composiciones o los anticuerpos para prevenir o demorar el establecimiento de los síntomas, complicaciones, o indicaciones bioquímicas de una enfermedad (por ejemplo, degeneración macular relacionada con la edad), para aliviar los síntomas o detener o inhibir el desarrollo adicional de la enfermedad, condición, o trastorno. El

tratamiento puede ser profiláctico (para prevenir o demorar el establecimiento de la enfermedad, o para prevenir la manifestación de los síntomas clínicos o subclínicos de la misma), o la supresión terapéutica o el alivio de los síntomas después de la manifestación de la enfermedad.

El término "vector" pretende referirse a una molécula de polinucleótido capaz de transportar a otro polinucleótido con el que se ha enlazado. Un tipo de vector es un "plásmido", el cual se refiere a un ciclo de ADN de doble cadena circular en donde se pueden ligar segmentos adicionales de ADN. Otro tipo de vector es un vector viral, en donde se pueden ligar segmentos de ADN adicionales en el genoma viral. Ciertos vectores son capaces de tener una réplica autónoma en una célula huésped en donde se introducen (por ejemplo, los vectores bacterianos que tienen un origen de réplica bacteriano, y los vectores de mamífero episomales). Otros vectores (por ejemplo, vectores de mamífero no episomales) se pueden integrar en el genoma de una célula huésped después de su introducción en la célula huésped, y de esta manera, se replican junto con el genoma del huésped. Más aún, ciertos vectores son capaces de dirigir la expresión de los genes con los que se enlazan operativamente. Estos vectores son referidos en la presente como "vectores de expresión recombinante" (o simplemente, "vectores de expresión"). En general, los vectores de expresión útiles en las técnicas de ADN recombinante están con frecuencia en la forma de plásmidos. En la presente memoria descriptiva, "plásmido" y "vector"

se pueden utilizar de una manera intercambiable, debido a que el plásmido es la forma más comúnmente utilizada de vector. Sin embargo, la invención pretende incluir las otras formas de vectores de expresión, tales como vectores virales (por ejemplo, retrovirus defectuosos en réplica, adenovirus, y virus adeno-asociados), los cuales sirven para funciones equivalentes.

4. BREVE DESCRIPCIÓN DE LAS FIGURAS.

La Figura 1 muestra las alineaciones de las regiones variables de los anticuerpos seleccionados con sus secuencias de la línea germinal humana más estrechamente relacionadas.

La Figura 2 muestra un ensayo hemolítico en donde se titula la C5 humana en el suero agotado de C5 humana, para determinar la actividad de C5.

La Figura 3 muestra la titulación del suero de cinomolgo en el suero agotado de C5 humana, para determinar la concentración de C5 de cinomolgo óptima, para el ensayo hemolítico de la senda alternativa.

La Figura 4 muestra ejemplos de los ensayos hemolíticos de la senda clásica con suero humano al 20 por ciento.

La Figura 5 muestra ejemplos de los ensayos hemolíticos de la senda alternativa con la C5 humana purificada 100 pM agregada al suero agotado de C5 humana.

La Figura 6 muestra los ejemplos de los ensayos hemolíticos de la senda alternativa con suero de cinomolgo al 0.025 por ciento agregado al suero agotado de C5 humana.

La Figura 7 muestra los ejemplos de los ensayos hemolíticos de la senda clásica (suero humano al 20 por ciento), con Fabs maduros, en comparación con sus progenitores respectivos.

La Figura 8 muestra los ejemplos de los ensayos hemolíticos de la senda clásica (suero de cinomolgo al 5 por ciento) con los Fabs maduros.

La Figura 9 muestra la caracterización de Fab madurado por afinidad en el ensayo hemolítico de la senda alternativa, utilizando la C5 humana 100 pM agregada al suero agotado de C5 humana al 20 por ciento.

La Figura 10 muestra la caracterización del Fab madurado por afinidad en el ensayo hemolítico de la senda alternativa, utilizando suero humano al 20 por ciento.

La Figura 11 muestra la caracterización del Fab madurado por afinidad en el ensayo hemolítico de la senda alternativa, utilizando C5 de cinomolgo 100 pM agregada al suero agotado de C5 humana al 20 por ciento.

La Figura 12 muestra la caracterización de las IgGs de la línea germinal del ensayo hemolítico de la senda clásica, utilizando suero humano al 20 por ciento.

La Figura 13 muestra la caracterización de las IgGs de la línea germinal en el ensayo hemolítico de la senda clásica, utilizando suero de cinomolgo al 5 por ciento.

La Figura 14 muestra la caracterización de las IgGs de la línea germinal en el ensayo hemolítico de la senda alternativa, con C5

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humana 100 pM.

La Figura 15 muestra la caracterización de las IgGs de la línea germinal final en el ensayo hemolítico de la senda alternativa, y el ELISA de generación de C5a, utilizando suero humano al 20 por ciento.

La Figura 16 muestra la caracterización del Fab madurado por afinidad en el ELISA de C5a, utilizando el sobrenadante a partir de los ensayos hemolíticos de suero humano al 20 por ciento.

La Figura 17 muestra el ELISA en solución de especificidad sobre el anticuerpo 7091 de prueba de C3, C4, C5 humanas, y C5 de cinomolgo, y sus derivados.

La Figura 18 muestra los ensayos de estabilidad en suero (enlace con la C5 humana en la presencia de suero al 50 por ciento) con los Fabs.

La Figura 19 muestra el enlace de epítopo de algunos Fabs mejorados por afinidad.

La Figura 20 muestra un ELISA para el enlace del anticuerpo a la C5 quimérica de ratón-humana o a la C5 humana, para determinar los enlazadores de la cadena alfa contra los enlazadores de la cadena beta. C5 fue presentada por 5G1.1, para determinar la competencia con 5G1.1.

La Figura 21 muestra el ELISA para probar los enlazadores de la cadena alfa contra los enlazadores de la cadena beta con la captura de 5G1.1.

La Figura 22 muestra los resultados del ensayo hemolítico para

la prueba de los enlazadores de la cadena alfa contra los enlazadores de la cadena beta.

La Figura 23 muestra la proteólisis de termolisina de los Fabs progenitores a 37°C (a los 0, 30, 60, y 90 minutos).

La Figura 24 muestra la proteólisis de termolisina de termolisina de los Fabs progenitores a 55°C (a los 0, 30, 60, y 90 minutos).

La Figura 25 muestra la sensibilidad a la termolisina de los Fabs maduros a 37°C.

La Figura 26 muestra la sensibilidad a la termolisina de los Fabs maduros a 55°C.

La Figura 27 muestra los ejemplos de la inhibición de Fab de la senda alternativa en el ensayo de depósito de MAC.

5. DESCRIPCIÓN DETALLADA DE LA INVENCIÓN.

La presente invención proporciona anticuerpos que se enlazan específicamente a la proteína de complemento C5 (por ejemplo, C5 humana, C5 de cinomolgo), composiciones farmacéuticas, métodos de producción, y métodos de uso de estos anticuerpos y composiciones.

5.1 Anticuerpos de C5.

La presente invención proporciona anticuerpos que se enlazan específicamente a C5 (por ejemplo, C5 humana, C5 de cinomolgo). En algunas modalidades, la presente invención proporciona anticuerpos que se enlazan específicamente a C5 tanto humana como de cinomolgo. Los anticuerpos de la invención incluyen, pero

no se limitan a, los anticuerpos monoclonales humanos, aislados como se describe en los ejemplos (véase la sección 6 más adelante).

La presente invención proporciona anticuerpos que se enlazan específicamente a una proteína C5 (por ejemplo, C5 humana y/o de cinomolgo), comprendiendo estos anticuerpos un dominio VH que tiene una secuencia de aminoácidos de las SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, ó 281. La presente invención también proporciona anticuerpos que se enlazan específicamente a una proteína C5 (por ejemplo, C5 humana y/o de cinomolgo), comprendiendo estos anticuerpos una VH CDR que tiene una secuencia de aminoácidos de cualquiera de las VH CDRs enlistadas en la Tabla 1 más adelante. En particular, la invención proporciona anticuerpos que se enlazan específicamente a una proteína C5 (por ejemplo, C5 humana y/o de cinomolgo), comprendiendo estos anticuerpos (o de una manera alternativa, consistiendo en) una, dos, tres, cuatro, cinco, o más VH CDRs, que tienen una secuencia de aminoácidos de cualquiera de las VH CDRs enlistadas en la Tabla 1 más adelante.

La presente invención proporciona anticuerpos que se enlazan específicamente a una proteína C5 (por ejemplo, C5 humana y/o de cinomolgo), comprendiendo estos anticuerpos un dominio VL que tiene una secuencia de aminoácidos de las SEQ ID NOs: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, ó 289. La presente invención también

proporciona anticuerpos que se enlazan específicamente a una proteína C5 (por ejemplo, C5 humana y/o de cinomolgo), comprendiendo estos anticuerpos una VL CDR que tiene una secuencia de aminoácidos de cualquiera de las VL CDRs enlistadas en la Tabla 1 más adelante. En particular, la invención proporciona anticuerpos que se enlazan específicamente a una proteína C5 (por ejemplo, C5 humana y/o de cinomolgo), comprendiendo estos anticuerpos (o de una manera alternativa, consistiendo en) una, dos, tres, o más VL CDRs, que tienen una secuencia de aminoácidos de cualquiera de las VL CDRs enlistadas en la Tabla 1 más adelante.

Otros anticuerpos de la invención incluyen los aminoácidos que se han mutado, y no obstante, tienen una identidad de cuando menos el 60, 70, 80, 90, o el 95 por ciento en las regiones CDR, con las regiones CDR ilustradas en las secuencias descritas en la Tabla 1. En algunas modalidades, incluyen secuencias de aminoácidos mutantes, en donde se han mutado no más de 1, 2, 3, 4, ó 5 aminoácidos en las regiones CDR, cuando se comparan con las regiones CDR ilustradas en la secuencia descrita en la Tabla 1.

La presente invención también proporciona secuencias de ácidos nucleicos que codifican VH, VL, la cadena pesada de longitud completa, y la cadena ligera de longitud completa, de los anticuerpos que se enlazan específicamente a una proteína C5 (por ejemplo, C5 humana y/o de cinomolgo). Estas secuencias de ácidos nucleicos se pueden optimizar para su expresión en células de mamífero (por ejemplo, la Tabla 1 muestra las secuencias de ácidos nucleicos

optimizadas para la cadena pesada y la cadena ligera de los anticuerpos 8109, 8110, 8111, 8113, 8114, 8112, 8125, 8126, 8127, 8128, 8129, 8130, 8131, 8132, y 8091).

Tabla 1

Ejemplos de los Anticuerpos para C5 de la Presente Invención y de las Proteínas C5

Anticuerpo 8109	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	1: SYAIS
CDRH2	2: GIGPFFGTANYAQKFQG
CDRH3	3:DTPYFDY
CDRL1	4:SGDSIPNYYVY
CDRL2	5: DDSNRPS
CDRL3	6:QSFDSSLNAEV
VH	7:EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIGPFFGTANYAQKFQGRVTITADES TSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTV SS
VL	8:SYELTQPLSVSVALGQTARITCSGDSIPNYYVYWYQQK PGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTISRAQ

	AGDEADYYCQSFDSSLNAEVFGGGTKLTVL
Cadena Pesada	9:EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIGPFFGTANYAQKFQGRVTITADES TSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAP EAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
Cadena ligera	10:SYELTQPLSVSVALGQTARITCSGDSIPNYYVYWYQQ KPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTISRA QAGDEADYYCQSFDSSLNAEVFGGGTKLTVLGQPKAAP SVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSS PVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSY SCQVTHEGSTVEKTVAPTECS
PN que codifica SEQ ID NO:7	11:GAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAA AAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAGCC TCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGGT GCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGATGGG

	CGGTATCGGTCCGTTTTTTGGCACTGCGAATTACGCGC AGAAGTTTCAGGGCCGGGTGACCATTACCGCGGATGA AAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTG CGTAGCGAAGATACGGCCGTGTATTATTGCGCGCGTG ATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCTG GTGACGGTTAGCTCA
PN que codifica SEQ ID NO:8	12:TCCTATGAACTCACACAGCCCCTGAGCGTGAGCGT GGCCCTGGGCCAGACCGCCCGGATCACCTGCTCCGG CGACAGCATCCCCAACTACTACGTGTACTGGTACCAG CAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTACG ACGACAGCAACCGGCCCAGCGGCATCCCCGAGCGGTT CAGCGGCAGCAACAGCGGCAACACCGCCACCCTGACC ATTTCCAGAGCACAGGCAGGCGACGAGGCCGACTACT ACTGCCAGAGCTTCGACAGCAGCCTGAACGCCGAGGT GTTCGGCGGAGGGACCAAGTTAACCGTCCTA
PN que codifica SEQ ID NO:9	13:GAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAA AAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAGCC TCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGGT GCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGATGGG CGGTATCGGTCCGTTTTTTGGCACTGCGAATTACGCGC AGAAGTTTCAGGGCCGGGTGACCATTACCGCGGATGA AAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTG CGTAGCGAAGATACGGCCGTGTATTATTGCGCGCGTG

	ATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCTG
	GTGACGGTTAGCTCAGCCTCCACCAAGGGTCCATCGG
	TCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGG
	GGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTA
	CTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGC
	GCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCC
	TACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGT
	GACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC
	ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGG
	TGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACT
	CACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGG
	GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAA
	GGACACCCTCATGATCTCCCGGACCCCTGAGGTCACA
	TGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGG
	TCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCA
	TAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAAC
	AGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGC
	ACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAA
	GGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAA
	ACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCAC
	AGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGAC
	CAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGC
	TTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCA
	ATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCC

	CGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGC AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCA CAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCG GGTAAA
PN que codifica SEQ ID NO:10	14:TCCTATGAACTCACACAGCCCCTGAGCGTGAGCGT GGCCCTGGGCCAGACCGCCCGGATCACCTGCTCCGG CGACAGCATCCCCAACTACTACGTGTACTGGTACCAG CAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTACG ACGACAGCAACCGGCCCAGCGGCATCCCCGAGCGGTT CAGCGGCAGCAACAGCGGCAACACCGCCACCCTGACC ATTTCCAGAGCACAGGCAGGCGACGAGGCCGACTACT ACTGCCAGAGCTTCGACAGCAGCCTGAACGCCGAGGT GTTCGGCGGAGGGACCAAGTTAACCGTCCTAGGTCAG CCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCT CCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGT GTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACA GTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCG GGAGTGGAGACCACCACACCCTCCAAACAAAGCAACA ACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCC TGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAG GTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGG CCCCTACAGAATGTTCA

PN optimizado que codifica SEQ ID NO:9	15:GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGA AGAAGCCCGGTAGCAGCGTCAAGGTGTCCTGCAAGGC CAGCGGCGGCACCTTCAGCAGCTACGCCATCAGCTGG GTGCGGCAGGCCCCAGGCCAGGGCCTGGAGTGGATG GGCGGCATCGGCCCATTCTTCGGCACCGCCAACTACG CCCAGAAGTTCCAGGGCAGGGTCACCATCACCGCCGA CGAGAGCACCAGCACCGCCTACATGGAGCTGTCCAGC CTGAGAAGCGAGGACACCGCCGTGTACTACTGCGCCA GAGACACCCCCTACTTCGACTACTGGGGCCAGGGCAC CCTGGTGACCGTGAGCAGCGCTAGCACCAAGGGCCCC AGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCT CCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGG ACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAG CGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCC GTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCG TGGTGACAGTGCCCAGCAGCAGCCTGGGCACCCAGAC CTACATCTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCGACA AGACCCACACCTGCCCCCCCTGCCCAGCCCCCGAAGC TGCAGGCGGCCCTTCCGTGTTCCTGTTCCCCCCCAAG CCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGG TGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCC AGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAG GTGCACAACGCCAAGACCAAGCCCAGAGAGGAGCAGT

	ACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGT GCTGCACCAGGACTGGCTGAACGGCAAAGAATACAAG TGCAAGGTCTCCAACAAGGCCCTGCCTGCCCCCATCG AAAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGA GCCCCAGGTGTACACCCTGCCCCCTTCTCGGGAGGAG ATGACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGA AGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGA GAGCAACGGCCAGCCCGAGAACAACTACAAGACCACC CCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGT ACAGCAAGCTGACCGTGGACAAGAGCAGGTGGCAGCA GGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCC CTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGT CACCCGGCAAG
PN optimizado que codifica SEQ ID NO:10	16:AGCTACGAGCTGACCCAGCCCCTGAGCGTGAGCGT GGCCCTGGGCCAGACCGCCAGGATCACCTGCAGCGG CGACAGCATCCCCAACTACTACGTGTACTGGTATCAGC AGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTACGA CGACAGCAACAGGCCCAGCGGCATCCCCGAGAGGTTC AGCGGCAGCAACAGCGGCAACACCGCCACCCTGACCA TCAGCAGAGCCCAGGCCGGCGACGAGGCCGACTACTA CTGCCAGAGCTTCGACAGCTCACTGAACGCCGAGGTG TTCGGCGGAGGGACCAAGCTGACCGTGCTGGGCCAG CCTAAGGCTGCCCCCAGCGTGACCCTGTTCCCCCCCA GCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGG

	TGTGCCTGATCAGCGACTTCTACCCAGGCGCCGTGAC CGTGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGC CGGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAAC AACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCC CCGAGCAGTGGAAGAGCCACAGGTCCTACAGCTGCCA GGTGACCCACGAGGGCAGCACCGTGGAAAAGACCGT GGCCCCAACCGAGTGCAGC
Anticuerpo 8110	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	17: NYIS
CDRH2	18: IIDPDDSYTEYSPSFQG
CDRH3	19: YEYGGFDI
CDRL1	20: SGDNIGNSYVH
CDRL2	21: KDNDRPS
CDRL3	22: GTYDIESYV
VH	23:EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVR QMPGKGLEWMGIIDPDDSYTEYSPSFQGQVTISADKSIS TAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTV SS
	24:SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQ

VL	QKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCGTYDIESYVFGGGTKLTVL
Cadena pesada	25:EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVR QMPGKGLEWMGIIDPDDSYTEYSPSFQGQVTISADKSIS TAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAP EAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
Cadena ligera	26:SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQ QKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCGTYDIESYVFGGGTKLTVLGQPKAAPSV TLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPV KAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTECS
PN que codifica SEQ ID	27:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAA AAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGGT TCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGC

NO:23	CAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATTA TTGATCCTGATGATTCTTATACTGAGTATTCTCCTTCTT TTCAGGGTCAGGTCACCATTAGCGCGGATAAAAGCATT AGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGA GCGATACGGCCATGTATTATTGCGCGCGTTATGAGTAT GGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGA CGGTTAGCTCA
PN que codifica SEQ ID NO:24	28:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGT TGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAG AAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAGG ATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGC GGATCCAACAGCGGCAACACCGCGACCCTGACCATTA GCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTG CGGTACTTATGATATTGAGTCTTATGTGTTTGGCGGCG GCACGAAGTTAACCGTCCTA
PN que codifica SEQ ID NO:25	29:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAA AAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGGT TCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGC CAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATTA TTGATCCTGATGATTCTTATACTGAGTATTCTCCTTCTT TTCAGGGTCAGGTCACCATTAGCGCGGATAAAAGCATT AGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGA

	GCGATACGGCCATGTATTATTGCGCGCGTTATGAGTAT
	GGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGA
	CGGTTAGCTCAGCCTCCACCAAGGGTCCATCGGTCTT
	CCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGC
	ACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCC
	CCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCT
	GACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAG
	TCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCG
	TGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTG
	CAACGTGAATCACAAGCCCAGCAACACCAAGGTGGAC
	AAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACAC
	ATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGGGG
	ACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACA
	CCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGT
	GGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAG
	TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATG
	CCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCAC
	GTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAG
	GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT
	CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCAT
	CTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTG
	TACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
	ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTA
	TCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGG

	CAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGC TGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTC ACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCT TCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCAC TACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
PN que codifica SEQ ID NO:26	30:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGT TGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAG AAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAGG ATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGC GGATCCAACAGCGGCAACACCGCGACCCTGACCATTA GCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTG CGGTACTTATGATATTGAGTCTTATGTGTTTGGCGGCG GCACGAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGC CCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAG CTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAG TGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAG GCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACC ACCACACCCTCCAAACAAAGCAACAACAAGTACGCGG CCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAA GTCCCACAGAAGCTACAGCTGCCAGGTCACGCATGAA GGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAAT GTTCA

PN optimizado que codifica SEQ ID NO:25	31:GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGA AAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAGGG CAGCGGCTACAGCTTCACCAACTACATCAGCTGGGTG CGGCAGATGCCCGGCAAGGGCCTGGAGTGGATGGGC ATCATCGACCCCGACGACAGCTACACCGAGTACAGCC CCAGCTTCCAGGGCCAGGTGACCATCAGCGCCGACAA GAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTG AAGGCCAGCGACACCGCCATGTACTACTGCGCCAGAT ACGAGTACGGCGGCTTCGACATCTGGGGCCAGGGCAC CCTGGTGACCGTCAGCTCAGCTAGCACCAAGGGCCCC AGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCT CCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGG ACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAG CGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCC GTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCG TGGTGACAGTGCCCAGCAGCAGCCTGGGCACCCAGAC CTACATCTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCGACA AGACCCACACCTGCCCCCCCCTGCCCAGCCCCCGAAGC TGCAGGCGGCCCTTCCGTGTTCCTGTTCCCCCCCAAG CCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGG TGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCC AGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAG GTGCACAACGCCAAGACCAAGCCCAGAGAGGAGCAGT

	ACAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGT GCTGCACCAGGACTGGCTGAACGGCAAAGAATACAAG TGCAAGGTCTCCAACAAGGCCCTGCCTGCCCCCATCG AAAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGA GCCCCAGGTGTACACCCTGCCCCCTTCTCGGGAGGAG ATGACCAAGAACCAGGTGTCCCTGACCTGTCTGGTGA AGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGA GAGCAACGGCCAGCCCGAGAACAACTACAAGACCACC CCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGT ACAGCAAGCTGACCGTGGACAAGAGCAGGTGGCAGCA GGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCC CTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGT CACCCGGCAAG
PN optimizado que codifica SEQ ID NO:26	32:AGCTACGAGCTGACCCAGCCCCCCAGCGTGAGCGT GGCCCCAGGCCAGACCGCCAGGATCAGCTGCAGCGG CGACAACATCGGCAACAGCTACGTGCACTGGTATCAG CAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTACA AGGACAACGACAGGCCCAGCGGCATCCCCGAGAGGTT CAGCGGCAGCAACTCCGGCAACACCGCCACCCTGACC ATCAGCGGCACCCAGGCCGAGGACGAGGCCGACTACT ACTGCGGCACCTACGACATCGAGTCATACGTGTTCGG CGGAGGGACCAAGCTGACCGTGCTGGGCCAGCCTAA GGCTGCCCCCAGCGTGACCCTGTTCCCCCCCAGCAGC GAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCC

	TGATCAGCGACTTCTACCCAGGCGCCGTGACCGTGGC CTGGAAGGCCGACAGCAGCCCCGTGAAGGCCGGCGT GGAGACCACCACCCCCAGCAAGCAGAGCAACAACAAG TACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGC AGTGGAAGAGCCACAGGTCCTACAGCTGCCAGGTGAC CCACGAGGGCAGCACCGTGGAAAAGACCGTGGCCCC AACCGAGTGCAGC
Anticuerpo 8111	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	33: TSGGGVS
CDRH2	34: NIDDADIKDYSPSLKS
CDRH3	35:GPYGFDS
CDRL1	36:TGTSSDIGTYNYVS
CDRL2	37: DDSNRPS
CDRL3	38:QSYDSQSIV
VH	39:EVTLKESGPALVKPTQTLTLTCTFSGFSLSTSGGGVS WIRQPPGKALEWLANIDDADIKDYSPSLKSRLTISKDTSK NQVVLTMTNMDPVDTATYYCARGPYGFDSWGQGTLVTV SS
VL	40:ESALTQPASVSGSPGQSITISCTGTSSDIGTYNYVSW

	YQQHPGKAPKLMIYDDSNRPSGVSNRFSGSKSGNTASL TISGLQAEDEADYYCQSYDSQSIVFGGGTKLTVL
Cadena pesada	41:EVTLKESGPALVKPTQTLTLTCTFSGFSLSTSGGGVS WIRQPPGKALEWLANIDDADIKDYSPSLKSRLTISKDTSK NQVVLTMTNMDPVDTATYYCARGPYGFDSWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAP EAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
Cadena ligera	42:ESALTQPASVSGSPGQSITISCTGTSSDIGTYNYVSW YQQHPGKAPKLMIYDDSNRPSGVSNRFSGSKSGNTASL TISGLQAEDEADYYCQSYDSQSIVFGGGTKLTVLGQPKA APSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHR SYSCQVTHEGSTVEKTVAPTECS
PN que codifica SEQ ID	43:GAGGTGACATTGAAAGAAAGCGGCCCGGCCCTGGT GAAACCGACCCAAACCCTGACCCTGACCTGTACCTTTT CCGGATTTAGCCTGTCTACTTCTGGTGGTGGTGTGTCT

NO:39	TGGATTCGCCAGCCGCCTGGGAAAGCCCTCGAGTGGC TGGCTAATATTGATGATGCTGATATTAAGGATTATTCTC CTTCTCTTAAGTCTCGTCTGACCATTAGCAAAGATACTT CGAAAAATCAGGTGGTGCTGACTATGACCAACATGGA CCCGGTGGATACGGCCACCTATTATTGCGCGCGTGGT CCTTATGGTTTTGATTCTTGGGGCCAAGGCACCCTGGT GACGGTTAGCTCA
PN que codifica SEQ ID NO:40	44:GAAAGCGCACTGACCCAGCCAGCTTCAGTGAGCGG CTCACCAGGTCAGAGCATTACCATCTCGTGTACGGGTA CTAGCAGCGATATTGGTACTTATAATTATGTGTCTTGGT ACCAGCAGCATCCCGGGAAGGCGCCGAAACTTATGAT TTATGATGATTCTAATCGTCCCTCAGGCGTGAGCAACC GTTTTAGCGGATCCAAAAGCGGCAACACCGCGAGCCT GACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGAT TATTATTGCCAGTCTTATGATTCTCAGTCTATTGTGTTT GGCGGCGGCACGAAGTTAACCGTCCTA
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	GACGGTTAGCTCAGCCTCCACCAAGGGTCCATCGGTC
	TTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGG
	GCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTT
	CCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
	CTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTAC
	AGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGAC
	CGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATC
	TGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGG
	ACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCAC
	ACATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGG
	GGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGG
	ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATG
	CGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTC
	AAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATA
	ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAG
	CACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCAC
	CAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGG
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	CATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAG
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	AGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTT
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	GGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCG TGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAG CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAAC GTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAA CCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT AAA
PN que codifica SEQ ID NO:42	46:GAAAGCGCACTGACCCAGCCAGCTTCAGTGAGCGG CTCACCAGGTCAGAGCATTACCATCTCGTGTACGGGTA CTAGCAGCGATATTGGTACTTATAATTATGTGTCTTGGT ACCAGCAGCATCCCGGGAAGGCGCCGAAACTTATGAT TTATGATGATTCTAATCGTCCCTCAGGCGTGAGCAACC GTTTTAGCGGATCCAAAAGCGGCAACACCGCGAGCCT GACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGAT TATTATTGCCAGTCTTATGATTCTCAGTCTATTGTGTTT GGCGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCA AGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTC TGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGT CTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGG CCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGT GGAGACCACCACACCCTCCAAACAAAGCAACAACAAG TACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGC AGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCAC GCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCT ACAGAATGTTCA

PN optimizado que codifica SEQ ID NO:41	47:GAGGTGACCCTGAAGGAGAGCGGCCCAGCCCTGG TGAAGCCCACCCAGACCCTGACCCTGACTTGCACCTT CAGCGGCTTCAGCCTGAGCACCAGCGGAGGGGGCGT GAGCTGGATCAGGCAGCCCCCAGGTAAGGCCCTGGA GTGGCTGGCCAATATCGACGACGCCGATATCAAGGAC TACAGCCCCAGCCTGAAGAGCAGGCTGACCATCAGCA AGGACACCAGCAAGAACCAGGTGGTGCTGACCATGAC CAATATGGACCCCGTGGACACCGCCACCTACTACTGC GCCAGAGGCCCCTACGGCTTCGACAGCTGGGGCCAG GGCACCCTGGTGACCGTCAGCTCAGCTAGCACCAAGG GCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAG CACCTCCGGCGGCACAGCCGCCCTGGGCTGCCTGGT GAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGG AACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTCC CCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTC CAGCGTGGTGACAGTGCCCAGCAGCAGCCTGGGCAC CCAGACCTACATCTGCAACGTGAACCACAAGCCCAGC AACACCAAGGTGGACAAGAGAGTGGAGCCCAAGAGCT GCGACAAGACCCACACCTGCCCCCCCTGCCCAGCCCC CGAAGCTGCAGGCGGCCCTTCCGTGTTCCTGTTCCCC CCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCC CCGAGGTGACCTGCGTGGTGGTGGACGTGAGCCACG AGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGG CGTGGAGGTGCACAACGCCAAGACCAAGCCCAGAGAG

AC4

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PN optimizado que codifica SEQ ID NO:42	48:GAGAGCGCCCTGACCCAGCCCGCCAGCGTGAGCG GCAGCCCAGGCCAGTCTATCACAATCAGCTGCACCGG CACCTCCAGCGATATCGGCACCTACAACTACGTGAGC TGGTATCAGCAGCACCCCGGCAAGGCCCCCAAGCTGA TGATCTACGACGACAGCAACAGGCCCAGCGGCGTGAG CAACAGGTTCAGCGGCAGCAAGAGCGGCAACACCGCC AGCCTGACAATCAGCGGCCTGCAGGCCGAGGACGAG GCCGACTACTACTGCCAGAGCTACGACAGCCAGTCAA TCGTGTTCGGCGGAGGGACCAAGCTGACCGTGCTGGG CCAGCCTAAGGCTGCCCCCAGCGTGACCCTGTTCCCC CCCAGCAGCGAGGAGCTGCAGGCCAACAAGGCCACC

165

166

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Anticuerpo 8113	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:17
CDRH2	49: IIDPDDSYTRYSPSFQG
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	50:ATWGSEDQV
VH	51:EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVR QMPGKGLEWMGIIDPDDSYTRYSPSFQGQVTISADKSIS TAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTV SS
VL	52:SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQ

167

	QKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCATWGSEDQVFGGGTKLTVL
Cadena pesada	53:EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVR QMPGKGLEWMGIIDPDDSYTRYSPSFQGQVTISADKSIS TAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTV SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAP EAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
Cadena ligera	54:SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQ QKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCATWGSEDQVFGGGTKLTVLGQPKAAPS VTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYS CQVTHEGSTVEKTVAPTECS
PN que codifica SEQ ID	55:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAA AAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGGT TCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGC

NO:51	CAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATTA TCGATCCGGATGATAGCTATACCCGTTATTCTCCGAGC TTTCAGGGACAGGTGACCATTAGCGCGGATAAAAGCA TTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGC GAGCGATACGGCCATGTATTATTGCGCGCGTTATGAGT ATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGT GACGGTTAGCTCA
PN que codifica SEQ ID NO:52	56:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGT TGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAG AAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAGG ATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGC GGATCCAACAGCGGCAACACCGCGACCCTGACCATTA GCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTG CGCTACTTGGGGTTCTGAGGATCAGGTGTTTGGCGGC GGCACGAAGTTAACCGTCCTA
PN que codifica SEQ ID NO:53	57:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAA AAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGGT TCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGC CAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATTA TCGATCCGGATGATAGCTATACCCGTTATTCTCCGAGC TTTCAGGGACAGGTGACCATTAGCGCGGATAAAAGCA TTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGC

	GAGCGATACGGCCATGTATTATTGCGCGCGTTATGAGT
	ATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGT
	GACGGTTAGCTCAGCCTCCACCAAGGGTCCATCGGTC
	TTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGG
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	CCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCC
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	AGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGAC
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	ACACCCTCATGATCTCCCGGACCCCTGAGGTCACATG
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PN que codifica SEQ ID NO:54	58:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGT TGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAG AAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAGG ATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGC GGATCCAACAGCGGCAACACCGCGACCCTGACCATTA GCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTG CGCTACTTGGGGTTCTGAGGATCAGGTGTTTGGCGGC GGCACGAAGTTAACCGTCCTAGGTCAGCCCAAGGCTG CCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGA GCTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAA GTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAA GGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGAC CACCACACCCTCCAAACAAAGCAACAACAAGTACGCG GCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGA AGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATGA AGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAA TGTTCA

PN optimizado que codifica SEQ ID NO:53	59:GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGA AAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAGGG CAGCGGCTACAGCTTCACCAACTACATCAGCTGGGTG CGGCAGATGCCCGGCAAGGGCCTGGAGTGGATGGGC ATCATCGACCCCGACGACAGCTACACCAGGTACAGCC CCAGCTTCCAGGGCCAGGTGACCATCAGCGCCGACAA GAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTG AAGGCCAGCGACACCGCCATGTACTACTGCGCCAGAT ACGAGTACGGCGGCTTCGACATCTGGGGCCAGGGCAC CCTGGTGACCGTCAGCTCAGCTAGCACCAAGGGCCCC AGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCT CCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGG ACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAG CGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCC GTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCG TGGTGACAGTGCCCAGCAGCAGCCTGGGCACCCAGAC CTACATCTGCAACGTGAACCACAAGCCCAGCAACACC AAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCGACA AGACCCACACCTGCCCCCCCCTGCCCAGCCCCCGAAGC TGCAGGCGGCCCTTCCGTGTTCCTGTTCCCCCCCAAG CCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGG TGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCC AGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAG GTGCACAACGCCAAGACCAAGCCCAGAGAGGAGCAGT

5 10 15 20 25

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PN optimizado que codifica SEQ ID NO:54	60:AGCTACGAGCTGACCCAGCCCCCCAGCGTGAGCGT GGCCCCAGGCCAGACCGCCAGGATCAGCTGCAGCGG CGACAATATCGGCAACAGCTACGTGCACTGGTATCAG CAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTACA AGGACAACGACAGGCCCAGCGGCATCCCCGAGAGGTT CAGCGGCAGCAACTCCGGCAACACCGCCACCCTGACA ATCAGCGGCACCCAGGCCGAGGACGAGGCCGACTACT ACTGCGCCACCTGGGGCTCAGAGGACCAGGTGTTCGG CGGAGGGACCAAGCTGACCGTGCTGGGCCAGCCTAA GGCTGCCCCCCAGCGTGACCCTGTTCCCCCCCCAGCAGC GAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGTGCC

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Anticuerpo 8114	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	61: SYYIG
CDRH2	62: IIDPTDSQTAYSPSFQG
CDRH3	63:YMMRGFDH
CDRL1	64:SGDSLGDYYAY
CDRL2	65: KDNNRPS
CDRL3	66:QTWDTGESGV
VH	67:EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWV RQMPGKGLEWMGIIDPTDSQTAYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLV TVSS
VL	68:SYELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQ

	QKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQTWDTGESGVFGGGTKLTVL
Cadena pesada	69:EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWV RQMPGKGLEWMGIIDPTDSQTAYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK
Cadena ligera	70:SYELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQ QKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDTGESGVFGGGTKLTVLGQPKA APSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS
PN que codifica SEQ ID	71:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAA AAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGGT TCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTG

NO:67	CGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCA TTATTGATCCTACTGATTCTCAGACTGCTTATTCTCCTT CTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAAAG CATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAG CGAGCGATACGGCCATGTATTATTGCGCGCGTTATATG ATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTGG TGACGGTTAGCTCA
PN que codifica SEQ ID NO:68	72:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGT TGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGACTTGGGATACTGGTGAGTCTGGTGTGTTTGG CGGCGGCACGAAGTTAACCGTCCTA
PN que codifica SEQ ID NO:69	73:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAA AAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGGT TCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTG CGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCA TTATTGATCCTACTGATTCTCAGACTGCTTATTCTCCTT CTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAAAG CATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAG

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	TGACGGTTAGCTCAGCCTCCACCAAGGGTCCATCGGT
	CTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGG
	GGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACT
	TCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGC
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	CAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGA
	CCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACAT
	CTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTG
	GACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCA
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	ATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAG
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PN que codifica SEQ ID NO:70	74:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGT TGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGACTTGGGATACTGGTGAGTCTGGTGTGTTTGG CGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCAAG GCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTG AGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCT CATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCC TGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTG GAGACCACCACACCCTCCAAACAAAGCAACAACAAGTA CGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAG TGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGC ATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTAC AGAATGTTCA

PN optimizado que codifica SEQ ID NO:69	75:GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGA
	AAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAGGG
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	GTGCGGCAGATGCCCGGCAAGGGCCTGGAGTGGATG
	GGCATCATCGACCCCACCGACAGCCAGACCGCCTACA
	GCCCCAGCTTCCAGGGCCAGGTGACCATCAGCGCCGA
	CAAGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGC
	CTGAAGGCCAGCGACACCGCCATGTACTACTGCGCCC
	GGTACATGATGAGGGGCTTCGACCACTGGGGTCAGGG
	CACCCTGGTGACCGTCAGCTCAGCTAGCACCAAGGGC
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	CCTCCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGA
	AGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAA
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	GCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCA
	GCGTGGTGACAGTGCCCAGCAGCAGCCTGGGCACCC
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	GCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAAT ACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCC CATCGAAAAGACCATCAGCAAGGCCAAGGGCCAGCCA CGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGG AGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCT GGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGA CCACCCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTT CCTGTACAGCAAGCTGACCGTGGACAAGAGCAGGTGG CAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACG AGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAG CCTGTCACCCGGCAAG
PN optimizado que codifica SEQ ID NO:70	76:AGCTACGAGCTGACCCAGCCCCCCAGCGTGAGCGT GGCCCCAGGCCAGACCGCCAGGATCAGCTGCAGCGG CGACAGCCTGGGCGACTACTACGCCTACTGGTATCAG CAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTACA AGGACAACAACAGGCCCAGCGGCATCCCCGAGAGGTT CAGCGGCAGCAACAGCGGCAACACCGCCACCCTGACA ATCAGCGGCACCCAGGCCGAGGACGAGGCCGACTACT ACTGCCAGACCTGGGACACCGGCGAGTCAGGCGTGTT CGGCGGAGGGACCAAGCTGACCGTGCTGGGTCAGCC TAAGGCTGCCCCCAGCGTGACCCTGTTCCCCCCCAGC AGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGT

	GCCTGATCAGCGACTTCTACCCAGGCGCCGTGACCGT GGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCCGG CGTGGAGACCACCACCCCCAGCAAGCAGAGCAACAAC AAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCG AGCAGTGGAAGAGCCACAGGTCCTACAGCTGCCAGGT GACCCACGAGGGCAGCACCGTGGAAAAGACCGTGGC CCCAACCGAGTGCAGC
Anticuerpo 8112	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:61
CDRH2	77: IIDPSDSHTTYSPSFQG
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	78:QTWDILPHGLV
VH	79:EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWV RQMPGKGLEWMGIIDPSDSHTTYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLV TVSS
VL	80:SYELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQ

	QKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYC QTWDILPHGLVFGGGTKLTVL
Cadena pesada	81:EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWV RQMPGKGLEWMGIIDPSDSHTTYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK
Cadena ligera	82:SYELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQ QKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQTWDILPHGLVFGGGTKLTVLGQPKAAP SVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSS PVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSY SCQVTHEGSTVEKTVAPTECS
PN que codifica SEQ ID	83:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAA AAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGGT TCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTG

NO:79	CGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCA TTATCGATCCGTCTGATAGCCATACCACTTATTCTCCG AGCTTTCAGGGCCAGGTGACCATTAGCGCGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAA GCGAGCGATACGGCCATGTATTATTGCGCGCGTTATAT GATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTG GTGACGGTTAGCTCA
PN que codifica SEQ ID NO:80	84:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGT TGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGACTTGGGATATTCTTCCTCATGGTCTTGTGTTT GGCGGCGGCACGAAGTTAACCGTCCTA
PN que codifica SEQ ID NO:81	85:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAA AAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGGT TCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTG CGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCA TTATCGATCCGTCTGATAGCCATACCACTTATTCTCCG AGCTTTCAGGGCCAGGTGACCATTAGCGCGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAA

	GCGAGCGATACGGCCATGTATTATTGCGCGCGTTATAT
	GATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTG
	GTGACGGTTAGCTCAGCCTCCACCAAGGGTCCATCGG
	TCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGG
	GGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTA
	CTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGC
	GCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCC
	TACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGT
	GACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC
	ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGG
	TGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACT
	CACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGG
	GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAA
	GGACACCCTCATGATCTCCCGGACCCCTGAGGTCACA
	TGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGG
	TCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCA
	TAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAAC
	AGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGC
	ACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAA
	GGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAA
	ACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCAC
	AGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGAC
	CAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGC
	TTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCA

	ATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCC CGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGC AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCA CAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCG GGTAAA
PN que codifica SEQ ID NO:82	66:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGT TGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGACTTGGGATATTCTTCCTCATGGTCTTGTGTTT GGCGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCA AGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTC TGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGT CTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGG CCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGT GGAGACCACCACACCCTCCAAACAAAGCAACAACAAG TACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGC AGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCAC GCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCT ACAGAATGTTCA

PN optimizado que codifica SEQ ID NO:81	87:GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGA AAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAGGG CAGCGGCTACAGCTTCACCAGCTACTACATCGGCTGG GTGCGGCAGATGCCCGGCAAGGGCCTGGAGTGGATG GGCATTATCGATCCGTCTGATAGCCATACCACTTATTC TCCGAGCTTTCAGGGCCAGGTGACCATCAGCGCCGAC AAGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCC TGAAGGCCAGCGACACCGCCATGTACTACTGCGCCCG GTACATGATGAGGGGCTTCGACCACTGGGGTCAGGGC ACCCTGGTGACCGTCAGCTCAGCTAGCACCAAGGGCC CCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCAC CTCCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAA GGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAAC AGCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCG CCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAG CGTGGTGACAGTGCCCAGCAGCAGCCTGGGCACCCA GACCTACATCTGCAACGTGAACCACAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCG ACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCCGA AGCTGCAGGCGGCCCTTCCGTGTTCCTGTTCCCCCCC AAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCG AGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGG ACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGT GGAGGTGCACAACGCCAAGACCAAGCCCAGAGAGGA

Q65

	GCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTG ACCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAAT ACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCC CATCGAAAAGACCATCAGCAAGGCCAAGGGCCAGCCA CGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGG AGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCT GGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGA CCACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTT CCTGTACAGCAAGCTGACCGTGGACAAGAGCAGGTGG CAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACG AGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAG CCTGTCACCCGGCAAG
PN optimizado que codifica SEQ ID NO:82	88:AGCTACGAGCTGACCCAGCCCCCCAGCGTGAGCGT GGCCCCAGGCCAGACCGCCAGGATCAGCTGCAGCGG CGACAGCCTGGGCGACTACTACGCCTACTGGTATCAG CAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTACA AGGACAACAACAGGCCCAGCGGCATCCCCGAGAGGTT CAGCGGCAGCAACAGCGGCAACACCGCCACCCTGACA ATCAGCGGCACCCAGGCCGAGGACGAGGCCGACTACT ACTGCCAGACTTGGGATATTCTTCCTCATGGTCTTGTG TTCGGCGGAGGGACCAAGCTGACCGTGCTGGGTCAGC CTAAGGCTGCCCCCAGCGTGACCCTGTTCCCCCCCAG

	CAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGT GTGCCTGATCAGCGACTTCTACCCAGGCGCCGTGACC GTGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCC GGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAACA ACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCC CGAGCAGTGGAAGAGCCACAGGTCCTACAGCTGCCAG GTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTG GCCCCAACCGAGTGCAGC
Anticuerpo 8125	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:77
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	89:QAWTDSPTGLV
VH	SEQ ID NO:79
VL	90:SYELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQ QKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTISG

	TQAEDEADYYCQAWTDSPTGLVFGGGTKLTVL
Cadena pesada	SEQ ID NO:81
Cadena ligera	91:SYELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQ QKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQAWTDSPTGLVFGGGTKLTVLGQPKAA PSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS
PN que codifica SEQ ID NO:79	SEQ ID NO:83
PN que codifica SEQ ID NO:90	92:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGT TGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGGCTTGGACTGATTCTCCTACTGGTCTTGTGTTT GGCGGCGGCACGAAGTTAACCGTCCTA

PN que codifica SEQ ID NO:81	SEQ ID NO:85
PN que codifica SEQ ID NO:91	93:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGT TGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGGC GATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGGCTTGGACTGATTCTCCTACTGGTCTTGTGTTT GGCGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCA AGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTC TGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGT CTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGG CCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGT GGAGACCACCACACCCTCCAAACAAAGCAACAACAAG TACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGC AGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCAC GCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCT ACAGAATGTTCA
PN opti-	SEQ ID NO:87

mizado que codifica SEQ ID NO:81	
PN optimizado que codifica SEQ ID NO:91	94:AGCTACGAGCTGACCCAGCCCCCCAGCGTGAGCGT GGCCCCAGGCCAGACCGCCAGGATCAGCTGCAGCGG CGACAGCCTGGGCGACTACTACGCCTACTGGTATCAG CAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTACA AGGACAACAACAGGCCCAGCGGCATCCCCGAGAGGTT CAGCGGCAGCAACAGCGGCAACACCGCCACCCTGACA ATCAGCGGCACCCAGGCCGAGGACGAGGCCGACTACT ACTGCCAGGCTTGGACTGATTCTCCTACTGGTCTTGTG TTCGGCGGAGGGACCAAGCTGACCGTGCTGGGTCAGC CTAAGGCTGCCCCCAGCGTGACCCTGTTCCCCCCCCAG CAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGT GTGCCTGATCAGCGACTTCTACCCAGGCGCCGTGACC GTGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCC GGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAACA ACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCC CGAGCAGTGGAAGAGCCACAGGTCCTACAGCTGCCAG GTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTG GCCCCAACCGAGTGCAGC

Anticuerpo 8126	IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:62
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	SEQ ID NO:89
VH	SEQ ID NO:67
VL	SEQ ID NO:90
Cadena pesada	SEQ ID NO:69
Cadena ligera	SEQ ID NO:91
PN que codifica SEQ ID NO:79	SEQ ID NO:71
PN que	SEQ ID NO:92

codifica SEQ ID NO:90	
PN que codifica SEQ ID NO:81	SEQ ID NO:73
PN que codifica SEQ ID NO:91	SEQ ID NO:93
PN optimizado que codifica SEQ ID NO:81	SEQ ID NO:75
PN optimizado que codifica SEQ ID	SEQ ID NO:94

NO:91	
Anticuerpo 8127	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:61
CDRH2	95: IIDPTDSYTVYSPSFQG
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	SEQ ID NO:89
VH	96:EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWV RQMPGKGLEWMGIIDPTDSYTVYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLV TVSS
VL	SEQ ID NO:90
Cadena pesada	97:EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWV RQMPGKGLEWMGIIDPTDSYTVYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS

	SLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLSLSPGK
Cadena ligera	SEQ ID NO:91
PN que codifica SEQ ID NO:96	96:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAA AAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGGT TCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTG CGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCA TTATTGATCCTACTGATTCTTATACTGTTTATTCTCCTT CTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAAAG CATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAG CGAGCGATACGGCCATGTATTATTGCGCGCGTTATATG ATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTGG TGACGGTTAGCTCAGC
PN que codifica SEQ ID NO:90	SEQ ID NO:92

PN que codifica SEQ ID NO:97	99:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAA AAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGGT TCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTG CGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCA TTATTGATCCTACTGATTCTTATACTGTTTATTCTCCTT CTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAAAG CATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAG CGAGCGATACGGCCATGTATTATTGCGCGCGTTATATG ATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTGG TGACGGTTAGCTCAGCGCCTCCACCAAGGGTCCATCG GTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTG GGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACT ACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGG CGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTC CTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGG TGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTA CATCTGCAACGTGAATCACAAGCCCAGCAACACCAAG GTGGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAAC TCACACATGCCCACCGTGCCCAGCACCTGAAGCAGCG GGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCA AGGACACCCTCATGATCTCCCGGACCCCTGAGGTCAC ATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGC ATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAA

	CAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTG CACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCA AGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAA AACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCA CAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGA CCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGG CTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGC AATGGGCAGCCGGAGAACAACTACAAGACCACGCCTC CCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAG CAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGG GAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGC ACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCC GGGTAAA
PN que codifica SEQ ID NO:91	SEQ ID NO:93
PN optimizado que codifica SEQ ID NO:97	100:GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTG AAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAGG GCAGCGGCTACAGCTTCACCAGCTACTACATCGGCTG GGTGCGGCAGATGCCCGGCAAGGGCCTGGAGTGGAT GGGCATTATTGATCCTACTGATTCTTATACTGTTTATTC TCCTTCTTTTCAGGGTCAGGTGACCATCAGCGCCGACA

	AGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCT
	GAAGGCCAGCGACACCGCCATGTACTACTGCGCCCGG
	TACATGATGAGGGGCTTCGACCACTGGGGTCAGGGCA
	CCCTGGTGACCGTCAGCTCAGCTAGCACCAAGGGCCC
	CAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACC
	TCCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAG
	GACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACA
	GCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCG
	CCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAG
	CGTGGTGACAGTGCCCAGCAGCAGCCTGGGCACCCA
	GACCTACATCTGCAACGTGAACCACAAGCCCAGCAAC
	ACCAAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCG
	ACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCCGA
	AGCTGCAGGCGGCCCTTCCGTGTTCCTGTTCCCCCCC
	AAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCG
	AGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGG
	ACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGT
	GGAGGTGCACAACGCCAAGACCAAGCCCAGAGAGGA
	GCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTG
	ACCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAAT
	ACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCC
	CATCGAAAAGACCATCAGCAAGGCCAAGGGCCAGCCA
	CGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGG
	AGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCT

	GGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGA CCACCCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTT CCTGTACAGCAAGCTGACCGTGGACAAGAGCAGGTGG CAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACG AGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAG CCTGTCACCCGGCAAG
PN optimizado que codifica SEQ ID NO:91	SEQ ID NO:94
Anticuerpo 8128	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:49
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21

CDRL3	101:STWDIEPTYV
VH	SEQ ID NO:51
VL	102:SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQ QKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCSTWDIEPTYVFGGGTKLTVL
Cadena pesada	SEQ ID NO:53
Cadena ligera	103:SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQ QKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCSTWDIEPTYVFGGGTKLTVLGQPKAAPS VTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYS CQVTHEGSTVEKTVAPTECS
PN que codifica SEQ ID NO:51	SEQ ID NO:55
PN que codifica SEQ ID NO:102	104:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG

	GATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCTCTACTTGGGATATTGAGCCTACTTATGTGTTTGGC GGCGGCACGAAGTTAACCGTCCTA
PN que codifica SEQ ID NO:53	SEQ ID NO:57
PN que codifica SEQ ID NO:103	105:AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCTCTACTTGGGATATTGAGCCTACTTATGTGTTTGGC GGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCAAGG CTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGA GGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTC ATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCT GGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGG AGACCACCACACCCTCCAAACAAAGCAACAACAAGTAC

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	GCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGT GGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCA TGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACA GAATGTTCA
PN optimizado que codifica SEQ ID NO:53	SEQ ID NO:59
PN optimizado que codifica SEQ ID NO:103	106:AGCTACGAGCTGACCCAGCCCCCCAGCGTGAGCG TGGCCCCAGGCCAGACCGCCAGGATCAGCTGCAGCG GCGACAATATCGGCAACAGCTACGTGCACTGGTATCA GCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTAC AAGGACAACGACAGGCCCAGCGGCATCCCCGAGAGGT TCAGCGGCAGCAACTCCGGCAACACCGCCACCCTGAC AATCAGCGGCACCCAGGCCGAGGACGAGGCCGACTA CTACTGCTCTACTTGGGATATTGAGCCTACTTATGTGT TCGGCGGAGGGACCAAGCTGACCGTGCTGGGCCAGC CTAAGGCTGCCCCCAGCGTGACCCTGTTCCCCCCCAG CAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGT GTGCCTGATCAGCGACTTCTACCCAGGCGCCGTGACC GTGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGGCC

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	GGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAACA ACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCC CGAGCAGTGGAAGAGCCACAGGTCCTACAGCTGCCAG GTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTG GCCCCAACCGAGTGCAGC
Anticuerpo 8129	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:17
CDRH2	107: IIDPQDSYTEYSPSFQG
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:22
VH	108:EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWV RQMPGKGLEWMGIIDPQDSYTEYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVT VSS
VL	SEQ ID NO:24
Cadena	109:EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWV

pesada	RQMPGKGLEWMGIIDPQDSYTEYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPA PEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK
Cadena ligera	SEQ ID NO:26
PN que codifica SEQ ID NO:108	110:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCG CCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATT ATTGATCCTCAGGATTCTTATACTGAGTATTCTCCTTCT TTTCAGGGTCAGGTCACCATTAGCGCGGATAAAAGCAT TAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCG AGCGATACGGCCATGTATTATTGCGCGCGTTATGAGTA TGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTG ACGGTTAGCTCA

PN que codifica SEQ ID NO:24	SEQ ID NO:28
PN que codifica SEQ ID NO:109	111:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCG CCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATT ATTGATCCTCAGGATTCTTATACTGAGTATTCTCCTTCT TTTCAGGGTCAGGTCACCATTAGCGCGGATAAAAGCAT TAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCG AGCGATACGGCCATGTATTATTGCGCGCGTTATGAGTA TGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTG ACGGTTAGCTCAGCCTCCACCAAGGGTCCATCGGTCT TCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGG CACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTC CCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCC TGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACA GTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACC GTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGA CAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACA CATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGGG GACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGAC

505

	ACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCG TGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAA GTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAAT GCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCA CGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCA GGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTC TCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGT GTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAG AACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGG GCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTG CTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCT CACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGT CTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAA A
PN que codifica SEQ ID NO:26	SEQ ID NO:30
PN opti-mizado	112:GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTG AAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAGG

que	GCAGCGGCTACAGCTTCACCAACTACATCAGCTGGGT
codifica	GCGGCAGATGCCCGGCAAGGGCCTGGAGTGGATGGG
SEQ ID	CATCATCGACCCCCAGGACAGCTACACCGAGTACAGC
NO:109	CCCAGCTTCCAGGGCCAGGTGACCATCAGCGCCGACA
	AGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCT
	GAAGGCCAGCGACACCGCCATGTACTACTGCGCCAGA
	TACGAGTACGGCGGCTTCGACATCTGGGGCCAGGGCA
	CCCTGGTGACCGTCAGCTCAGCTAGCACCAAGGGCCC
	CAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACC
	TCCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAG
	GACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACA
	GCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCG
	CCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAG
	CGTGGTGACAGTGCCCAGCAGCAGCCTGGGCACCCA
	GACCTACATCTGCAACGTGAACCACAAGCCCAGCAAC
	ACCAAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCG
	ACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCCGA
	AGCTGCAGGCGGCCCTTCCGTGTTCCTGTTCCCCCCC
	AAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCG
	AGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGG
	ACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGT
	GGAGGTGCACAACGCCAAGACCAAGCCCAGAGAGGA
	GCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTG
	ACCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAAT

	ACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCC CATCGAAAAGACCATCAGCAAGGCCAAGGGCCAGCCA CGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGG AGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCT GGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAG TGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGA CCACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTT CCTGTACAGCAAGCTGACCGTGGACAAGAGCAGGTGG CAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACG AGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAG CCTGTCACCCGGCAAG
PN optimizado que codifica SEQ ID NO:26	SEQ ID NO:32
Anticuerpo 8130	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:107
CDRH3	SEQ ID NO:19

CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:101
VH	SEQ ID NO:108
VL	SEQ ID NO:102
Cadena pesada	SEQ ID NO:109
Cadena ligera	SEQ ID NO:103
PN que codifica SEQ ID NO:108	SEQ ID NO:110
PN que codifica SEQ ID NO:102	SEQ ID NO:104
PN que codifica SEQ ID	SEQ ID NO:111

NO:109	
PN que codifica SEQ ID NO:103	SEQ ID NO:105
PN optimizado que codifica SEQ ID NO:109	SEQ ID NO:112
PN optimizado que codifica SEQ ID NO:103	SEQ ID NO:106
Anticuerpo 8131	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:17
CDRH2	113: IIDPEDSHTEYSPSFQG

S10

CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:22
VH	114:EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWV RQMPGKGLEWMGIIDPEDSHTEYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVT VSS
VL	SEQ ID NO:24
Cadena pesada	115:EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWV RQMPGKGLEWMGIIDPEDSHTEYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPA PEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK

Cadena ligera	SEQ ID NO:26
PN que codifica SEQ ID NO:114	116:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCG CCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATT ATTGATCCTGAGGATTCTCATACTGAGTATTCTCCTTCT TTTCAGGGTCAGGTGACCATTAGCGCGGATAAAAGCAT TAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCG AGCGATACGGCCATGTATTATTGCGCGCGTTATGAGTA TGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTG ACGGTTAGCTCA
PN que codifica SEQ ID NO:24	SEQ ID NO:28
PN que codifica SEQ ID NO:115	117:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCG CCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATT ATTGATCCTGAGGATTCTCATACTGAGTATTCTCCTTCT TTTCAGGGTCAGGTGACCATTAGCGCGGATAAAAGCAT TAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCG

	AGCGATACGGCCATGTATTATTGCGCGCGTTATGAGTA
	TGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTG
	ACGGTTAGCTCAGCCTCCACCAAGGGTCCATCGGTCT
	TCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGG
	CACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTC
	CCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCC
	TGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACA
	GTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACC
	GTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCT
	GCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGA
	CAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACA
	CATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGGG
	GACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGAC
	ACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCG
	TGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAA
	GTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAAT
	GCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCA
	CGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCA
	GGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTC
	TCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA
	TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGT
	GTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAG
	AACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT
	ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGG

	GCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTG CTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCT CACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGT CTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC ACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAA A
PN que codifica SEQ ID NO:26	SEQ ID NO:30
PN opti-mizado que codifica SEQ ID NO:115	118:GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTG AAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAGG GCAGCGGCTACAGCTTCACCAACTACATCAGCTGGGT GCGGCAGATGCCCGGCAAGGGCCTGGAGTGGATGGG CATCATCGACCCCGAGGACAGCCATACCGAGTACAGC CCCAGCTTCCAGGGCCAGGTGACCATCAGCGCCGACA AGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCT GAAGGCCAGCGACACCGCCATGTACTACTGCGCCAGA TACGAGTACGGCGGCTTCGACATCTGGGGCCAGGGCA CCCTGGTGACCGTCAGCTCAGCTAGCACCAAGGGCCC CAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACC TCCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAG GACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACA

	GCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCG
	CCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAG
	CGTGGTGACAGTGCCCAGCAGCAGCCTGGGCACCCA
	GACCTACATCTGCAACGTGAACCACAAGCCCAGCAAC
	ACCAAGGTGGACAAGAGAGTGGAGCCCAAGAGCTGCG
	ACAAGACCCACACCTGCCCCCCCTGCCCAGCCCCCGA
	AGCTGCAGGCGGCCCTTCCGTGTTCCTGTTCCCCCCC
	AAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCG
	AGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGG
	ACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGT
	GGAGGTGCACAACGCCAAGACCAAGCCCAGAGAGGA
	GCAGTACAACAGCACCTACAGGGTGGTGTCCGTGCTG
	ACCGTGCTGCACCAGGACTGGCTGAACGGCAAAGAAT
	ACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCC
	CATCGAAAAGACCATCAGCAAGGCCAAGGGCCAGCCA
	CGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGG
	AGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCT
	GGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAG
	TGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGA
	CCACCCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTT
	CCTGTACAGCAAGCTGACCGTGGACAAGAGCAGGTGG
	CAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACG
	AGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAG
	CCTGTCACCCGGCAAG

PN optimizado que codifica SEQ ID NO:26	SEQ ID NO:32
Anticuerpo 8132	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:113
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:101
VH	SEQ ID NO:114
VL	SEQ ID NO:102
Cadena pesada	SEQ ID NO:115
Cadena	SEQ ID NO:103

ligera	
PN que codifica SEQ ID NO:114	SEQ ID NO:116
PN que codifica SEQ ID NO:102	SEQ ID NO:104
PN que codifica SEQ ID NO:115	SEQ ID NO:117
PN que codifica SEQ ID NO:103	SEQ ID NO:105
PN optimizado que codifica SEQ ID	SEQ ID NO:118

NO:115	
PN optimizado que codifica SEQ ID NO:103	SEQ ID NO:106
Anticuerpo 8091	**Identificador de Secuencia (SEQ ID NO:) o comentarios/detalles**
CDRH1	SEQ ID NO:1
CDRH2	119: NIGPFFGIANYAQKFQG
CDRH3	SEQ ID NO:3
CDRL1	SEQ ID NO:4
CDRL2	SEQ ID NO:5
CDRL3	120:QTYDDGSTAEV
VH	121:QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAIS WVRQAPGQGLEWMGNIGPFFGIANYAQKFQGRVTITAD ESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTL VTVSS

VL	122:DIELTQPPSVSVAPGQTARISCSGDSIPNYYVYWYQ QKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQTYDDGSTAEVFGGGTKLTVL
Cadena pesada	123:QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAIS WVRQAPGQGLEWMGNIGPFFGIANYAQKFQGRVTITAD ESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTL VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPA PPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVV HQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQV YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
Cadena ligera	124:DIELTQPPSVSVAPGQTARISCSGDSIPNYYVYWYQ QKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQTYDDGSTAEVFGGGTKLTVLGQPKAA PSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS
PN que codifica	125:CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGA AAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAGC

SEQ ID NO:121	CTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGG TGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGATGG GCAATATCGGTCCGTTTTTTGGCATTGCGAATTACGCG CAGAAGTTTCAGGGCCGGGTGACCATTACCGCGGATG AAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCT GCGTAGCGAAGATACGGCCGTGTATTATTGCGCGCGT GATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCT GGTGACGGTTAGCTCA
PN que codifica SEQ ID NO:122	126:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTATTCCTAATTATTATGTTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATGAT GATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGACTTATGATGATGGTTCTACTGCTGAGGTGTTT GGCGGCGGCACGAAGTTAACCGTTCTT
PN que codifica SEQ ID NO:123	127:CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGA AAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAGC CTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGG TGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGATGG GCAATATCGGTCCGTTTTTTGGCATTGCGAATTACGCG CAGAAGTTTCAGGGCCGGGTGACCATTACCGCGGATG

	AAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCT
	GCGTAGCGAAGATACGGCCGTGTATTATTGCGCGCGT
	GATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCT
	GGTGACGGTTAGCTCAGCTTCCACCAAGGGCCCCAGC
	GTGTTCCCCCTGGCCCCCTGCAGCAGAAGCACCAGCG
	AGAGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTA
	CTTCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGA
	GCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGC
	TGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGT
	GACCGTGCCCAGCAGCAACTTCGGCACCCAGACCTAC
	ACCTGCAACGTGGACCACAAGCCCAGCAACACCAAGG
	TGGACAAGACCGTGGAGCGGAAGTGCTGCGTGGAGTG
	CCCCCCCTGCCCTGCCCCTCCTGTGGCCGGACCCTCC
	GTGTTCCTGTTCCCCCCCCAAGCCCAAGGACACCCTGA
	TGATCAGCCGGACCCCCGAGGTGACCTGCGTGGTGGT
	GGACGTGAGCCACGAGGACCCCGAGGTGCAGTTCAAC
	TGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGA
	CCAAGCCCCGGGAGGAACAGTTCAACAGCACCTTCCG
	GGTGGTGTCCGTGCTGACCGTGGTGCACCAGGACTGG
	CTGAACGGCAAAGAATACAAGTGCAAGGTGTCCAACA
	AGGGCCTGCCTGCCCCCATCGAGAAAACCATCAGCAA
	GACAAAGGGCCAGCCCCAGGGAACCCCAGGTGTACACC
	CTGCCCCCCCAGCCGGGAGGAAATGACCAAGAACCAGG
	TGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAG

	CGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCC CGAGAACAACTACAAGACCACCCCCCCCATGCTGGAC AGCGACGGCAGCTTCTTCCTGTACAGCAAGCTGACAG TGGACAAGAGCCGGTGGCAGCAGGGCAACGTGTTCAG CTGCAGCGTGATGCACGAGGCCCTGCACAACCACTAC ACCCAGAAGAGCCTGAGCCTGTCCCCCGGCAAA
PN que codifica SEQ ID NO:124	128:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTATTCCTAATTATTATGTTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATGAT GATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGACTTATGATGATGGTTCTACTGCTGAGGTGTTT GGCGGCGGCACGAAGTTAACCGTTCTTGGTCAGCCCA AGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTC TGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGT CTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGG CCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGT GGAGACCACCACACCCTCCAAACAAAGCAACAACAAG TACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGC AGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCAC GCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCT

52

	ACAGAATGTTCA
PN optimizado que codifica SEQ ID NO:123	129:CAGGTGCAGCTGGTGCAGTCCGGCGCCGAGGTG AAGAAGCCCGGCTCCTCCGTGAAGGTGTCCTGCAAGG CCTCCGGCGGCACCTTCTCCTCCTACGCCATCTCCTG GGTGCGGCAGGCCCCCGGCCAGGGCCTGGAGTGGAT GGGCAACATCGGCCCCTTCTTCGGCATCGCCAACTAC GCCCAGAAGTTCCAGGGCCGGGTGACCATCACCGCCG ACGAGTCCACCTCCACCGCCTACATGGAGCTGTCCTC CCTGCGGTCCGAGGACACCGCCGTGTACTACTGCGCC CGGGACACCCCCTACTTCGACTACTGGGGCCAGGGCA CCCTGGTGACCGTGTCCTCCGCCTCCACCAAGGGCCC CTCCGTGTTCCCCCTGGCCCCCTGCTCCCGGTCCACC TCCGAGTCCACCGCCGCCCTGGGCTGCCTGGTGAAGG ACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACTC CGGCGCCCTGACCTCCGGCGTGCACACCTTCCCCGCC GTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCG TGGTGACCGTGCCCTCCTCCAACTTCGGCACCCAGAC CTACACCTGCAACGTGGACCACAAGCCCTCCAACACC AAGGTGGACAAGACCGTGGAGCGGAAGTGCTGCGTG GAGTGCCCCCCCTGCCCCGCCCCCCCCGTGGCCGGC CCCTCCGTGTTCCTGTTCCCCCCCAAGCCCAAGGACA CCCTGATGATCTCCCGGACCCCCGAGGTGACCTGCGT GGTGGTGGACGTGTCCCACGAGGACCCCGAGGTGCA GTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAAC

	GCCAAGACCAAGCCCCGGGAGGAGCAGTTCAACTCCA CCTTCCGGGTGGTGTCCGTGCTGACCGTGGTGCACCA GGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTG TCCAACAAGGGCCTGCCCGCCCCCATCGAGAAGACCA TCTCCAAGACCAAGGGCCAGCCCCGGGAGCCCCAGGT GTACACCCTGCCCCCCTCCCGGGAGGAGATGACCAAG AACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCT ACCCCTCCGACATCGCCGTGGAGTGGGAGTCCAACGG CCAGCCCGAGAACAACTACAAGACCACCCCCCCCATG CTGGACTCCGACGGCTCCTTCTTCCTGTACTCCAAGCT GACCGTGGACAAGTCCCGGTGGCAGCAGGGCAACGT GTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAAC CACTACACCCAGAAGTCCCTGTCCCTGTCCCCCGGCA AG
PN optimizado que codifica SEQ ID NO:124	130:GACATCGAGCTGACCCAGCCCCCCTCCGTGTCCG TGGCCCCCGGCCAGACCGCCCGGATCTCCTGCTCCG GCGACTCCATCCCCAACTACTACGTGTACTGGTACCAG CAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATCTACG ACGACTCCAACCGGCCCTCCGGCATCCCCGAGCGGTT CTCCGGCTCCAACTCCGGCAACACCGCCACCCTGACC ATCTCCGGCACCCAGGCCGAGGACGAGGCCGACTACT ACTGCCAGACCTACGACGACGGCTCCACCGCCGAGGT GTTCGGCGGCGGCACCAAGCTGACCGTGCTGGGCCA GCCTAAGGCTGCCCCCAGCGTGACCCTGTTCCCCCCC

	AGCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTG GTGTGCCTGATCAGCGACTTCTACCCAGGCGCCGTGA CCGTGGCCTGGAAGGCCGACAGCAGCCCCGTGAAGG CCGGCGTGGAGACCACCACCCCCAGCAAGCAGAGCAA CAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACC CCCGAGCAGTGGAAGAGCCACAGGTCCTACAGCTGCC AGGTGACCCACGAGGGCAGCACCGTGGAAAAGACCGT GGCCCCAACCGAGTGCAGC
Anticuerpo 6525	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	131: SYWIS
CDRH2	132: IIDPDDSKTNYSPSFQG
CDRH3	133:RSYYPMDY
CDRL1	134:TGTSSDVVGVYNFVS
CDRL2	135: YVDNRPS
CDRL3	136:QSFDGFGIDMV
VH	137:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWISW VRQMPGKGLEWMGIIDPDDSKTNYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARRSYYPMDYWGQGTLV TVSS

VL	138:DIALTQPASVSGSPGQSITISCTGTSSDVVGVYNFVS WYQQHPGKAPKLMIYYVDNRPSGVSNRFSGSKSGNTAS LTISGLQAEDEADYYCQSFDGFGIDMVFGGGTKLTVL
Cadena pesada	139:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWISW VRQMPGKGLEWMGIIDPDDSKTNYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARRSYYPMDYWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)
Cadena ligera	140:DIALTQPASVSGSPGQSITISCTGTSSDVVGVYNFVS WYQQHPGKAPKLMIYYVDNRPSGVSNRFSGSKSGNTAS LTISGLQAEDEADYYCQSFDGFGIDMVFGGGTKLTVLGQ PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTEX (X puede ser CS ó A)
PN que codifica SEQ ID NO:137	141:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTTCTTATTGGATTTCTTGGGT GCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGG CATTATCGATCCGGATGATAGCAAGACCAATTATTCTC CGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGATAA

	AAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGA AAGCGAGCGATACGGCCATGTATTATTGCGCGCGTCG TTCTTATTATCCTATGGATTATTGGGGCCAAGGCACCC TGGTGACGGTTAGCTCA
PN que codifica SEQ ID NO:138	142:GATATCGCACTGACCCAGCCAGCTTCAGTGAGCG GCTCACCAGGTCAGAGCATTACCATCTCGTGTACGGG TACTAGCAGCGATGTTGTTGGTGTTTATAATTTTGTGTC TTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTT ATGATTTATTATGTTGATAATCGTCCCTCAGGCGTGAG CAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGCG AGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAG CGGATTATTATTGCCAGTCTTTTGATGGTTTTGGTATTG ATATGGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN que codifica SEQ ID NO:139	143:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTTCTTATTGGATTTCTTGGGT GCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGG CATTATCGATCCGGATGATAGCAAGACCAATTATTCTC CGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGATAA AAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGA AAGCGAGCGATACGGCCATGTATTATTGCGCGCGTCG TTCTTATTATCCTATGGATTATTGGGGCCAAGGCACCC TGGTGACGGTTAGCTCAGCGTCGACCAAAGGTCCAAG

	CGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGC GGCGGCACGGCTGCCCTGGGCTGCCTGGTTAAAGATT ATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGG GGCGCTGACCAGCGGCGTGCATACCTTTCCGGCGGTG CTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTG TGACCGTGCCGAGCAGCAGCTTAGGCACTCAGACCTA TATTTGCAACGTGAACCATAAACCGAGCAACACCAAAG TGGATAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)
PN que codifica SEQ ID NO:140	144:GATATCGCACTGACCCAGCCAGCTTCAGTGAGCG GCTCACCAGGTCAGAGCATTACCATCTCGTGTACGGG TACTAGCAGCGATGTTGTTGGTGTTTATAATTTTGTGTC TTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTT ATGATTTATTATGTTGATAATCGTCCCTCAGGCGTGAG CAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGCG AGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAG CGGATTATTATTGCCAGTCTTTTGATGGTTTTGGTATTG ATATGGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTT GGCCAGCCGAAAGCCGCACCGAGTGTGACGCTGTTTC CGCCGAGCAGCGAAGAATTGCAGGCGAACAAAGCGAC CCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCC GTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCA AGGCGGGAGTGGAGACCACCACACCCTCCAAACAAAG CAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTG

	ACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCT GCCAGGTCACGCATGAGGGGAGCACCGTGGAAAAAAC CGTTGCGCCGACTGAGX (X puede ser TGCAGC ó GCC)
Anticuerpo 6756	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	145: SYWIA
CDRH2	146: IIYPGDSDTNYSPSFQG
CDRH3	147:SKYGSFDY
CDRL1	148:TGTSSDVGGYNYVS
CDRL2	149: NVNSRPS
CDRL3	150:QSYDDGQDNEV
VH	151:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIAW VRQMPGKGLEWMGIIYPGDSDTNYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARSKYGSFDYWGQGTLV TVSS
VL	152:DIALTQPASVSGSPGQSITISCTGTSSDVGGYNYVS WYQQHPGKAPKLMIYNVNSRPSGVSNRFSGSKSGNTAS LTISGLQAEDEADYYCQSYDDGQDNEVFGGGTKLTVL

Cadena pesada	153:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIAW VRQMPGKGLEWMGIIYPGDSDTNYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARSKYGSFDYWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)
Cadena ligera	154:DIALTQPASVSGSPGQSITISCTGTSSDVGGYNYVS WYQQHPGKAPKLMIYNVNSRPSGVSNRFSGSKSGNTAS LTISGLQAEDEADYYCQSYDDGQDNEVFGGGTKLTVLG QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVA WKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQW KSHRSYSCQVTHEGSTVEKTVAPTEX (X puede ser CS ó A)
PN que codifica SEQ ID NO:151	155:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTTCTTATTGGATTGCTTGGGT GCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGG CATTATCTATCCGGGTGATAGCGATACCAATTATTCTC CGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGATAA AAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGA AAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTC TAAGTATGGTTCTTTTGATTATTGGGGCCAAGGCACCC

	TGGTGACGGTTAGCTCA
PN que codifica SEQ ID NO:152	156:GATATCGCACTGACCCAGCCAGCTTCAGTGAGCG GCTCACCAGGTCAGAGCATTACCATCTCGTGTACGGG TACTAGCAGCGATGTTGGTGGTTATAATTATGTGTCTT GGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTTAT GATTTATAATGTTAATTCTCGTCCCTCAGGCGTGAGCA ACCGTTTTAGCGGATCCAAAAGCGGCAACACCGCGAG CCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCG GATTATTATTGCCAGTCTTATGATGATGGTCAGGATAAT GAGGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN que codifica SEQ ID NO:153	157:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTTCTTATTGGATTGCTTGGGT GCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGG CATTATCTATCCGGGTGATAGCGATACCAATTATTCTC CGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGATAA AAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGA AAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTC TAAGTATGGTTCTTTTGATTATTGGGGCCAAGGCACCC TGGTGACGGTTAGCTCAGCGTCGACCAAAGGTCCAAG CGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGC GGCGGCACGGCTGCCCTGGGCTGCCTGGTTAAAGATT ATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGG

	GGCGCTGACCAGCGGCGTGCATACCTTTCCGGCGGTG CTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTG TGACCGTGCCGAGCAGCAGCTTAGGCACTCAGACCTA TATTTGCAACGTGAACCATAAACCGAGCAACACCAAAG TGGATAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)
PN que codifica SEQ ID NO:154	158:GATATCGCACTGACCCAGCCAGCTTCAGTGAGCG GCTCACCAGGTCAGAGCATTACCATCTCGTGTACGGG TACTAGCAGCGATGTTGGTGGTTATAATTATGTGTCTT GGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTTAT GATTTATAATGTTAATTCTCGTCCCTCAGGCGTGAGCA ACCGTTTTAGCGGATCCAAAAGCGGCAACACCGCGAG CCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCG GATTATTATTGCCAGTCTTATGATGATGGTCAGGATAAT GAGGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTG GCCAGCCGAAAGCCGCACCGAGTGTGACGCTGTTTCC GCCGAGCAGCGAAGAATTGCAGGCGAACAAAGCGACC CTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCG TGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAA GGCGGGAGTGGAGACCACCACACCCTCCAAACAAAGC AACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGA CGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTG CCAGGTCACGCATGAGGGGAGCACCGTGGAAAAAACC GTTGCGCCGACTGAGX (X puede ser TGCAGC ó GCC)

Anticuerpo 6757	IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES
CDRH1	159: SYAMH
CDRH2	160: AISSSGSSTYYADSVKG
CDRH3	161:ESWFLDL
CDRL1	162:RASQSISNWLA
CDRL2	163: LASSLQS
CDRL3	164:QQYYDFSDT
VH	165:QVQLVESGGGLVQPGGSLRLSCAASGFTFTSYAMH WVRQAPGKGLEWVSAISSSGSSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARESWFLDLWGQGTLV TVSS
VL	166:DIQMTQSPSSLSASVGDRVTITCRASQSISNWLAWY QQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFAVYYCQQYYDFSDTFGQGTKVEIK
Cadena pesada	167:QVQLVESGGGLVQPGGSLRLSCAASGFTFTSYAMH WVRQAPGKGLEWVSAISSSGSSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARESWFLDLWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS

	SLGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)
Cadena ligera	168:DIQMTQSPSSLSASVGDRVTITCRASQSISNWLAWY QQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFAVYYCQQYYDFSDTFGQGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEX (X puede ser C ó A)
PN que codifica SEQ ID NO:165	169:CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTG GTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGCG GCCTCCGGATTTACCTTTACTTCTTATGCTATGCATTG GGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGT GAGCGCTATCTCTTCTTCTGGTAGCTCTACCTATTATG CGGATAGCGTGAAAGGCCGTTTTACCATTTCACGTGAT AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCT GCGTGCGGAAGATACGGCCGTGTATTATTGCGCGCGT GAGTCTTGGTTTCTTGATCTTTGGGGCCAAGGCACCCT GGTGACGGTTAGCTCA
PN que codifica SEQ ID NO:166	170:GATATCCAGATGACCCAGAGCCCGTCTAGCCTGA GCGCGAGCGTGGGTGATCGTGTGACCATTACCTGCAG AGCGAGCCAGTCTATTTCTAATTGGCTGGCTTGGTACC AGCAGAAACCAGGTAAAGCACCGAAACTATTAATTTAT CTTGCTTCTTCTTTGCAAAGCGGGGTCCCGTCCCGTTT

	TAGCGGCTCTGGATCCGGCACTGATTTTACCCTGACCA TTAGCAGCCTGCAACCTGAAGACTTTGCGGTTTATTAT TGCCAGCAGTATTATGATTTTTCTGATACCTTTGGCCA GGGTACGAAAGTTGAAATTAAA
PN que codifica SEQ ID NO:167	171:CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTG GTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGCG GCCTCCGGATTTACCTTTACTTCTTATGCTATGCATTG GGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGT GAGCGCTATCTCTTCTTCTGGTAGCTCTACCTATTATG CGGATAGCGTGAAAGGCCGTTTTACCATTTCACGTGAT AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCT GCGTGCGGAAGATACGGCCGTGTATTATTGCGCGCGT GAGTCTTGGTTTCTTGATCTTTGGGGCCAAGGCACCCT GGTGACGGTTAGCTCAGCGTCGACCAAAGGTCCAAGC GTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCG GCGGCACGGCTGCCCTGGGCTGCCTGGTTAAAGATTA TTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGG GCGCTGACCAGCGGCGTGCATACCTTTCCGGCGGTGC TGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGT GACCGTGCCGAGCAGCAGCTTAGGCACTCAGACCTAT ATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGT GGATAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)

PN que codifica SEQ ID NO:168	172:GATATCCAGATGACCCAGAGCCCGTCTAGCCTGA GCGCGAGCGTGGGTGATCGTGTGACCATTACCTGCAG AGCGAGCCAGTCTATTTCTAATTGGCTGGCTTGGTACC AGCAGAAACCAGGTAAAGCACCGAAACTATTAATTTAT CTTGCTTCTTCTTTGCAAAGCGGGGTCCCGTCCCGTTT TAGCGGCTCTGGATCCGGCACTGATTTTACCCTGACCA TTAGCAGCCTGCAACCTGAAGACTTTGCGGTTTATTAT TGCCAGCAGTATTATGATTTTTCTGATACCTTTGGCCA GGGTACGAAAGTTGAAATTAAACGTACGGTGGCTGCT CCGAGCGTGTTTATTTTTCCGCCGAGCGATGAACAACT GAAAAGCGGCACGGCGAGCGTGGTGTGCCTGCTGAAC AACTTTTATCCGCGTGAAGCGAAAGTTCAGTGGAAAGT AGACAACGCGCTGCAAAGCGGCAACAGCCAGGAAAGC GTGACCGAACAGGATAGCAAAGATAGCACCTATTCTCT GAGCAGCACCCTGACCCTGAGCAAAGCGGATTATGAA AAACATAAAGTGTATGCGTGCGAAGTGACCCATCAAGG TCTGAGCAGCCCGGTGACTAAATCTTTTAATCGTGGCG AGX (X puede ser TGC ó GCC)
Anticuerpo 6763	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	173: NYGMH
CDRH2	174: VSYAGSFTNYADSVKG

CDRH3	175:SWLFGYPDIFDY
CDRL1	176:TGTSSDVGGYNYVS
CDRL2	177: DVNNRPS
CDRL3	178:SSYDKFQTV
VH	179:QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGMH WVRQAPGKGLEWVSVSYAGSFTNYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARSWLFGYPDIFDYWG QGTLVTVSS
VL	180:DIALTQPASVSGSPGQSITISCTGTSSDVGGYNYVS WYQQHPGKAPKLMIYDVNNRPSGVSNRFSGSKSGNTAS LTISGLQAEDEADYYCSSYDKFQTVFGGGTKLTVL
Cadena pesada	181:QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGMH WVRQAPGKGLEWVSVSYAGSFTNYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARSWLFGYPDIFDYWG QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)
Cadena ligera	182:DIALTQPASVSGSPGQSITISCTGTSSDVGGYNYVS WYQQHPGKAPKLMIYDVNNRPSGVSNRFSGSKSGNTAS LTISGLQAEDEADYYCSSYDKFQTVFGGGTKLTVLGQPK

	AAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTEX (X puede ser CS ó A)
PN que codifica SEQ ID NO:179	183:CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTG GTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGCG GCCTCCGGATTTACCTTTTCTAATTATGGTATGCATTG GGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGT GAGCGTTTCTTATGCTGGTAGCTTTACCAATTATGCGG ATAGCGTGAAAGGCCGTTTTACCATTTCACGTGATAAT TCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCG TGCGGAAGATACGGCCGTGTATTATTGCGCGCGTTCTT GGCTTTTTGGTTATCCTGATATTTTTGATTATTGGGGCC AAGGCACCCTGGTGACGGTTAGCTCA
PN que codifica SEQ ID NO:180	184:GATATCGCACTGACCCAGCCAGCTTCAGTGAGCG GCTCACCAGGTCAGAGCATTACCATCTCGTGTACGGG TACTAGCAGCGATGTTGGTGGTTATAATTATGTGTCTT GGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTTAT GATTTATGATGTTAATAATCGTCCCTCAGGCGTGAGCA ACCGTTTTAGCGGATCCAAAAGCGGCAACACCGCGAG CCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCG GATTATTATTGCTCTTCTTATGATAAGTTTCAGACTGTG TTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN que	185:CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTG

codifica SEQ ID NO:181	GTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGCG GCCTCCGGATTTACCTTTTCTAATTATGGTATGCATTG GGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGGGT GAGCGTTTCTTATGCTGGTAGCTTTACCAATTATGCGG ATAGCGTGAAAGGCCGTTTTACCATTTCACGTGATAAT TCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCG TGCGGAAGATACGGCCGTGTATTATTGCGCGCGTTCTT GGCTTTTTGGTTATCCTGATATTTTTGATTATTGGGGCC AAGGCACCCTGGTGACGGTTAGCTCAGCGTCGACCAA AGGTCCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAAA AGCACCAGCGGCGGCACGGCTGCCCTGGGCTGCCTG GTTAAAGATTATTTCCCGGAACCAGTCACCGTGAGCTG GAACAGCGGGGCGCTGACCAGCGGCGTGCATACCTTT CCGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTGA GCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGCAC TCAGACCTATATTTGCAACGTGAACCATAAACCGAGCA ACACCAAAGTGGATAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)
PN que codifica SEQ ID NO:182	186:GATATCGCACTGACCCAGCCAGCTTCAGTGAGCG GCTCACCAGGTCAGAGCATTACCATCTCGTGTACGGG TACTAGCAGCGATGTTGGTGGTTATAATTATGTGTCTT GGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTTAT GATTTATGATGTTAATAATCGTCCCTCAGGCGTGAGCA ACCGTTTTAGCGGATCCAAAAGCGGCAACACCGCGAG

	CCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCG GATTATTATTGCTCTTCTTATGATAAGTTTCAGACTGTG TTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGC CGAAAGCCGCACCGAGTGTGACGCTGTTTCCGCCGAG CAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTG TGCCTGATTAGCGACTTTTATCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGG AGTGGAGACCACCACACCCTCCAAACAAAGCAACAAC AAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTG AGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGT CACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCG CCGACTGAGX (X puede ser TGCAGC ó GCC)
Anticuerpo 7086	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:1
CDRH2	SEQ ID NO:2
CDRH3	SEQ ID NO:3
CDRL1	SEQ ID NO:4
CDRL2	SEQ ID NO:5
CDRL3	SEQ ID NO:6

VH	187:QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAIS WVRQAPGQGLEWMGGIGPFFGTANYAQKFQGRVTITAD ESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTL VTVSS
VL	188:DIELTQPPSVSVAPGQTARISCSGDSIPNYYVYWYQ QKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQSFDSSLNAEVFGGGTKLTVL
Cadena pesada	189:QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAIS WVRQAPGQGLEWMGGIGPFFGTANYAQKFQGRVTITAD ESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTL VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)
Cadena ligera	190:DIELTQPPSVSVAPGQTARISCSGDSIPNYYVYWYQ QKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQSFDSSLNAEVFGGGTKLTVLGQPKAA PSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTEX (X puede ser CS ó A)

PN que codifica SEQ ID NO:187	191:CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGA AAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAGC CTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGG TGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGATGG GCGGTATCGGTCCGTTTTTTGGCACTGCGAATTACGC GCAGAAGTTTCAGGGCCGGGTGACCATTACCGCGGAT GAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCC TGCGTAGCGAAGATACGGCCGTGTATTATTGCGCGCG TGATACTCCTTATTTTGATTATTGGGGCCAAGGCACCC TGGTGACGGTTAGCTCA
PN que codifica SEQ ID NO:188	192:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTATTCCTAATTATTATGTTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATGAT GATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGTCTTTTGATTCTTCTCTTAATGCTGAGGTGTTTG GCGGCGGCACGAAGTTAACCGTTCTT
PN que codifica SEQ ID NO:189	193:CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGA AAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAGC CTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGG TGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGATGG

	GCGGTATCGGTCCGTTTTTTGGCACTGCGAATTACGC GCAGAAGTTTCAGGGCCGGGTGACCATTACCGCGGAT GAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCC TGCGTAGCGAAGATACGGCCGTGTATTATTGCGCGCG TGATACTCCTTATTTTGATTATTGGGGCCAAGGCACCC TGGTGACGGTTAGCTCAGCGTCGACCAAAGGTCCAAG CGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGC GGCGGCACGGCTGCCCTGGGCTGCCTGGTTAAAGATT ATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGG GGCGCTGACCAGCGGCGTGCATACCTTTCCGGCGGTG CTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTG TGACCGTGCCGAGCAGCAGCTTAGGCACTCAGACCTA TATTTGCAACGTGAACCATAAACCGAGCAACACCAAAG TGGATAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)
PN que codifica SEQ ID NO:190	194:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTATTCCTAATTATTATGTTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATGAT GATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGTCTTTTGATTCTTCTCTTAATGCTGAGGTGTTTG GCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAA

	AGCCGCACCGAGTGTGACGCTGTTTCCGCCGAGCAGC GAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCC TGATTAGCGACTTTTATCCGGGAGCCGTGACAGTGGC CTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGT GGAGACCACCACACCCTCCAAACAAAGCAACAACAAG TACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGC AGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCAC GCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCG ACTGAGX (X puede ser TGCAGC ó GCC)
Anticuerpo 7087	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	195: SYYIS
CDRH2	196: GIIPIFGTANYAQKFQG
CDRH3	197: GEIWHVHQPYKSGVYGAAY
CDRL1	198: RASQGISNWLN
CDRL2	199: GTSSLQS
CDRL3	200: QQLDSFPAT
VH	201:QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYYIS WVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARGEIWHVHQPYKSGVY

	GAAYWGQGTLVTVSS
VL	202:DIQMTQSPSSLSASVGDRVTITCRASQGISNWLNWY QQKPGKAPKLLIYGTSSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQLDSFPATFGQGTKVEIK
Cadena pesada	203:QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYYIS WVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARGEIWHVHQPYKSGVY GAAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SX (X puede ser C, EF ó CEF)
Cadena ligera	204:DIQMTQSPSSLSASVGDRVTITCRASQGISNWLNWY QQKPGKAPKLLIYGTSSLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYYCQQLDSFPATFGQGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEX (X puede ser C ó A)
PN que codifica SEQ ID NO:201	205:CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGA AAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAGC CTCCGGAGGCACTTTTTCTTCTTATTATATTTCTTGGGT GCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGATGGG CGGTATCATTCCGATTTTTGGCACTGCGAATTACGCGC

	AGAAGTTTCAGGGCCGGGTGACCATTACCGCGGATGA AAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTG CGTAGCGAAGATACGGCCGTGTATTATTGCGCGCGTG GTGAGATTTGGCATGTTCATCAGCCTTATAAGTCTGGT GTTTATGGTGCTGCTTATTGGGGCCAAGGCACCCTGG TGACGGTTAGCTCA
PN que codifica SEQ ID NO:202	206:GATATCCAGATGACCCAGAGCCCGTCTAGCCTGA GCGCGAGCGTGGGTGATCGTGTGACCATTACCTGCAG AGCGAGCCAGGGTATTTCTAATTGGCTGAATTGGTACC AGCAGAAACCAGGTAAAGCACCGAAACTATTAATTTAT GGTACTTCTTCTTTGCAAAGCGGGGTCCCGTCCCGTTT TAGCGGCTCTGGATCCGGCACTGATTTTACCCTGACCA TTAGCAGCCTGCAACCTGAAGACTTTGCGACTTATTAT TGCCAGCAGCTTGATTCTTTTCCTGCTACCTTTGGCCA GGGTACGAAAGTTGAAATTAAA
PN que codifica SEQ ID NO:203	207:CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGA AAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAGC CTCCGGAGGCACTTTTTCTTCTTATTATATTTCTTGGGT GCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGATGGG CGGTATCATTCCGATTTTTGGCACTGCGAATTACGCGC AGAAGTTTCAGGGCCGGGTGACCATTACCGCGGATGA AAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTG CGTAGCGAAGATACGGCCGTGTATTATTGCGCGCGTG

	GTGAGATTTGGCATGTTCATCAGCCTTATAAGTCTGGT GTTTATGGTGCTGCTTATTGGGGCCAAGGCACCCTGG TGACGGTTAGCTCAGCGTCGACCAAAGGTCCAAGCGT GTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGC GGCACGGCTGCCCTGGGCTGCCTGGTTAAAGATTATT TCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGGGC GCTGACCAGCGGCGTGCATACCTTTCCGGCGGTGCTG CAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGA CCGTGCCGAGCAGCAGCTTAGGCACTCAGACCTATAT TTGCAACGTGAACCATAAACCGAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)
PN que codifica SEQ ID NO:204	208:GATATCCAGATGACCCAGAGCCCGTCTAGCCTGA GCGCGAGCGTGGGTGATCGTGTGACCATTACCTGCAG AGCGAGCCAGGGTATTTCTAATTGGCTGAATTGGTACC AGCAGAAACCAGGTAAAGCACCGAAACTATTAATTTAT GGTACTTCTTCTTTGCAAAGCGGGGTCCCGTCCCGTTT TAGCGGCTCTGGATCCGGCACTGATTTTACCCTGACCA TTAGCAGCCTGCAACCTGAAGACTTTGCGACTTATTAT TGCCAGCAGCTTGATTCTTTTCCTGCTACCTTTGGCCA GGGTACGAAAGTTGAAATTAAACGTACGGTGGCTGCT CCGAGCGTGTTTATTTTTCCGCCGAGCGATGAACAACT GAAAAGCGGCACGGCGAGCGTGGTGTGCCTGCTGAAC AACTTTTATCCGCGTGAAGCGAAAGTTCAGTGGAAAGT

	AGACAACGCGCTGCAAAGCGGCAACAGCCAGGAAAGC GTGACCGAACAGGATAGCAAAGATAGCACCTATTCTCT GAGCAGCACCCTGACCCTGAGCAAAGCGGATTATGAA AAACATAAAGTGTATGCGTGCGAAGTGACCCATCAAGG TCTGAGCAGCCCGGTGACTAAATCTTTTAATCGTGGCG AGX (X puede ser TGC ó GCC)
Anticuerpo 7091	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:77
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	209:QSWTDSPNTLV
VH	210:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGW VRQMPGKGLEWMGIIDPSDSHTTYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLV TVSS
VL	211:DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQ QKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTISG

	TQAEDEADYYCQSWTDSPNTLVFGGGTKLTVL
Cadena pesada	212:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGW VRQMPGKGLEWMGIIDPSDSHTTYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)
Cadena ligera	213:DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQ QKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQSWTDSPNTLVFGGGTKLTVLGQPKAA PSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTEX (X puede ser CS ó A)
PN que codifica SEQ ID NO:210	214:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGT GCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGG CATTATCGATCCGTCTGATAGCCATACCACTTATTCTC CGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGATAA AAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGA AAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTAT ATGATGCGTGGTTTTGATCATTGGGGCCAAGGCACCC

	TGGTGACGGTTAGCTCA
PN que codifica SEQ ID NO:211	215:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGTCTTGGACTGATTCTCCTAATACTCTTGTGTTT GGCGGCGGCACGAAGTTAACCGTTCTT
PN que codifica SEQ ID NO:212	216:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGT GCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGG CATTATCGATCCGTCTGATAGCCATACCACTTATTCTC CGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGATAA AAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGA AAGCGAGCGATACGGCCATGTATTATTGCGCGCGTTAT ATGATGCGTGGTTTTGATCATTGGGGCCAAGGCACCC TGGTGACGGTTAGCTCAGCGTCGACCAAAGGTCCAAG CGTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGC GGCGGCACGGCTGCCCTGGGCTGCCTGGTTAAAGATT ATTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGG

	GGCGCTGACCAGCGGCGTGCATACCTTTCCGGCGGTG CTGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTG TGACCGTGCCGAGCAGCAGCTTAGGCACTCAGACCTA TATTTGCAACGTGAACCATAAACCGAGCAACACCAAAG TGGATAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)
PN que codifica SEQ ID NO:213	217:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGTCTTGGACTGATTCTCCTAATACTCTTGTGTTT GGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGA AAGCCGCACCGAGTGTGACGCTGTTTCCGCCGAGCAG CGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGC CTGATTAGCGACTTTTATCCGGGAGCCGTGACAGTGG CCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGT GGAGACCACCACACCCTCCAAACAAAGCAACAACAAG TACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGC AGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCAC GCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCG ACTGAGX (X puede ser TGCAGC ó GCC)

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Anticuerpo 7092	IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:49
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:22
VH	218:QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWV RQMPGKGLEWMGIIDPDDSYTRYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVT VSS
VL	219:DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQ QKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCGTYDIESYVFGGGTKLTVL
Cadena pesada	220:QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWV RQMPGKGLEWMGIIDPDDSYTRYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS

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	LGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)
Cadena ligera	221:DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQ QKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCGTYDIESYVFGGGTKLTVLGQPKAAPSV TLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPV KAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSC QVTHEGSTVEKTVAPTEX (X puede ser CS ó A)
PN que codifica SEQ ID NO:218	222:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCG CCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATT ATCGATCCGGATGATAGCTATACCCGTTATTCTCCGAG CTTTCAGGGACAGGTGACCATTAGCGCGGATAAAAGC ATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGC GAGCGATACGGCCATGTATTATTGCGCGCGTTATGAGT ATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGT GACGGTTAGCTCA
PN que codifica SEQ ID NO:219	223:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAG

	CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCGGTACTTATGATATTGAGTCTTATGTGTTTGGCGGC GGCACGAAGTTAACCGTTCTT
PN que codifica SEQ ID NO:220	224:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCG CCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATT ATCGATCCGGATGATAGCTATACCCGTTATTCTCCGAG CTTTCAGGGACAGGTGACCATTAGCGCGGATAAAAGC ATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGC GAGCGATACGGCCATGTATTATTGCGCGCGTTATGAGT ATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGT GACGGTTAGCTCAGCGTCGACCAAAGGTCCAAGCGTG TTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCG GCACGGCTGCCCTGGGCTGCCTGGTTAAAGATTATTT CCCGGAACCAGTCACCGTGAGCTGGAACAGCGGGGC GCTGACCAGCGGCGTGCATACCTTTCCGGCGGTGCTG CAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGA CCGTGCCGAGCAGCAGCTTAGGCACTCAGACCTATAT TTGCAACGTGAACCATAAACCGAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)

PN que codifica SEQ ID NO:221	225:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCGGTACTTATGATATTGAGTCTTATGTGTTTGGCGGC GGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCG CACCGAGTGTGACGCTGTTTCCGCCGAGCAGCGAAGA ATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATT AGCGACTTTTATCCGGGAGCCGTGACAGTGGCCTGGA AGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGA CCACCACACCCTCCAAACAAAGCAACAACAAGTACGC GGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGG AAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATG AGGGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGA GX (X puede ser TGCAGC ó GCC)
Anticuerpo 7093	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:33
CDRH2	226: HIFSDDDKYYSTSLKT

CDRH3	SEQ ID NO:35
CDRL1	SEQ ID NO:36
CDRL2	SEQ ID NO:37
CDRL3	SEQ ID NO:38
VH	227:QVQLKESGPALVKPTQTLTLTCTFSGFSLSTSGGGV SWIRQPPGKALEWLAHIFSDDDKYYSTSLKTRLTISKDTS KNQVVLTMTNMDPVDTATYYCARGPYGFDSWGQGTLVT VSS
VL	228:DIALTQPASVSGSPGQSITISCTGTSSDIGTYNYVSW YQQHPGKAPKLMIYDDSNRPSGVSNRFSGSKSGNTASL TISGLQAEDEADYYCQSYDSQSIVFGGGTKLTVL
Cadena pesada	229:QVQLKESGPALVKPTQTLTLTCTFSGFSLSTSGGGV SWIRQPPGKALEWLAHIFSDDDKYYSTSLKTRLTISKDTS KNQVVLTMTNMDPVDTATYYCARGPYGFDSWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)
Cadena ligera	230:DIALTQPASVSGSPGQSITISCTGTSSDIGTYNYVSW YQQHPGKAPKLMIYDDSNRPSGVSNRFSGSKSGNTASL TISGLQAEDEADYYCQSYDSQSIVFGGGTKLTVLGQPKA

	APSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHR SYSCQVTHEGSTVEKTVAPTEX (X puede ser CS ó A)
PN que codifica SEQ ID NO:227	231:CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGG TGAAACCGACCCAAACCCTGACCCTGACCTGTACCTTT TCCGGATTTAGCCTGTCTACTTCTGGTGGTGGTGTGTC TTGGATTCGCCAGCCGCCTGGGAAAGCCCTCGAGTGG CTGGCTCATATCTTTTCTGATGATGATAAGTATTATAGC ACCAGCCTGAAAACGCGTCTGACCATTAGCAAAGATAC TTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGG ACCCGGTGGATACGGCCACCTATTATTGCGCGCGTGG TCCTTATGGTTTTGATTCTTGGGGCCAAGGCACCCTGG TGACGGTTAGCTCA
PN que codifica SEQ ID NO:228	232:GATATCGCACTGACCCAGCCAGCTTCAGTGAGCG GCTCACCAGGTCAGAGCATTACCATCTCGTGTACGGG TACTAGCAGCGATATTGGTACTTATAATTATGTGTCTTG GTACCAGCAGCATCCCGGGAAGGCGCCGAAACTTATG ATTTATGATGATTCTAATCGTCCCTCAGGCGTGAGCAA CCGTTTTAGCGGATCCAAAAGCGGCAACACCGCGAGC CTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGG ATTATTATTGCCAGTCTTATGATTCTCAGTCTATTGTGT TTGGCGGCGGCACGAAGTTAACCGTTCTT
PN que	233:CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGG

codifica SEQ ID NO:229	TGAAACCGACCCAAACCCTGACCCTGACCTGTACCTTT TCCGGATTTAGCCTGTCTACTTCTGGTGGTGGTGTGTC TTGGATTCGCCAGCCGCCTGGGAAAGCCCTCGAGTGG CTGGCTCATATCTTTTCTGATGATGATAAGTATTATAGC ACCAGCCTGAAAACGCGTCTGACCATTAGCAAAGATAC TTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGG ACCCGGTGGATACGGCCACCTATTATTGCGCGCGTGG TCCTTATGGTTTTGATTCTTGGGGCCAAGGCACCCTGG TGACGGTTAGCTCAGCGTCGACCAAAGGTCCAAGCGT GTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGC GGCACGGCTGCCCTGGGCTGCCTGGTTAAAGATTATT TCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGGGC GCTGACCAGCGGCGTGCATACCTTTCCGGCGGTGCTG CAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGA CCGTGCCGAGCAGCAGCTTAGGCACTCAGACCTATAT TTGCAACGTGAACCATAAACCGAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)
PN que codifica SEQ ID NO:230	234:GATATCGCACTGACCCAGCCAGCTTCAGTGAGCG GCTCACCAGGTCAGAGCATTACCATCTCGTGTACGGG TACTAGCAGCGATATTGGTACTTATAATTATGTGTCTTG GTACCAGCAGCATCCCGGGAAGGCGCCGAAACTTATG ATTTATGATGATTCTAATCGTCCCTCAGGCGTGAGCAA CCGTTTTAGCGGATCCAAAAGCGGCAACACCGCGAGC

	CTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGG ATTATTATTGCCAGTCTTATGATTCTCAGTCTATTGTGT TTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCC GAAAGCCGCACCGAGTGTGACGCTGTTTCCGCCGAGC AGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGT GCCTGATTAGCGACTTTTATCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGG AGTGGAGACCACCACACCCTCCAAACAAAGCAACAAC AAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTG AGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGT CACGCATGAGGGGAGCACCGTGGAAAAAACCGTTGCG CCGACTGAGX (X puede ser TGCAGC ó GCC)
Anticuerpo 7094	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	235: TSGMSVG
CDRH2	236: LIDWDEDKSYSTSLKT
CDRH3	237:YNWYNPPGFDN
CDRL1	238:SGSSSNIGSNYVS
CDRL2	239: RNDKRPS
CDRL3	240: QSADSSSMV

VH	241:QVQLKESGPALVKPTQTLTLTCTFSGFSLSTSGMSV GWIRQPPGKALEWLALIDWDEDKSYSTSLKTRLTISKDTS KNQVVLTMTNMDPVDTATYYCARYNWYNPPGFDNWGQ GTLVTVSS
VL	242:DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSNYVSW YQQLPGTAPKLLIYRNDKRPSGVPDRFSGSKSGTSASLAI TGLQSEDEADYYCQSADSSSMVFGGGTKLTVL
Cadena pesada	243:QVQLKESGPALVKPTQTLTLTCTFSGFSLSTSGMSV GWIRQPPGKALEWLALIDWDEDKSYSTSLKTRLTISKDTS KNQVVLTMTNMDPVDTATYYCARYNWYNPPGFDNWGQ GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)
Cadena ligera	244:DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSNYVSW YQQLPGTAPKLLIYRNDKRPSGVPDRFSGSKSGTSASLAI TGLQSEDEADYYCQSADSSSMVFGGGTKLTVLGQPKAA PSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTEX (X puede ser CS ó A)
PN que codifica	245:CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGG TGAAACCGACCCAAACCCTGACCCTGACCTGTACCTTT

S60

SEQ ID NO:241	TCCGGATTTAGCCTGTCTACTTCTGGTATGTCTGTGGG TTGGATTCGCCAGCCGCCTGGGAAAGCCCTCGAGTGG CTGGCTCTTATCGATTGGGATGAGGATAAGTCTTATAG CACCAGCCTGAAAACGCGTCTGACCATTAGCAAAGATA CTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATG GACCCGGTGGATACGGCCACCTATTATTGCGCGCGTT ATAATTGGTATAATCCTCCTGGTTTTGATAATTGGGGC CAAGGCACCCTGGTGACGGTTAGCTCA
PN que codifica SEQ ID NO:242	246:GATATCGTGCTGACCCAGCCGCCTTCAGTGAGTG GCGCACCAGGTCAGCGTGTGACCATCTCGTGTAGCGG CAGCAGCAGCAACATTGGTTCTAATTATGTGTCTTGGT ACCAGCAGTTGCCCGGGACGGCGCCGAAACTTCTGAT TTATCGTAATGATAAGCGTCCCTCAGGCGTGCCGGATC GTTTTAGCGGATCCAAAAGCGGCACCAGCGCGAGCCT TGCGATTACGGGCCTGCAAAGCGAAGACGAAGCGGAT TATTATTGCCAGTCTGCTGATTCTTCTTCTATGGTGTTT GGCGGCGGCACGAAGTTAACCGTTCTT
PN que codifica SEQ ID NO:243	247:CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGG TGAAACCGACCCAAACCCTGACCCTGACCTGTACCTTT TCCGGATTTAGCCTGTCTACTTCTGGTATGTCTGTGGG TTGGATTCGCCAGCCGCCTGGGAAAGCCCTCGAGTGG CTGGCTCTTATCGATTGGGATGAGGATAAGTCTTATAG CACCAGCCTGAAAACGCGTCTGACCATTAGCAAAGATA

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	CTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATG GACCCGGTGGATACGGCCACCTATTATTGCGCGCGTT ATAATTGGTATAATCCTCCTGGTTTTGATAATTGGGGC CAAGGCACCCTGGTGACGGTTAGCTCAGCGTCGACCA AAGGTCCAAGCGTGTTTCCGCTGGCTCCGAGCAGCAA AAGCACCAGCGGCGGCACGGCTGCCCTGGGCTGCCT GGTTAAAGATTATTTCCCGGAACCAGTCACCGTGAGCT GGAACAGCGGGGCGCTGACCAGCGGCGTGCATACCTT TCCGGCGGTGCTGCAAAGCAGCGGCCTGTATAGCCTG AGCAGCGTTGTGACCGTGCCGAGCAGCAGCTTAGGCA CTCAGACCTATATTTGCAACGTGAACCATAAACCGAGC AACACCAAAGTGGATAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)
PN que codifica SEQ ID NO:244	248:GATATCGTGCTGACCCAGCCGCCTTCAGTGAGTG GCGCACCAGGTCAGCGTGTGACCATCTCGTGTAGCGG CAGCAGCAGCAACATTGGTTCTAATTATGTGTCTTGGT ACCAGCAGTTGCCCGGGACGGCGCCGAAACTTCTGAT TTATCGTAATGATAAGCGTCCCTCAGGCGTGCCGGATC GTTTTAGCGGATCCAAAAGCGGCACCAGCGCGAGCCT TGCGATTACGGGCCTGCAAAGCGAAGACGAAGCGGAT TATTATTGCCAGTCTGCTGATTCTTCTTCTATGGTGTTT GGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGA AAGCCGCACCGAGTGTGACGCTGTTTCCGCCGAGCAG CGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGC

562

	CTGATTAGCGACTTTTATCCGGGAGCCGTGACAGTGG CCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGT GGAGACCACCACACCCTCCAAACAAAGCAACAACAAG TACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGC AGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCAC GCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCG ACTGAGX (X puede ser TGCAGC ó GCC)
Anticuerpo 7821	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:1
CDRH2	SEQ ID NO:119
CDRH3	SEQ ID NO:3
CDRL1	SEQ ID NO:4
CDRL2	SEQ ID NO:5
CDRL3	SEQ ID NO:6
VH	SEQ ID NO:121
VL	SEQ ID NO:188
Cadena pesada	249:QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAIS WVRQAPGQGLEWMGNIGPFFGIANYAQKFQGRVTITAD

	ESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTL VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)
Cadena ligera	SEQ ID NO:190
PN que codifica SEQ ID NO:121	SEQ ID NO:125
PN que codifica SEQ ID NO:188	SEQ ID NO:192
PN que codifica SEQ ID NO:249	250:CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGA AAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAGC CTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGG TGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGATGG GCAATATCGGTCCGTTTTTTGGCATTGCGAATTACGCG CAGAAGTTTCAGGGCCGGGTGACCATTACCGCGGATG AAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCT

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	GCGTAGCGAAGATACGGCCGTGTATTATTGCGCGCGT GATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCT GGTGACGGTTAGCTCAGCGTCGACCAAAGGTCCAAGC GTGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCG GCGGCACGGCTGCCCTGGGCTGCCTGGTTAAAGATTA TTTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGG GCGCTGACCAGCGGCGTGCATACCTTTCCGGCGGTGC TGCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGT GACCGTGCCGAGCAGCAGCTTAGGCACTCAGACCTAT ATTTGCAACGTGAACCATAAACCGAGCAACACCAAAGT GGATAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)
PN que codifica SEQ ID NO:190	SEQ ID NO:194
Anticuerpo 7865	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:1
CDRH2	SEQ ID NO:2
CDRH3	SEQ ID NO:3

CDRL1	SEQ ID NO:4
CDRL2	SEQ ID NO:5
CDRL3	SEQ ID NO:120
VH	SEQ ID NO:187
VL	SEQ ID NO:122
Cadena pesada	SEQ ID NO:189
Cadena ligera	251:DIELTQPPSVSVAPGQTARISCSGDSIPNYYVYWYQ QKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQTYDDGSTAEVFGGGTKLTVLGQPKAA PSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTEX (X puede ser CS ó A)
PN que codifica SEQ ID NO:187	SEQ ID NO:191
PN que codifica SEQ ID	SEQ ID NO:126

NO:122	
PN que codifica SEQ ID NO:189	SEQ ID NO:193
PN que codifica SEQ ID NO:251	252:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTATTCCTAATTATTATGTTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATGAT GATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGACTTATGATGATGGTTCTACTGCTGAGGTGTTT GGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGA AAGCCGCACCGAGTGTGACGCTGTTTCCGCCGAGCAG CGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGC CTGATTAGCGACTTTTATCCGGGAGCCGTGACAGTGG CCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGT GGAGACCACCACACCCTCCAAACAAAGCAACAACAAG TACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGC AGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCAC GCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCG ACTGAGX (X puede ser TGCAGC ó GCC)

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Anticuerpo 7829	IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:62
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	SEQ ID NO:209
VH	253:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGW VRQMPGKGLEWMGIIDPTDSQTAYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLV TVSS
VL	SEQ ID NO:211
Cadena pesada	254:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGW VRQMPGKGLEWMGIIDPTDSQTAYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)

Cadena ligera	SEQ ID NO:213
PN que codifica SEQ ID NO:253	255:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGT GCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGG CATTATTGATCCTACTGATTCTCAGACTGCTTATTCTCC TTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAA GCGAGCGATACGGCCATGTATTATTGCGCGCGTTATAT GATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTG GTGACGGTTAGCTCA
PN que codifica SEQ ID NO:211	SEQ ID NO:215
PN que codifica SEQ ID NO:254	256:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGT GCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGG CATTATTGATCCTACTGATTCTCAGACTGCTTATTCTCC TTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAA

	GCGAGCGATACGGCCATGTATTATTGCGCGCGTTATAT GATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTG GTGACGGTTAGCTCAGCGTCGACCAAAGGTCCAAGCG TGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGG CGGCACGGCTGCCCTGGGCTGCCTGGTTAAAGATTAT TTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGGG CGCTGACCAGCGGCGTGCATACCTTTCCGGCGGTGCT GCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTG ACCGTGCCGAGCAGCAGCTTAGGCACTCAGACCTATA TTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)
PN que codifica SEQ ID NO:213	SEQ ID NO:217
Anticuerpo 7830	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:95
CDRH3	SEQ ID NO:63

CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	SEQ ID NO:209
VH	257:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGW VRQMPGKGLEWMGIIDPTDSYTVYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLV TVSS
VL	SEQ ID NO:211
Cadena pesada	258:QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGW VRQMPGKGLEWMGIIDPTDSYTVYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLV TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)
Cadena ligera	SEQ ID NO:213
PN que codifica SEQ ID NO:257	259:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGT GCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGG

	CATTATTGATCCTACTGATTCTTATACTGTTTATTCTCC TTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAA GCGAGCGATACGGCCATGTATTATTGCGCGCGTTATAT GATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTG GTGACGGTTAGCTCA
PN que codifica SEQ ID NO:211	SEQ ID NO:215
PN que codifica SEQ ID NO:258	260:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGT GCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGG CATTATTGATCCTACTGATTCTTATACTGTTTATTCTCC TTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAA GCGAGCGATACGGCCATGTATTATTGCGCGCGTTATAT GATGCGTGGTTTTGATCATTGGGGCCAAGGCACCCTG GTGACGGTTAGCTCAGCGTCGACCAAAGGTCCAAGCG TGTTTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGG CGGCACGGCTGCCCTGGGCTGCCTGGTTAAAGATTAT TTCCCGGAACCAGTCACCGTGAGCTGGAACAGCGGGG

	CGCTGACCAGCGGCGTGCATACCTTTCCGGCGGTGCT GCAAAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTG ACCGTGCCGAGCAGCAGCTTAGGCACTCAGACCTATA TTTGCAACGTGAACCATAAACCGAGCAACACCAAAGTG GATAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)
PN que codifica SEQ ID NO:213	SEQ ID NO:217
Anticuerpo 7871	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:77
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	SEQ ID NO:66
VH	SEQ ID NO:210

VL	261:DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQ QKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQTWDTGESGVFGGGTKLTVL
Cadena pesada	SEQ ID NO:212
Cadena ligera	262:DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQ QKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQTWDTGESGVFGGGTKLTVLGQPKAAP SVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSS PVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSY SCQVTHEGSTVEKTVAPTEX (X puede ser CS ó A)
PN que codifica SEQ ID NO:210	SEQ ID NO:214
PN que codifica SEQ ID NO:261	263:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT

	GCCAGACTTGGGATACTGGTGAGTCTGGTGTGTTTGG CGGCGGCACGAAGTTAACCGTTCTT
PN que codifica SEQ ID NO:212	SEQ ID NO:216
PN que codifica SEQ ID NO:262	264:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGACTTGGGATACTGGTGAGTCTGGTGTGTTTGG CGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAA GCCGCACCGAGTGTGACGCTGTTTCCGCCGAGCAGCG AAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCT GATTAGCGACTTTTATCCGGGAGCCGTGACAGTGGCC TGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTG GAGACCACCACACCCTCCAAACAAAGCAACAACAAGTA CGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAG TGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGC ATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCGAC

	TGAGX (X puede ser TGCAGC ó GCC)
Anticuerpo 7872	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:77
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64
CDRL2	SEQ ID NO:65
CDRL3	SEQ ID NO:78
VH	SEQ ID NO:210
VL	265:DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQ QKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQTWDILPHGLVFGGGTKLTVL
Cadena pesada	SEQ ID NO:212
Cadena ligera	266:DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQ QKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQTWDILPHGLVFGGGTKLTVLGQPKAAP SVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSS

	PVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSY SCQVTHEGSTVEKTVAPTEX (X puede ser CS ó A)
PN que codifica SEQ ID NO:210	SEQ ID NO:214
PN que codifica SEQ ID NO:265	267:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGACTTGGGATATTCTTCCTCATGGTCTTGTGTTT GGCGGCGGCACGAAGTTAACCGTTCTT
PN que codifica SEQ ID NO:212	SEQ ID NO:216
PN que codifica SEQ ID	268:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCA

NO:266	GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGACTTGGGATATTCTTCCTCATGGTCTTGTGTTT GGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGA AAGCCGCACCGAGTGTGACGCTGTTTCCGCCGAGCAG CGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGC CTGATTAGCGACTTTTATCCGGGAGCCGTGACAGTGG CCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGT GGAGACCACCACACCCTCCAAACAAAGCAACAACAAG TACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGC AGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCAC GCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCG ACTGAGX (X puede ser TGCAGC ó GCC)
Anticuerpo 7873	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:61
CDRH2	SEQ ID NO:77
CDRH3	SEQ ID NO:63
CDRL1	SEQ ID NO:64

CDRL2	SEQ ID NO:65
CDRL3	SEQ ID NO:89
VH	SEQ ID NO:210
VL	269:DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQ QKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQAWTDSPTGLVFGGGTKLTVL
Cadena pesada	SEQ ID NO:212
Cadena ligera	270:DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQ QKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCQAWTDSPTGLVFGGGTKLTVLGQPKAA PSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTEX (X puede ser CS ó A)
PN que codifica SEQ ID NO:210	SEQ ID NO:214
PN que codifica SEQ ID	271:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCA

NO:269	GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGGCTTGGACTGATTCTCCTACTGGTCTTGTGTTT GGCGGCGGCACGAAGTTAACCGTTCTT
PN que codifica SEQ ID NO:212	SEQ ID NO:216
PN que codifica SEQ ID NO:270	272:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCCAGGCTTGGACTGATTCTCCTACTGGTCTTGTGTTT GGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGA AAGCCGCACCGAGTGTGACGCTGTTTCCGCCGAGCAG CGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGC CTGATTAGCGACTTTTATCCGGGAGCCGTGACAGTGG CCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGT

	GGAGACCACCACACCCTCCAAACAAAGCAACAACAAG TACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGC AGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCAC GCATGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCG ACTGAGX (X puede ser TGCAGC ó GCC)
Anticuerpo 7832	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:18
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:22
VH	273:QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWV RQMPGKGLEWMGIIDPDDSYTEYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVT VSS
VL	SEQ ID NO:219
Cadena	274:QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWV

pesada	RQMPGKGLEWMGIIDPDDSYTEYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)
Cadena ligera	SEQ ID NO:221
PN que codifica SEQ ID NO:273	275:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCG CCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATT ATTGATCCTGATGATTCTTATACTGAGTATTCTCCTTCT TTTCAGGGTCAGGTCACCATTAGCGCGGATAAAAGCAT TAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCG AGCGATACGGCCATGTATTATTGCGCGCGTTATGAGTA TGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTG ACGGTTAGCTCA
PN que codifica SEQ ID NO:219	SEQ ID NO:223

PN que codifica SEQ ID NO:274	276:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCG CCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATT ATTGATCCTGATGATTCTTATACTGAGTATTCTCCTTCT TTTCAGGGTCAGGTCACCATTAGCGCGGATAAAAGCAT TAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCG AGCGATACGGCCATGTATTATTGCGCGCGTTATGAGTA TGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTG ACGGTTAGCTCAGCGTCGACCAAAGGTCCAAGCGTGT TTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGG CACGGCTGCCCTGGGCTGCCTGGTTAAAGATTATTTCC CGGAACCAGTCACCGTGAGCTGGAACAGCGGGGCGC TGACCAGCGGCGTGCATACCTTTCCGGCGGTGCTGCA AAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACC GTGCCGAGCAGCAGCTTAGGCACTCAGACCTATATTT GCAACGTGAACCATAAACCGAGCAACACCAAAGTGGA TAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)
Anticuerpo 7909	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:107

CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:22
VH	277:QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWV RQMPGKGLEWMGIIDPQDSYTEYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVT VSS
VL	SEQ ID NO:219
Cadena pesada	278:QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWV RQMPGKGLEWMGIIDPQDSYTEYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)
Cadena ligera	SEQ ID NO:221
PN que codifica	279:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG

SEQ ID NO:277	TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCG CCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATT ATTGATCCTCAGGATTCTTATACTGAGTATTCTCCTTCT TTTCAGGGTCAGGTCACCATTAGCGCGGATAAAAGCAT TAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCG AGCGATACGGCCATGTATTATTGCGCGCGTTATGAGTA TGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTG ACGGTTAGCTCA
PN que codifica SEQ ID NO:219	SEQ ID NO:223
PN que codifica SEQ ID NO:278	280:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCG CCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATT ATTGATCCTCAGGATTCTTATACTGAGTATTCTCCTTCT TTTCAGGGTCAGGTCACCATTAGCGCGGATAAAAGCAT TAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCG AGCGATACGGCCATGTATTATTGCGCGCGTTATGAGTA TGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTG ACGGTTAGCTCAGCGTCGACCAAAGGTCCAAGCGTGT TTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGG

	CACGGCTGCCCTGGGCTGCCTGGTTAAAGATTATTTCC CGGAACCAGTCACCGTGAGCTGGAACAGCGGGGCGC TGACCAGCGGCGTGCATACCTTTCCGGCGGTGCTGCA AAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACC GTGCCGAGCAGCAGCTTAGGCACTCAGACCTATATTT GCAACGTGAACCATAAACCGAGCAACACCAAAGTGGA TAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)
Anticuerpo 7910	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:113
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:22
VH	281:QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWV RQMPGKGLEWMGIIDPEDSHTEYSPSFQGQVTISADKSI

	STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVT VSS
VL	SEQ ID NO:219
Cadena pesada	282:QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWV RQMPGKGLEWMGIIDPEDSHTEYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSX (X puede ser C, EF ó CEF)
Cadena ligera	SEQ ID NO:221
PN que codifica SEQ ID NO:281	283:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCG CCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATT ATTGATCCTGAGGATTCTCATACTGAGTATTCTCCTTCT TTTCAGGGTCAGGTGACCATTAGCGCGGATAAAAGCAT TAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCG AGCGATACGGCCATGTATTATTGCGCGCGTTATGAGTA TGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTG ACGGTTAGCTCA

PN que codifica SEQ ID NO:219	SEQ ID NO:223
PN que codifica SEQ ID NO:282	284:CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGA AAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCG CCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCATT ATTGATCCTGAGGATTCTCATACTGAGTATTCTCCTTCT TTTCAGGGTCAGGTGACCATTAGCGCGGATAAAAGCAT TAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCG AGCGATACGGCCATGTATTATTGCGCGCGTTATGAGTA TGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTG ACGGTTAGCTCAGCGTCGACCAAAGGTCCAAGCGTGT TTCCGCTGGCTCCGAGCAGCAAAAGCACCAGCGGCGG CACGGCTGCCCTGGGCTGCCTGGTTAAAGATTATTTCC CGGAACCAGTCACCGTGAGCTGGAACAGCGGGGCGC TGACCAGCGGCGTGCATACCTTTCCGGCGGTGCTGCA AAGCAGCGGCCTGTATAGCCTGAGCAGCGTTGTGACC GTGCCGAGCAGCAGCTTAGGCACTCAGACCTATATTT GCAACGTGAACCATAAACCGAGCAACACCAAAGTGGA TAAAAAAGTGGAACCGAAAAGCX (X puede ser TGC, GAATTC ó TGCGAATTC)

Anticuerpo 7876	IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:49
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21
CDRL3	SEQ ID NO:50
VH	SEQ ID NO:218
VL	285:DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCATWGSEDQVFGGGTKLTVL
Cadena pesada	SEQ ID NO:220
Cadena ligera	286:DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCATWGSEDQVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYS

	CQVTHEGSTVEKTVAPTEX (X puede ser CS ó A)
PN que codifica SEQ ID NO:218	SEQ ID NO:222
PN que codifica SEQ ID NO:285	287:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCGCTACTTGGGGTTCTGAGGATCAGGTGTTTGGCGG CGGCACGAAGTTAACCGTTCTT
PN que codifica SEQ ID NO:220	SEQ ID NO:224
PN que codifica SEQ ID NO:286	288:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG

	GATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCGCTACTTGGGGTTCTGAGGATCAGGTGTTTGGCGG CGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCC GCACCGAGTGTGACGCTGTTTCCGCCGAGCAGCGAAG AATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGAT TAGCGACTTTTATCCGGGAGCCGTGACAGTGGCCTGG AAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAG ACCACCACACCCTCCAAACAAAGCAACAACAAGTACGC GGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGG AAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATG AGGGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGA GX (X puede ser TGCAGC ó GCC)
Anticuerpo 7878	**IDENTIFICADOR DE SECUENCIA (SEQ ID NO:) O COMENTARIOS/DETALLES**
CDRH1	SEQ ID NO:17
CDRH2	SEQ ID NO:49
CDRH3	SEQ ID NO:19
CDRL1	SEQ ID NO:20
CDRL2	SEQ ID NO:21

CDRL3	SEQ ID NO:101
VH	SEQ ID NO:218
VL	289:DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQ QKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCSTWDIEPTYVFGGGTKLTVL
Cadena pesada	SEQ ID NO:220
Cadena ligera	290:DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQ QKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTISG TQAEDEADYYCSTWDIEPTYVFGGGTKLTVLGQPKAAPS VTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYS CQVTHEGSTVEKTVAPTEX (X puede ser CS ó A)
PN que codifica SEQ ID NO:218	SEQ ID NO:222
PN que codifica SEQ ID NO:289	291:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG

	GATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCTCTACTTGGGATATTGAGCCTACTTATGTGTTTGGC GGCGGCACGAAGTTAACCGTTCTT
PN que codifica SEQ ID NO:220	SEQ ID NO:224
PN que codifica SEQ ID NO:290	292:GATATCGAACTGACCCAGCCGCCTTCAGTGAGCG TTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCA GAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAAG GATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAG CGGATCCAACAGCGGCAACACCGCGACCCTGACCATT AGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATT GCTCTACTTGGGATATTGAGCCTACTTATGTGTTTGGC GGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAG CCGCACCGAGTGTGACGCTGTTTCCGCCGAGCAGCGA AGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTG ATTAGCGACTTTTATCCGGGAGCCGTGACAGTGGCCT GGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGG

	AGACCACCACACCCTCCAAACAAAGCAACAACAAGTAC GCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGT GGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCA TGAGGGGAGCACCGTGGAAAAAACCGTTGCGCCGACT GAGX (X puede ser TGCAGC ó GCC)
C5 Humana (*Homo sapiens*)	296:MGLLGILCFLIFLGKTWGQEQTYVISAPKIFRVGASE NIVIQVYGYTEAFDATISIKSYPDKKFSYSSGHVHLSSENK FQNSAILTIQPKQLPGGQNPVSYVYLEVVSKHFSKSKRM PITYDNGFLFIHTDKPVYTPDQSVKVRVYSLNDDLKPAKR ETVLTFIDPEGSEVDMVEEIDHIGIISFPDFKIPSNPRYGM WTIKAKYKEDFSTTGTAYFEVKEYVLPHFSVSIEPEYNFI GYKNFKNFEITIKARYFYNKVVTEADVYITFGIREDLKDDQ KEMMQTAMQNTMLINGIAQVTFDSETAVKELSYYSLEDL NNKYLYIAVTVIESTGGFSEEAEIPGIKYVLSPYKLNLVAT PLFLKPGIPYPIKVQVKDSLDQLVGGVPVTLNAQTIDVNQ ETSDLDPSKSVTRVDDGVASFVLNLPSGVTVLEFNVKTD APDLPEENQAREGYRAIAYSSLSQSYLYIDWTDNHKALL VGEHLNIIVTPKSPYIDKITHYNYLILSKGKIIHFGTREKFS DASYQSINIPVTQNMVPSSRLLVYYIVTGEQTAELVSDSV WLNIEEKCGNQLQVHLSPDADAYSPGQTVSLNMATGMD SWVALAAVDSAVYGVQRGAKKPLERVFQFLEKSDLGCG AGGGLNNANVFHLAGLTFLTNANADDSQENDEPCKEILR PRRTLQKKIEEIAAKYKHSVVKKCCYDGACVNNDETCEQ RAARISLGPRCIKAFTECCVVASQLRANISHKDMQLGRLH

	MKTLLPVSKPEIRSYFPESWLWEVHLVPRRKQLQFALPD SLTTWEIQGVGISNTGICVADTVKAKVFKDVFLEMNIPYS VVRGEQIQLKGTVYNYRTSGMQFCVKMSAVEGICTSESP VIDHQGTKSSKCVRQKVEGSSSHLVTFTVLPLEIGLHNIN FSLETWFGKEILVKTLRVVPEGVKRESYSGVTLDPRGIYG TISRRKEFPYRIPLDLVPKTEIKRILSVKGLLVGEILSAVLS QEGINILTHLPKGSAEAELMSVVPVFYVFHYLETGNHWNI FHSDPLIEKQKLKKKLKEGMLSIMSYRNADYSYSVWKGG SASTWLTAFALRVLGQVNKYVEQNQNSICNSLLWLVENY QLDNGSFKENSQYQPIKLQGTLPVEARENSLYLTAFTVIG IRKAFDICPLVKIDTALIKADNFLLENTLPAQSTFTLAISAY ALSLGDKTHPQFRSIVSALKREALVKGNPPIYRFWKDNL QHKDSSVPNTGTARMVETTAYALLTSLNLKDINYVNPVIK WLSEEQRYGGGFYSTQDTINAIEGLTEYSLLVKQLRLSM DIDVSYKHKGALHNYKMTDKNFLGRPVEVLLNDDLIVSTG FGSGLATVHVTTVVHKTSTSEEVCSFYLKIDTQDIEASHY RGYGNSDYKRIVACASYKPSREESSSGSSHAVMDISLPT GISANEEDLKALVEGVDQLFTDYQIKDGHVILQLNSIPSS DFLCVRFRIFELFEVGFLSPATFTVYEYHRPDKQCTMFYS TSNIKIQKVCEGAACKCVEADCGQMQEELDLTISAETRK QTACKPEIAYAYKVSITSITVENVFVKYKATLLDIYKTGEA VAEKDSEITFIKKVTCTNAELVKGRQYLIMGKEALQIKYNF SFRYIYPLDSLTWIEYWPRDTTCSSCQAFLANLDEFAEDI FLNGC

5k

C5 de Macaco Cino-molgo (*Macaca fascicularis*)	297:MGLLGILCFLIFLGKTWGQEQTYVISAPKIFRVGASE NIVIQVYGYTEAFDATISIKSYPDKKFSYSSGHVHLSSENK FQNSAVLTIQPKQLPGGQNQVSYVYLEVVSKHFSKSKKI PITYDNGFLFIHTDKPVYTPDQSVKVRVYSLNDDLKPAKR ETVLTFIDPEGSEIDMVEEIDHIGIISFPDFKIPSNPRYGM WTIQAKYKEDFSTTGTAFFEVKEYVLPHFSVSVEPESNFI GYKNFKNFEITIKARYFYNKVVTEADVYITFGIREDLKDDQ KEMMQTAMQNTMLINGIAQVTFDSETAVKELSYYSLEDL NNKYLYIAVTVIESTGGFSEEAEIPGIKYVLSPYKLNLVAT PLFLKPGIPYSIKVQVKDALDQLVGGVPVTLNAQTIDVNQ ETSDLEPRKSVTRVDDGVASFVVNLPSGVTVLEFNVKTD APDLPDENQAREGYRAIAYSSLSQSYLYIDWTDNHKALL VGEYLNIIVTPKSPYIDKITHYNYLILSKGKIIHFGTREKLSD ASYQSINIPVTQNMVPSSRLLVYYIVTGEQTAELVSDSVW LNIEEKCGNQLQVHLSPDADTYSPGQTVSLNMVTGMDS WVALTAVDSAVYGVQRRAKKPLERVFQFLEKSDLGCGA GGGLNNANVFHLAGLTFLTNANADDSQENDEPCKEIIRP RRMLQEKIEEIAAKYKHLVVKKCCYDGVRINHDETCEQR AARISVGPRCVKAFTECCVVASQLRANNSHKDLQLGRLH MKTLLPVSKPEIRSYFPESWLWEVHLVPRRKQLQFALPD SVTTWEIQGVGISNSGICVADTIKAKVFKDVFLEMNIPYSV VRGEQVQLKGTVYNYRTSGMQFCVKMSAVEGICTSESP VIDHQGTKSSKCVRQKVEGSSNHLVTFTVLPLEIGLQNIN FSLETSFGKEILVKSLRVVPEGVKRESYSGITLDPRGIYG

	TISRRKEFPYRIPLDLVPKTEIKRILSVKGLLVGEILSAVLS REGINILTHLPKGSAEAELMSVVPVFYVFHYLETGNHWNI FHSDPLIEKRNLEKKLKEGMVSIMSYRNADYSYSVWKGG SASTWLTAFALRVLGQVHKYVEQNQNSICNSLLWLVENY QLDNGSFKENSQYQPIKLQGTLPVEARENSLYLTAFTVIG IRKAFDICPLVKINTALIKADTFLLENTLPAQSTFTLAISAY ALSLGDKTHPQFRSIVSALKREALVKGNPPIYRFWKDSLQ HKDSSVPNTGTARMVETTAYALLTSLNLKDINYVNPIIKW LSEEQRYGGGFYSTQDTINAIEGLTEYSLLVKQLRLNMDI DVAYKHKGPLHNYKMTDKNFLGRPVEVLLNDDLVVSTGF GSGLATVHVTTVVHKTSTSEEVCSFYLKIDTQDIEASHYR GYGNSDYKRIVACASYKPSKEESSSGSSHAVMDISLPTGI NANEEDLKALVEGVDQLFTDYQIKDGHVILQLNSIPSSDF LCVRFRIFELFEVGFLSPATFTVYEYHRPDKQCTMFYSTS NIKIQKVCEGATCKCIEADCGQMQKELDLTISAETRKQTA CNPEIAYAYKVIITSITTENVFVKYKATLLDIYKTGEAVAEK DSEITFIKKVTCTNAELVKGRQYLIMGKEALQIKYNFTFRY IYPLDSLTWIEYWPRDTTCSSCQAFLANLDEFAEDIFLNG C

Otros anticuerpos de la invención incluyen aquéllos en donde los aminoácidos o los ácidos nucleicos que codifican los aminoácidos, se han mutado, y no obstante, tienen una identidad de cuando menos el 60, el 70, el 80, el 90, o el 95 por ciento con las

secuencias descritas en la Tabla 1. En algunas modalidades incluyen las secuencias de aminoácidos mutantes, en donde se han mutado no más de 1, 2, 3, 4, ó 5 aminoácidos en las regiones variables, comparándose con las regiones variables ilustradas en la secuencia descrita en la Tabla 1, mientras que retiene sustancialmente la misma actividad terapéutica.

Debido a que cada uno de estos anticuerpos se pueden enlazar a C5, las secuencias de VH, VL, cadena ligera de longitud completa, y cadena pesada de longitud completa (secuencias de aminoácidos y secuencias de nucleótidos que codifican las secuencias de aminoácidos), se pueden "mezclar y emparejar", para crear otros anticuerpos de enlace de C5 de la invención. Estos anticuerpos de enlace de C5 "mezclados y emparejados" se pueden probar utilizando los ensayos de enlace conocidos en la técnica (por ejemplo, ELISAs, y otros ensayos descritos en la sección de ejemplos). Cuando estas cadenas se mezclan y se emparejan, una secuencia VH a partir de un par de VH/VL particular debe ser reemplazada con una secuencia VH estructuralmente similar. De la misma manera, una secuencia de cadena pesada de longitud completa a partir de un par particular de cadena pesada de longitud completa/cadena ligera de longitud completa, debe ser reemplazada con una secuencia de cadena pesada de longitud completa estructuralmente similar. De la misma manera, una secuencia VL a partir de un par particular de VH/VL debe ser reemplazada con una secuencia VL estructuralmente similar. De la misma manera, una

secuencia de cadena ligera de longitud completa a partir de un par particular de cadena pesada de longitud completa/cadena ligera de longitud completa, debe ser reemplazada con una secuencia de cadena ligera de longitud completa estructuralmente similar. De conformidad con lo anterior, en un aspecto, la invención proporciona un anticuerpo monoclonal aislado, o una región de enlace de antígeno del mismo, que tiene: una región variable de cadena pesada que comprende una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, y 281; y una región variable de cadena ligera que comprende una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285; en donde el anticuerpo se enlaza específicamente a C5 (por ejemplo, C5 humana y/o de cinomolgo).

En otro aspecto, la invención proporciona: (i) un anticuerpo monoclonal aislado, el cual tiene: una cadena pesada de longitud completa que comprende una secuencia de aminoácidos que se ha optimizado para su expresión en la célula de un mamífero, seleccionada a partir del grupo que consiste en las SEQ ID NOs: 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, y 282; y una cadena ligera de longitud completa que comprende una secuencia de aminoácidos que se ha optimizado para su expresión en la célula de

un mamífero, seleccionada a partir del grupo que consiste en las SEQ ID NOs: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, y 290; o (ii) una proteína funcional que comprende una porción de enlace de antígeno del mismo.

En otro aspecto, la presente invención proporciona anticuerpos de enlace de C5 que comprenden las CDR1s, CDR2s, y CDR3s de cadena pesada y de cadena ligera, como se describen en la Tabla 1, o combinaciones de las mismas. Las secuencias de aminoácidos de las VH CDR1s de los anticuerpos se muestran en las SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, y 235. Las secuencias de aminoácidos de la VH CDR2s de los anticuerpos se muestran en las SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, y 236. Las secuencias de aminoácidos de las VH CDR3s de los anticuerpos se muestran en las SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, y 237. Las secuencias de aminoácidos de las VL CDR1s de los anticuerpos se muestran en las SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, y 238. Las secuencias de aminoácidos de las VL CDR2s de los anticuerpos se muestran en las SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, y 239. Las secuencias de aminoácidos de las VL CDR3s de los anticuerpos se muestran en las SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, y 240. Las regiones CDR están delineadas utilizando el sistema de Kabat (Kabat, E. A. y colaboradores, 1991 Sequences of Proteins of Immunological

Interest, Quinta Edición, Departamento de Salud y Servicios Humanos de los Estados Unidos, NIH Publicación Número 91-3242).

Dado que cada uno de estos anticuerpos puede enlazarse a C5, y que la especificidad de enlace de antígeno es proporcionada primordialmente por las regiones CDR1, 2, y 3, las secuencias CDR1, 2, y 3 VH, y las secuencias CDR1, 2, y 3 VL, se pueden "mezclar y emparejar" (es decir, las CDRs de diferentes anticuerpos se pueden mezclar y emparejar, aunque cada anticuerpo debe contener una CDR1, 2, y 3 VH y una CDR1, 2, y 3 VL, para crear otras moléculas de enlace de C5 de la invención. Estos anticuerpos de enlace de C5 "mezclados y emparejados" se pueden probar utilizando los ensayos de enlace conocidos en la técnica, y aquéllos descritos en los Ejemplos (por ejemplo, ELISAs). Cuando las secuencias VH CDR se mezclan y se emparejan, la secuencia CDR1, CDR2, y/o CDR3 a partir de una secuencia VH particular debe ser reemplazada con una secuencia de CDR estructuralmente similar. De la misma manera, cuando las secuencias VL CDR se mezclan y se emparejan, la secuencia de CDR1, CDR2, y/o CDR3 a partir de una secuencia VL particular, debe ser reemplazada con una secuencia de CDR estructuralmente similar. Será fácilmente evidente para el experto ordinario que se pueden crear secuencias VH y VL novedosas, sustituyendo una o más secuencias de la región CDR VH y/o VL con secuencias estructuralmente similares a partir de las secuencias CDR mostradas en la presente para los anticuerpos monoclonales de la presente invención.

De conformidad con lo anterior, la presente invención proporciona un anticuerpo monoclonal aislado o una región de enlace de antígeno del mismo, que comprende una CDR1 de región variable de cadena pesada que comprende una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, y 235; una CDR2 de región variable de cadena pesada que comprende una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, y 236; una CDR3 de región variable de cadena pesada que comprende una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, y 237; una CDR1 de región variable de cadena ligera que comprende una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, y 238; una CDR2 de región variable de cadena ligera que comprende una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, y 239; y una CDR3 de región variable de cadena ligera que comprende una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, y 240; en donde el anticuerpo se enlaza específicamente a C5.

En una modalidad específica, un anticuerpo que se enlaza específicamente C5, comprende una CDR1 de región variable de

cadena pesada de la SEQ ID NO: 1; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 2; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 3; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 4; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 5; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 6. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 17; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 18; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 19; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 20; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 21; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 22.

En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 33; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 34; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 35; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 36; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 37; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 38. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 17; una CDR2 de región variable de cadena pesada de

la SEQ ID NO: 49; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 19; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 20; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 21; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 50.

En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 61; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 62; y una CDR3 de región variable de cadena pesada de la SEQ ID NO: 63; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 64; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 65; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 66. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 61; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 77; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 63; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 64; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 65; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 78.

En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 61; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 77; y una CDR3 de región

variable de cadena pesada de la SEQ ID NO: 63; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 64; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 65; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 89. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 61; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 62; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 63; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 64; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 65; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 89.

En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 61; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 95; y una CDR3 de región variable de cadena pesada de la SEQ ID NO: 63; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 64; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 65; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 89. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 17; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 49; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 19; una CDR1 de región variable de cadena ligera

de la SEQ ID NO: 20; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 21; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 101.

En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 17; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 107; y una CDR3 de región variable de cadena pesada de la SEQ ID NO: 19; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 20; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 21; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 22. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 17; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 107; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 19; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 20; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 21; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 101.

En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 17; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 113; y una CDR3 de región variable de cadena pesada de la SEQ ID NO: 19; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 20; una CDR2 de

región variable de cadena ligera de la SEQ ID NO: 21; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 22. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 17; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 113; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 19; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 20; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 21; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 101.

En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 1; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 119; y una CDR3 de región variable de cadena pesada de la SEQ ID NO: 3; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 4; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 5; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 120. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 131; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 132; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 133; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 134; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 135; y una CDR3 de región variable de cadena

ligera de la SEQ ID NO: 136.

En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 145; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 146; y una CDR3 de región variable de cadena pesada de la SEQ ID NO: 147; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 148; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 149; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 150. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 159; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 160; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 161; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 162; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 163; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 164.

En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 173; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 174; y una CDR3 de región variable de cadena pesada de la SEQ ID NO: 175; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 176; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 177; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 178. En otra

modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 195; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 196; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 197; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 198; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 199; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 200.

En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 61; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 77; y una CDR3 de región variable de cadena pesada de la SEQ ID NO: 63; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 64; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 65; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 209. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 17; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 49; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 19; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 20; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 21; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 22.

En otra modalidad específica, un anticuerpo que se enlaza

específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 33; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 226; y una CDR3 de región variable de cadena pesada de la SEQ ID NO: 35; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 36; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 37; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 38. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 235; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 236; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 237; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 238; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 239; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 240.

En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 1; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 119; y una CDR3 de región variable de cadena pesada de la SEQ ID NO: 3; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 4; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 5; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 6. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la

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SEQ ID NO: 1; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 2; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 3; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 4; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 5; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 120.

En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 61; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 62; y una CDR3 de región variable de cadena pesada de la SEQ ID NO: 63; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 64; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 65; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 209. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 61; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 95; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 63; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 64; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 65; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 209.

En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 61; una CDR2 de región variable

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de cadena pesada de la SEQ ID NO: 77; y una CDR3 de región variable de cadena pesada de la SEQ ID NO: 63; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 64; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 65; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 66. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 61; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 77; una CDR3 de región variable de cadena pesada de la SEQ ID NO: 63; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 64; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 65; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 76.

En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 61; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 77; y una CDR3 de región variable de cadena pesada de la SEQ ID NO: 63; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 64; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 65; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 89. En otra modalidad específica, un anticuerpo que se enlaza específicamente a C5, comprende una CDR1 de región variable de cadena pesada de la SEQ ID NO: 17; una CDR2 de región variable de cadena pesada de la SEQ ID NO: 107; una CDR3 de región variable de cadena pesada

de la SEQ ID NO: 19; una CDR1 de región variable de cadena ligera de la SEQ ID NO: 20; una CDR2 de región variable de cadena ligera de la SEQ ID NO: 21; y una CDR3 de región variable de cadena ligera de la SEQ ID NO: 22.

En ciertas modalidades, un anticuerpo que se enlaza a C5 es un anticuerpo que se describe en la Tabla 1.

Como se utiliza en la presente, un anticuerpo humano comprende las regiones variables de cadena pesada o ligera o las cadenas pesada o ligera de longitud completa que son "el producto de" o "derivadas a partir de" una secuencia de la línea germinal particular, si las regiones variables o las cadenas de longitud completa del anticuerpo se obtienen a partir de un sistema que utilice genes de inmunoglobulina de la línea germinal humana. Estos sistemas incluyen la inmunización de un ratón transgénico que lleve genes de inmunoglobulina humana con el antígeno de interés, o el rastreo de una biblioteca de genes de inmunoglobulina humana exhibida sobre fagos con el antígeno de interés. Un anticuerpo humano que es "el producto de" o "derivado a partir de" una secuencia de inmunoglobulina de la línea germinal humana se puede identificar como tal mediante la comparación de la secuencia de aminoácidos del anticuerpo humano con las secuencias de aminoácidos de las inmunoglobulinas de la línea germinal humana, y se selecciona la secuencia de inmunoglobulina de la línea germinal humana que esté más cerca en la secuencia (es decir, mayor porcentaje de identidad), con la secuencia del anticuerpo humano.

Un anticuerpo humano que es "el producto de" o "derivado a partir de" una secuencia de inmunoglobulina de la línea germinal humana particular, puede contener diferencias de aminoácidos, comparándose con la secuencia de la línea germinal, debido, por ejemplo, a las mutaciones somáticas que se presentan naturalmente, o a la introducción intencional de mutaciones dirigidas al sitio. Sin embargo, en las regiones de estructura VH ó VL, un anticuerpo humano seleccionado típicamente es cuando menos el 90 por ciento idéntico en la secuencia de aminoácidos a una secuencia de aminoácidos codificada por un gen de inmunoglobulina de la línea germinal humana, y contiene residuos de aminoácidos que identifican el anticuerpo humano como humano cuando se compara con las secuencias de aminoácidos de inmunoglobulina de la línea germinal de otras especies (por ejemplo, las secuencias de la línea germinal de murino). En ciertos casos, un anticuerpo humano puede ser cuando menos el 60 por ciento, el 70 por ciento, el 80 por ciento, el 90 por ciento, o cuando menos el 95 por ciento, o inclusive cuando menos el 96 por ciento, el 97 por ciento, el 98 por ciento, o el 99 por ciento idéntico en la secuencia de aminoácidos a la secuencia de aminoácidos codificada por el gen de inmunoglobulina de la línea germinal. Típicamente, un anticuerpo humano recombinante exhibirá no más de diez diferencias de aminoácidos de la secuencia de aminoácidos codificada por el gen de inmunoglobulina de la línea germinal humana en las regiones de estructura VH ó VL. En ciertos casos, el anticuerpo humano puede exhibir no más de cinco, o

inclusive no más de cuatro, tres, dos, o una diferencia de aminoácidos de la secuencia de aminoácidos codificada por el gen de inmunoglobulina de la línea germinal.

Anticuerpos Homólogos

En todavía otra modalidad, la presente invención proporciona un anticuerpo o un fragmento de enlace de antígeno del mismo, que comprende secuencias de aminoácidos que son homólogas a las secuencias descritas en la Tabla 1, y este anticuerpo se enlaza a una proteína C5 (por ejemplo, C5 humana y/o de cinomolgo), y retiene las propiedades funcionales deseadas de estos anticuerpos descritos en la Tabla 1.

Por ejemplo, la invención proporciona un anticuerpo monoclonal aislado (o un fragmento de enlace de antígeno funcional del mismo) que comprende una región variable de cadena pesada y una región variable de cadena ligera, en donde la región variable de cadena pesada comprende una secuencia de aminoácidos que es cuando menos el 80 por ciento, cuando menos el 90 por ciento, o cuando menos el 95 por ciento idéntica a una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, ó 281; la región variable de cadena ligera comprende una secuencia de aminoácidos que es cuando menos el 80 por ciento, cuando menos el 90 por ciento, o cuando menos el 95 por ciento idéntica a una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ

ID NOs: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, ó 289; el anticuerpo se enlaza específicamente a C5 (por ejemplo, C5 humana y/o de cinomolgo), y el anticuerpo puede inhibir la lisis de los glóbulos rojos sanguíneos en un ensayo hemolítico. En un ejemplo específico, estos anticuerpos tienen un valor de IC_{50} en un ensayo hemolítico de 20 a 200 pM, cuando se utiliza suero agotado de C5 humana que se reconstituya con C5 humana 100 pM.

En otras modalidades, las secuencias de aminoácidos VH y/o VL pueden ser el 50 por ciento, 60 por ciento, 70 por ciento, 80 por ciento, 90 por ciento, 95 por ciento, 96 por ciento, 97 por ciento, 98 por ciento, o el 99 por ciento idénticas a las secuencias estipuladas en la Tabla 1. En otras modalidades, las secuencias de aminoácidos VH y/l VL pueden ser idénticas, excepto por una sustitución de aminoácido en no más de una, dos, tres, cuatro, o cinco posiciones de aminoácidos. Un anticuerpo que tenga las regiones VH y VL con una alta identidad (es decir, del 80 por ciento o mayor) con las regiones VH y VL de las descritas en la Tabla 1, se puede obtener mediante mutagénesis (por ejemplo, mutagénesis dirigida al sitio o mediada por reacción en cadena de la polimerasa) de las moléculas de ácidos nucleicos que codifiquen las SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, ó 281; y 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, ó 289, respectivamente, seguido por la prueba del

anticuerpo alterado codificado para determinar la función retenida, utilizando los ensayos funcionales descritos en la presente.

En otras modalidades, las secuencias de aminoácidos de cadena pesada de longitud completa y/o de cadena ligera de longitud completa pueden ser el 50 por ciento, 60 por ciento, 70 por ciento, 80 por ciento, 90 por ciento, 95 por ciento, 96 por ciento, 97 por ciento, 98 por ciento, o el 99 por ciento idénticas a las secuencias estipuladas en la Tabla 1. Un anticuerpo que tenga una cadena pesada de longitud completa y una cadena ligera de longitud completa con una alta identidad (es decir, del 80 por ciento o mayor) con las cadenas pesadas de longitud completa de cualquiera de las SEQ ID NOs: 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, y 282 y con las cadenas ligeras de longitud completa de cualquiera de las SEQ ID NOs: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, y 290, respectivamente, se puede obtener mediante mutagénesis (por ejemplo, mutagénesis dirigida al sitio o mutagénesis mediada por reacción en cadena de la polimerasa) de las moléculas de ácidos nucleicos que codifiquen estos polipéptidos, respectivamente, seguido por la prueba del anticuerpo alterado codificado para determinar la función retenida, utilizando los ensayos funcionales descritos en la presente.

En otras modalidades, las secuencias de nucleótidos de cadena pesada de longitud completa y/o de cadena ligera de longitud

completa pueden ser el 60 por ciento, el 70 por ciento, el 80 por ciento, el 90 por ciento, el 95 por ciento, el 96 por ciento, el 97 por ciento, el 98 por ciento o el 99 por ciento idénticas a las secuencias estipuladas anteriormente.

En otras modalidades, las regiones variables de las secuencias de nucleótidos de cadena pesada y/o de cadena ligera pueden ser el 60 por ciento, el 70 por ciento, el 80 por ciento, el 90 por ciento, el 95 por ciento, el 96 por ciento, el 97 por ciento, el 98 por ciento o el 99 por ciento idénticas a las secuencias estipuladas anteriormente.

Como se utiliza en la presente, el porcentaje de identidad entre las dos secuencias es una función del número de posiciones idénticas compartidas por las secuencias (es decir, el porcentaje de identidad es igual al número de posiciones idénticas/número total de posiciones x 100), tomando en cuenta el número de huecos, y la longitud de cada hueco, que se necesite introducir para la alineación óptima de las dos secuencias. La comparación de las secuencias y la determinación del porcentaje de identidad entre dos secuencias, se pueden llevar a cabo utilizando un algoritmo matemático, como se describe en los ejemplos no limitantes que se encuentran más adelante.

De una manera adicional o alternativa, las secuencias de proteína de la presente invención se pueden utilizar adicionalmente como una "secuencia pedida", para llevar a cabo una búsqueda contra las bases de datos públicas, por ejemplo, con el fin de identificar las secuencias relacionadas. Por ejemplo, estas

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búsquedas se pueden llevar a cabo utilizando el programa BLAST (Versión 2.0) de Altschul y colaboradores, 1990 J. Mol. Biol. 215:403-10.

Anticuerpos con Modificaciones Conservadoras.

En ciertas modalidades, un anticuerpo de la invención tiene una región variable de cadena pesada que comprende las secuencias de CDR1, CDR2, y CDR3, y una región variable de cadena ligera que comprende las secuencias de CDR1, CDR2, y CDR3, en donde una o más de estas secuencias de CDR tienen secuencias de aminoácidos especificadas basadas en los anticuerpos descritos en la presente, o modificaciones conservadoras de las mismas, y en donde los anticuerpos retienen las propiedades funcionales deseadas de los anticuerpos de enlace de C5 de la invención. De conformidad con lo anterior, la invención proporciona un anticuerpo monoclonal aislado, o un fragmento de enlace de antígeno funcional del mismo, que consiste en una región variable de cadena pesada que comprende las secuencias de CDR1, CDR2, y CDR3, y una región variable de cadena ligera que comprende las secuencias de CDR1, CDR2, y CDR3, en donde: las secuencias de aminoácidos de CDR1 de región variable de cadena pesada se seleccionan a partir del grupo que consiste en las SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, y 235, y las modificaciones conservadoras de las mismas; las secuencias de aminoácido de CDR2 de región variable de cadena pesada se seleccionan a partir del grupo que consiste en las SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174,

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196, 226, y 236, y las modificaciones conservadoras de las mismas; las secuencias de aminoácidos de CDR3 de región variable de cadena pesada se seleccionan a partir del grupo que consiste en las SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, y 237, y las modificaciones conservadoras de las mismas; las secuencias de aminoácidos de CDR1 de región variable de cadena ligera se seleccionan a partir del grupo que consiste en las SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, y 238, y las modificaciones conservadoras de las mismas; las secuencias de aminoácidos de CDR2 de región variable de cadena ligera se seleccionan a partir del grupo que consiste en las SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, y 239, y las modificaciones conservadoras de las mismas; las secuencias de aminoácidos de CDR3 de región variable de cadena ligera se seleccionan a partir del grupo que consiste en las SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, y 240, y las modificaciones conservadoras de las mismas; el anticuerpo o el fragmento de enlace de antígeno del mismo se enlaza específicamente a C5, e inhibe la lisis de los glóbulos rojos sanguíneos en un ensayo hemolítico, como se describe en la presente.

En otras modalidades, un anticuerpo de la invención optimizado para la expresión en una célula de mamífero, tiene una secuencia de cadena pesada de longitud completa y una secuencia de cadena ligera de longitud completa, en donde una o más de estas secuencias tienen secuencias de aminoácidos especificadas basadas

en los anticuerpos descritos en la presente, o modificaciones conservadoras de las mismas, y en donde los anticuerpos retienen las propiedades funcionales deseadas de los anticuerpos de enlace de C5 de la invención. De conformidad con lo anterior, la invención proporciona un anticuerpo monoclonal aislado optimizado para su expresión en una célula de mamífero, que consiste en una cadena pesada de longitud completa y una cadena ligera de longitud completa, en donde: la cadena pesada de longitud completa tiene las secuencias de aminoácidos seleccionadas a partir del grupo que consiste en las SEQ ID NOs: 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, y 282, y las modificaciones conservadoras de las mismas; y la cadena ligera de longitud completa tiene las secuencias de aminoácidos seleccionadas a partir del grupo que consiste en las SEQ ID NOs: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, y 290, y las secuencias conservadoras de las mismas; el anticuerpo se enlaza específicamente a C5 (por ejemplo, C5 humana y/o de cinomolgo); y el anticuerpo inhibe la lisis de los glóbulos rojos sanguíneos en un ensayo hemolítico, como se describe en la presente. En una modalidad específica, estos anticuerpos tienen un valor IC_{50} en un ensayo hemolítico de 20 a 200 pM, cuando se utiliza el suero agotado de C5 humana que se reconstituya con C5 humana 100 pM.

Anticuerpos que se Enlazan al Mismo Epítopo.

La presente invención proporciona anticuerpos que se enlazan

al mismo epítopo que los anticuerpos de enlace de C5 descritos en la Tabla 1. Por consiguiente, se pueden identificar anticuerpos adicionales basándose en su capacidad para competir cruzadamente (por ejemplo, para inhibir de una manera competitiva el enlace de, en una forma estadísticamente significativa) con otros anticuerpos de la invención en los ensayos de enlace de C5. La capacidad de un anticuerpo de prueba para inhibir el enlace de los anticuerpos de la presente invención a una proteína C5 (por ejemplo, C5 humana y/o de cinomolgo), demuestra que el anticuerpo de prueba puede competir con este anticuerpo por el enlace con C5; este anticuerpo, de acuerdo con una teoría no limitante, se puede enlazar al mismo epítopo o a un epítopo relacionado (por ejemplo, un epítopo estructuralmente similar o espacialmente proximal) sobre la proteína C5 que el anticuerpo con el que compite. En cierta modalidad, el anticuerpo que se enlaza al mismo epítopo sobre C5 que los anticuerpos de la presente invención, es un anticuerpo monoclonal humano. Estos anticuerpos monoclonales humanos se pueden preparar y aislar como se describe en la presente.

Anticuerpos Diseñados y Modificados.

Un anticuerpo de la invención se puede preparar además utilizando un anticuerpo que tenga una o más de las secuencias VH y/o VL mostradas en la presente como material de partida para diseñar un anticuerpo modificado, cuyo anticuerpo modificado puede tener propiedades alteradas del anticuerpo de partida. Un anticuerpo se puede diseñar mediante la modificación de uno o más residuos

dentro de una o ambas regiones variables (es decir, VH y/o VL), por ejemplo, dentro de una o más regiones CDR, y/o dentro de una o más regiones de estructura. De una manera adicional o alternativa, un anticuerpo se puede diseñar mediante la modificación de los residuos dentro de las regiones constantes, por ejemplo, para alterar las funciones efectoras del anticuerpo.

Un tipo de diseño de región variable que se puede llevar a cabo es el injerto de CDR. Los anticuerpos interactúan con los antígenos objetivo predominantemente a través de los residuos de aminoácidos que se localizan en las seis regiones determinantes de complementariedad (CDRs) de cadena pesada y ligera. Por esta razón, las secuencias de aminoácidos dentro de las regiones determinantes de complementariedad son más diversos entre los anticuerpos individuales que las secuencias que están fuera de las regiones determinantes de complementariedad. Debido a que las secuencias de regiones determinantes de complementariedad son responsables de la mayoría de las interacciones de anticuerpo-antígeno, es posible expresar los anticuerpos que imiten las propiedades de los anticuerpos que se presenten naturalmente específicos, mediante la construcción de vectores de expresión que incluyan secuencias de las regiones determinantes de complementariedad a partir del anticuerpo que se presente naturalmente específico, injertadas sobre las secuencias de estructura a partir de un anticuerpo diferente con propiedades diferentes (véanse, por ejemplo, Riechmann, L. y colaboradores,

1998 Nature 332:323-327; Jones, P. y colaboradores, 1986 Nature 321:522-525; Queen, C. y colaboradores, 1989 Proc. Natl. Acad., E.U.A. 86:10029-10033; Patente de los Estados Unidos de Norteamérica Número 5,225,539 a Winter, y Patentes de los Estados Unidos de Norteamérica Números 5,530,101; 5,585,089; 5,693,762 y 6,180,370 a Queen y colaboradores).

De conformidad con lo anterior, otra modalidad de la invención pertenece a un anticuerpo monoclonal aislado, o a un fragmento de enlace de antígeno del mismo, que comprende una región variable de cadena pesada que comprende las secuencias de CDR1 que tienen una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, y 235; secuencias de CDR2 que tienen una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, y 236; secuencias de CDR3 que tienen una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, y 237, respectivamente; y una región variable de cadena ligera que tiene las secuencias de CDR1 que tiene un secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, y 238; secuencias de CDR2 que tienen una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, y 239; y secuencias de CDR3 que consisten en una secuencia

de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, y 240, respectivamente. Por consiguiente, estos anticuerpos contienen las secuencias VH y VL de CDR de los anticuerpos monoclonales, y no obstante, pueden contener diferentes secuencias de estructura de estos anticuerpos.

Estas secuencias de estructura se pueden obtener a partir de las bases de datos de ADN públicas o de las referencias publicadas que incluyan secuencias de genes de anticuerpos de la línea germinal. Por ejemplo, las secuencias de ADN de la línea germinal para los genes de región variable de cadena pesada y ligera humanos se pueden encontrar en la base de datos de secuencias de la línea germinal humana "VBase" (disponible en la Internet en www.mrc-cpe.cam.ac.uk/vbase), así como en Kabat, E. A. y colaboradores, 1991 Sequences of Proteins of Immunological Interest, Quinta Edición, Departamento de Salud y Servicios Humanos de los Estados Unidos, NIH Publicación Número 91-3242; Tomlinson, I. M. y colaboradores, 1992 J. Mol. Biol. 227:776-798; y Cox, J. P. L. y colaboradores, 1994 Eur. J. Immunol. 24:827-836; el contenido de cada uno de los cuales se incorpora expresamente a la presente como referencia.

Un ejemplo de las secuencias de estructura para utilizarse en los anticuerpos de la invención es el de aquéllas que son estructuralmente similares a las secuencias de estructura utilizadas por los anticuerpos seleccionados de la invención, por ejemplo, las

secuencias en consenso y/o las secuencias de estructura utilizadas por los anticuerpos monoclonales de la invención. Las secuencias de CDR1, CDR2, y CDR3 VH, y las secuencias de CDR1, CDR2, y CDR3 VL, se pueden injertar en las regiones de estructura que tengan una secuencia idéntica a la que se encuentra en el gen de inmunoglobulina de la línea germinal a partir del cual se derive la secuencia de estructura, o las secuencias de CDR se pueden injertar en las regiones de estructura que contengan una o más mutaciones, comparándose con las secuencias de la línea germinal. Por ejemplo, se ha encontrado que, en ciertos casos, es benéfico mutar los residuos de las regiones de estructura para mantener o mejorar la capacidad de enlace de antígeno del anticuerpo (véanse, por ejemplo, las Patentes de los Estados Unidos de Norteamérica Números 5,530,101; 5,585,089; 5,693,762 y 6,180,370 a Queen y colaboradores).

Otro tipo de modificación de región variable es mutar los residuos de aminoácidos dentro de las regiones CDR1, CDR2, y/o CDR3 VH y/o VL, para mejorar de esta manera una o más propiedades de enlace (por ejemplo, la afinidad) del anticuerpo de interés, conocida como "maduración de afinidad". Se puede llevar a cabo mutagénesis dirigida al sitio o mutagénesis mediada por reacción en cadena de la polimerasa para introducir las mutaciones, y se puede evaluar el efecto sobre el enlace del anticuerpo, u otra propiedad funcional de interés, en ensayos *in vitro* o *in vivo*, como se describe en la presente, y como se proporciona en los ejemplos. Se

pueden introducir modificaciones conservadoras (como se discute anteriormente). Las mutaciones pueden ser sustituciones, adiciones, o supresiones de aminoácidos. Más aún, típicamente no se alteran más de 1, 2, 3, 4, ó 5 residuos dentro de una región CDR.

De conformidad con lo anterior, en otra modalidad, la invención proporciona anticuerpos monoclonales de enlace de C5 aislados, o un fragmento de enlace de antígeno de los mismos, que consisten en una región variable de cadena pesada que tiene: una región VH CDR1 que consiste en una secuencia de aminoácidos seleccionada a partir del grupo que tiene las SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, y 235, o una secuencia de aminoácidos que tiene 1, 2, 3, 4, ó 5 sustituciones, supresiones, o adiciones de aminoácidos, comparándose con las SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, y 235; una región VH CDR2 que tiene una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, y 236, o una secuencia de aminoácidos que tiene 1, 2, 3, 4, ó 5 sustituciones, supresiones, o adiciones de aminoácidos, comparándose con las SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, y 236; una región VH CDR3 que tiene una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, y 237, o una secuencia de aminoácidos que tiene 1, 2, 3, 4, ó 5 sustituciones, supresiones, o adiciones de aminoácidos, comparándose con las SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161,

175, 197, y 237; una región VL CDR1 que tiene una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, y 238, o una secuencia de aminoácidos que tiene 1, 2, 3, 4, ó 5 sustituciones, supresiones, o adiciones de aminoácidos, comparándose con las SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, y238; una región VL CDR2 que tiene una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, y 239, o una secuencia de aminoácidos que tiene una 1, 2, 3, 4, ó 5 sustituciones, supresiones, o adiciones de aminoácidos, comparándose con las SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, y 239; y una región VL CDR3 que tiene una secuencia de aminoácidos seleccionada a partir del grupo que consiste en las SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, y 240, o una secuencia de aminoácidos que tiene 1, 2, 3, 4, ó 5 sustituciones, supresiones, o adiciones de aminoácidos, comparándose con las SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, y 240.

Injerto de Dominios de Enlace de Antígeno en Estructuras o Andamiajes Alternativos.

Se pueden emplear una amplia variedad de estructuras o andamiajes de anticuerpos/inmunoglobulina, siempre que el polipéptido resultante incluya cuando menos una región de enlace que se enlace específicamente a C5. Estas estructuras o andamiajes incluyen los cinco idiotipos principales de las inmunoglobulinas

humanas, o fragmentos de los mismos, e incluyen las inmunoglobulinas de otras especies de animales, que tengan de preferencia aspectos humanizados. En este aspecto, son de un interés particular los anticuerpos de cadena pesada individuales, tales como aquéllos identificados en los camélidos. Los expertos en la materia continúan descubriendo y desarrollando novedosas estructuras, andamiajes, y fragmentos.

En un aspecto, la invención pertenece a la generación de anticuerpos no basados en inmunoglobulina, utilizando andamiajes que no son de inmunoglobulina, sobre los cuales se pueden injertar las regiones determinantes de complementariedad de la invención. Se pueden emplear las estructuras o andamiajes que no sean de inmunoglobulina conocidos o futuros, siempre que comprendan una región de enlace específica para la proteína C5 objetivo (por ejemplo, C5 humana y/o de cinomolgo). Las estructuras o andamiajes que no son de inmunoglobulina conocidos incluyen, pero no se limitan a, fibronectina (Compound Therapeutics, Inc., Waltham, MA), anquirina (Molecular Partners AG, Zurich, Suiza), anticuerpos de dominio (Domantis, Ltd., Cambridge, MA, y Ablynx nv, Zwijnaarde, Bélgica), lipocalina (Pieris Proteolab AG, Freising, Alemania), productos inmuno-farmacéuticos modulares pequeños (Trubion Pharmaceuticals Inc., Seattle, WA), maxicuerpos (Avidia, Inc., Mountain View, CA), Proteína A (Affibody AG, Suecia), y afilina (gamma-cristalina o ubiquitina) (Scil Proteins GmbH, Halle, Alemania).

Los andamiajes de fibronectina se basan en el dominio de fibronectina tipo III (por ejemplo, el décimo módulo de la fibronectina tipo III (dominio 10 Fn3)). El dominio de fibronectina tipo III tiene 7 u 8 cadenas beta, que están distribuidas entre dos hojas beta, que ellas mismas se empacan una contra la otra para formar el núcleo de la proteína, y que además contienen ciclos (de una manera análoga a las regiones determinantes de complementariedad), que conectan las cadenas beta unas a otras, y se exponen al solvente. Existen cuando menos tres de estos ciclos en cada orilla del emparedado de hojas beta, en donde la orilla es el límite de la proteína perpendicular a la dirección de las cadenas beta (véase la Patente de los Estados Unidos de Norteamérica Número US 6,818,418). Estos andamiajes basados en fibronectina no son una inmunoglobulina, aunque el pliegue global está estrechamente relacionado con aquél del fragmento de anticuerpo funcional más pequeño, la región variable de la cadena pesada, que comprende la unidad de reconocimiento de antígeno entera en la IgG de camello y de llama. Debido a esta estructura, el anticuerpo que no es de inmunoglobulina, imita las propiedades de enlace de antígeno que son de una naturaleza y afinidad similares a aquéllas de los anticuerpos. Estos andamiajes se pueden utilizar en una estrategia de selección aleatoria y mezcla de ciclos *in vitro*, que es similar al proceso de maduración de afinidad de los anticuerpos *in vivo*. Estas moléculas basadas en fibronectina se pueden utilizar como andamiajes, en donde las regiones de ciclo de la molécula pueden

ser reemplazadas con regiones determinantes de complementariedad de la invención, empleando técnicas de clonación convencionales.

La tecnología de anquirina se basa en la utilización de proteínas con módulos de repetición derivados de anquirina como andamiajes, para soportar las regiones variables, que se pueden utilizar para el enlace con diferentes objetivos. El módulo de repetición de anquirina es un polipéptido de 33 aminoácidos que consiste en dos hélices-α anti-paralelas y una vuelta-β. El enlace de las regiones variables se optimiza en su mayor parte mediante la utilización de exhibición de ribosomas.

Los avímeros se derivan a partir de la proteína que contiene el dominio-A natural, tal como LRP1. Estos dominios son utilizados por la naturaleza para las interacciones de proteína-proteína, y en el ser humano, más de 250 proteínas están estructuralmente basadas en los dominios-A. Los avímeros consisten en un número de diferentes monómeros de "dominio-A" (de 2 a 10) enlazados por medio de enlazadores de aminoácidos. Se pueden crear avímeros que se puedan enlazar al antígeno objetivo utilizando la metodología descrita, por ejemplo, en las Publicaciones de las Solicitudes de Patente de los Estados Unidos de Norteamérica Números 20040175756; 20050053973; 20050048512; y 20060008844.

Los ligandos de afinidad de aficuerpo son proteínas simples pequeñas compuestas de un haz de tres hélices basado en el andamiaje de uno de los dominios de enlace de IgG de la Proteína A. La Proteína A es una proteína superficial a partir de la bacteria

Staphylococcus aureus. Este dominio de andamiaje consiste en 58 aminoácidos, 13 de los cuales se seleccionan aleatoriamente para generar las bibliotecas de aficuerpos con un gran número de variantes de ligandos (véase, por ejemplo, la Patente de los Estados Unidos de Norteamérica Número US 5,831,012). Las moléculas de aficuerpos imitan a los anticuerpos, tienen un peso molecular de 6 kDa, comparándose con el peso molecular de los anticuerpos, que es de 150 kDa. A pesar de su pequeño tamaño, el sitio de enlace de las moléculas de aficuerpo es similar a aquél de un anticuerpo.

Las anticalinas son productos desarrollados por la compañía Pieris ProteoLab AG. Se derivan a partir de las lipocalinas, un grupo ampliamente extendido de proteínas pequeñas y robustas que normalmente están involucradas en el transporte o almacenamiento fisiológico de los compuestos químicamente sensibles o insolubles. Existen varias lipocalinas naturales en los tejidos o líquidos corporales humanos. La arquitectura de la proteína recuerda a las inmunoglobulinas, con ciclos hipervariables encima de una estructura rígida. Sin embargo, en contraste con los anticuerpos o con sus fragmentos recombinantes, las lipocalinas se componen de una sola cadena de polipéptido con 160 a 180 residuos de aminoácidos, que es justo marginalmente mayor que un solo dominio de inmunoglobulina. El conjunto de cuatro ciclos, que forma la buchaca de enlace, muestra una plasticidad estructural pronunciada, y tolera una variedad de cadenas laterales. Por consiguiente, el sitio de enlace se puede reconfigurar en un proceso registrado, con el objeto

de reconocer las moléculas objetivo prescritas de diferente forma con una alta afinidad y especificidad. Se ha utilizado una proteína de la familia de lipocalina, la proteína de enlace de bilina (BBP) de Pieris Brassicae, para desarrollar anticalinas, mutando el conjunto de cuatro ciclos. Un ejemplo de una solicitud de patente que describe las anticalinas está en la Publicación del TCP Número WO 199916873.

Las moléculas de afilina son pequeñas proteínas que no son de inmunoglobulina, que están diseñadas para afinidades específicas hacia las proteínas y las moléculas pequeñas. Las nuevas moléculas de afilina se pueden seleccionar muy rápidamente a partir de dos bibliotecas, cada una de las cuales se basa en una proteína de andamiaje derivada de humano diferente. Las moléculas de afilina no muestran ninguna homología estructural con las proteínas de inmunoglobulina. En la actualidad, se emplean dos andamiajes de afilina, uno de los cuales es gamma-cristalino, una proteína de lente de ojo estructural humana, y el otro es de las proteínas de la superfamilia de "ubiquitina". Ambos andamiajes humanos son muy pequeños, muestran una alta estabilidad a la temperatura, y son casi resistentes a los cambios de pH y a los agentes desnaturalizantes. Esta alta estabilidad se debe principalmente a la estructura de hoja beta expandida de las proteínas. Los ejemplos de las proteínas derivadas de gamma-cristalino se describen en la Publicación Internacional Número WO200104144, y los ejemplos de las proteínas de "tipo ubiquitina" se describen en la Publicación Internacional

Número WO2004106368.

Los miméticos de epítopos de proteína (PEM) son moléculas tipo péptido cíclicas, de tamaño mediano (peso molecular de 1 a 2 kDa), que imitan las estructuras secundarias de horquilla-beta de las proteínas, la principal estructura secundaria involucrada en las interacciones de proteína-proteína.

En algunas modalidades, los Fabs se convierten hasta el formato de IgG1 silencioso, cambiando la región Fc. Por ejemplo, los anticuerpos 6525-7910 de la Tabla 1 se pueden convertir hasta el formato de IgG1 silencioso, sustituyendo la "X" en las secuencias de aminoácidos para la cadena pesada, con:

CDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 293),

y sustituyendo la "X" en la secuencia de aminoácidos para la cadena ligera, con: CS si la cadena ligera es lambda, o C si la cadena ligera es kappa. Como se utiliza en la presente, una "IgG1 silenciosa" es una secuencia de Fc de IgG1 en donde la secuencia de aminoácidos se ha alterado para reducir las funciones efectoras mediadas por Fc (por ejemplo, ADCC y/o CDC). Este anticuerpo típicamente tendrá un enlace reducido con los receptores de Fc y/o con C1q.

En algunas otras modalidades, los Fabs se convierten hasta el

formato de IgG2. Por ejemplo, los anticuerpos 6525-7910 de la Tabla 1 se pueden convertir hasta el formato de IgG2 sustituyendo la secuencia constante:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSX (SEQ ID NO: 294)

con la secuencia constante para la cadena pesada de IgG2:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDK
TVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQD
WLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYS
KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 295), y sustituyendo la "X" en la secuencia de aminoácidos para la cadena ligera, con CS si la cadena ligera es lambda, o con C si la cadena ligera es kappa.

Anticuerpos Humanos o Humanizados.

La presente invención proporciona anticuerpos completamente humanos que se enlazan específicamente a una proteína C5 (por ejemplo, C5 humana y/o de cinomolgo). Comparándose con los anticuerpos quiméricos o humanizados, los anticuerpos de enlace de C5 humanos de la invención tienen una antigenicidad adicionalmente reducida cuando se administran a sujetos humanos.

Los anticuerpos de enlace de C5 humanos se pueden generar

empleando los métodos que son conocidos en este campo. Por ejemplo, la tecnología de humano-diseño (humaneering) utilizada para convertir los anticuerpos no humanos en anticuerpos humanos diseñados. La Publicación de Patente de los Estados Unidos de Norteamérica Número 20050008625 describe un método *in vivo* para reemplazar una región variable de un anticuerpo no humano con una región variable humana en un anticuerpo, mientras que se mantienen las mismas características de enlace, o se proporcionan mejores características de enlace, en relación con aquéllas del anticuerpo no humano. El método se apoya en el reemplazo guiado por el epítopo de las regiones variables de un anticuerpo de referencia no humano con un anticuerpo completamente humano. El anticuerpo humano resultante generalmente no está relacionado estructuralmente con el anticuerpo no humano de referencia, pero se enlaza al mismo epítopo sobre el mismo antígeno que el anticuerpo de referencia. Dicho de una manera breve, se hace posible el planteamiento de reemplazo de complementariedad guiado por el epítopo en serie mediante el establecimiento de una competencia en las células entre un "competidor" y una biblioteca de diversos híbridos del anticuerpo de referencia ("anticuerpos de prueba") por el enlace con cantidades limitantes de antígeno en la presencia de un sistema reportero que responde al enlace del anticuerpo de prueba con el antígeno. El competidor puede ser el anticuerpo de referencia o un derivado del mismo, tal como un fragmento Fv de una sola cadena. El competidor también puede ser un ligando natural o artificial del antígeno que se

enlace al mismo epítopo que el anticuerpo de referencia. Los únicos requerimientos del competidor son que se enlace al mismo epítopo que el anticuerpo de referencia, y que compita con el anticuerpo de referencia por el enlace del antígeno. Los anticuerpos de prueba tienen una región-V de enlace de antígeno en común a partir del anticuerpo de referencia no humano, y la otra región-V seleccionada al azar a partir de una fuente diversa, tal como una biblioteca de repertorio de anticuerpos humanos. La región-V común a partir del anticuerpo de referencia sirve como una guía, colocando a los anticuerpos de prueba sobre el mismo epítopo sobre el antígeno, y en la misma orientación, de tal manera que se fuerza la selección hacia la fidelidad de enlace de antígeno más alta con el anticuerpo de referencia.

Se pueden utilizar muchos tipos de sistemas reporteros para detectar las interacciones deseadas entre los anticuerpos de prueba y el antígeno. Por ejemplo, se pueden enlazar fragmentos de reporteros de complemento al antígeno y al anticuerpo de prueba, respectivamente, de tal manera que la activación del reportero mediante la complementación del fragmento solamente ocurre cuando el anticuerpo de prueba se enlaza al antígeno. Cuando se co-expresan fusiones del anticuerpo de prueba- y del antígeno-fragmento de reportero con un competidor, la activación del reportero se hace dependiente de la capacidad del anticuerpo de prueba para competir con el competidor, lo cual es proporcional a la afinidad del anticuerpo de prueba por el antígeno. Otros sistemas reporteros que

se pueden utilizar incluyen el reactivador de un sistema de reactivación de reportero auto-inhibido (RAIR), como se da a conocer en la Solicitud de Patente de los Estados Unidos de Norteamérica con Número de Serie 10/208,730 (Publicación Número 20030198971), o el sistema de activación competitiva dado a conocer en la Solicitud de Patente de los Estados Unidos de Norteamérica con Número DE Serie 10/076,845 (Publicación Número 20030157579).

Con el sistema de reemplazo de complementariedad guiado por el epítopo en serie, se hace una selección para identificar las células que expresen un solo anticuerpo de prueba junto con el competidor, antígeno, y componentes reporteros. En estas células, cada anticuerpo de prueba compite uno a uno con el competidor por el enlace con una cantidad limitante de antígeno. La actividad del reportero es proporcional a la cantidad de antígeno enlazado al anticuerpo de prueba, la cual a su vez es proporcional a la afinidad del anticuerpo de prueba por el antígeno y a la estabilidad del anticuerpo de prueba. Los anticuerpos de prueba inicialmente se seleccionan con base en su actividad en relación con aquélla del anticuerpo de referencia cuando se expresan como el anticuerpo de prueba. El resultado de la primera ronda de selección es un conjunto de anticuerpos "híbridos", cada uno de los cuales está comprendido de la misma región-V no humana a partir del anticuerpo de referencia, y una región-V humana a partir de la biblioteca, y cada uno de los cuales se enlaza al mismo epítopo sobre el antígeno que

el anticuerpo de referencia. Uno o más de los anticuerpos híbridos seleccionados en la primera ronda tendrán una afinidad por el antígeno comparable con, o más alta que, aquélla del anticuerpo de referencia.

En el segundo paso de reemplazo de la región-V, se utilizan las regiones-V humanas seleccionadas en el primer paso como una guía para la selección de los reemplazos humanos para la región-V del anticuerpo de referencia no humano restante, con una biblioteca diversa de regiones-V humanas cognadas. Los anticuerpos híbridos seleccionados en la primera ronda también se pueden utilizar como competidores para la segunda ronda de selección. El resultado de la segunda ronda de selección es un conjunto de anticuerpos completamente humanos que difieren estructuralmente del anticuerpo de referencia, pero que compiten con el anticuerpo de referencia por el enlace con el mismo antígeno. Algunos de los anticuerpos humanos seleccionados se enlazan al mismo epítopo sobre el mismo antígeno que el anticuerpo de referencia. Entre estos anticuerpos humanos seleccionados, uno o más se enlazan al mismo epítopo con una afinidad que es comparable a, o más alta que, aquélla del anticuerpo de referencia.

Utilizando uno de los anticuerpos de enlace de C5 de ratón o quiméricos descritos anteriormente como el anticuerpo de referencia, este método se puede emplear fácilmente para generar anticuerpos humanos que se enlacen a la C5 humana con la misma especificidad de enlace y con la misma o mejor afinidad de enlace. En adición,

estos anticuerpos de enlace de C5 humanos también se obtener comercialmente en las compañías que producen por costumbre anticuerpos humanos, por ejemplo, KaloBios, Inc. (Mountain View, CA).

Anticuerpos de Camélido.

Las proteínas de anticuerpo obtenidas a partir de los miembros de la familia del camello y del dromedario (*Camelus bactrianus* y *Calelus dromaderius*), incluyendo los miembros del nuevo mundo, tales como las especies de llama (*Lama paccos, Lama glama,* y *Lama vicugna*), se han caracterizado con respecto al tamaño, la complejidad estructural, y la antigenicidad para sujetos humanos. Ciertos anticuerpos de IgG de esta familia de mamíferos, como se encuentran en la naturaleza, carecen de cadenas ligeras, y por lo tanto, son estructuralmente distintos de la estructura cuaternaria de cuatro cadenas típica que tiene dos cadenas pesadas y dos cadenas ligeras, para los anticuerpos de otros animales. Véase la Publicación del TCP Número PCT/EP93/02214 (Publicación Internacional Número WO 94/04678 publicada el 3 de marzo de 1994).

Se puede obtener una región del anticuerpo de camélido que es el dominio variable individual pequeño identificado como VHH, mediante ingeniería genética, para proporcionar una proteína pequeña que tiene una alta afinidad por un objetivo, dando como resultado una proteína derivada de anticuerpo de bajo peso molecular conocida como un "nanocuerpo de camélido". Véase la Patente de los Estados Unidos de Norteamérica Número 5,759,808

expedida el 2 de junio de 1998; véanse también Stijlemans, B. y colaboradores, 2004 J. Biol. Chem. 279: 1256-1261; Dumoulin, M. y colaboradores, 2003 Nature 424: 783-788; Pleschberger, M. y colaboradores, 2003 Bioconjugate Chem 14: 440-448; Cortez-Retamozo, V. y colaboradores, 2002 Int. J. Cancer 89: 456-62; y Lauwereys, M. y colaboradores, 1998 EMBO J 17: 3512-3520. Las bibliotecas diseñadas de anticuerpos de camélido y fragmentos de anticuerpos están comercialmente disponibles, por ejemplo, en Ablynx, Ghent, Bélgica. Como con otros anticuerpos de origen no humano, una secuencia de aminoácidos de un anticuerpo de camélido se puede alterar de una manera recombinante para obtener una secuencia que se parezca más estrechamente a una secuencia humana, es decir, el nanocuerpo se puede "humanizar". Por consiguiente, se puede reducir adicionalmente la baja antigenicidad natural de los anticuerpos de camélido para los seres humanos.

El nanocuerpo de camélido tiene un peso molecular de aproximadamente una décima parte de aquél de una molécula de IgG humana, y la proteína tiene un diámetro físico de solamente unos cuantos nanómetros. Una consecuencia del pequeño tamaño es la capacidad de los nanocuerpos de camélido para enlazarse a los sitios antigénicos que son funcionalmente invisibles para las proteínas de anticuerpo más grandes, es decir, los nanocuerpos de camélido son útiles como reactivos para detectar antígenos que de otra manera son crípticos utilizando las técnicas inmunológicas clásicas, y como posibles agentes terapéuticos. Por consiguiente,

todavía otra consecuencia del tamaño pequeño es que un nanocuerpo de camélido puede inhibir, como un resultado del enlace a un sitio específico en una ranura o hendidura estrecha, a una proteína objetivo, y por consiguiente, puede servir en una capacidad que se parezca más estrechamente a la función de un fármaco de bajo peso molecular clásico que la de un anticuerpo clásico.

El bajo peso molecular y el tamaño compacto dan como resultado además que los nanocuerpos de camélido sean extremadamente termoestables, estables a un pH extremo y a la digestión proteolítica, y pobremente antigénicos. Otra consecuencia es que los nanocuerpos de camélido se mueven fácilmente desde el sistema circulatorio hacia los tejidos, e inclusive cruzan la barrera hematoencefálica, y pueden tratar trastornos que afecten al tejido nervioso. Los nanocuerpos pueden facilitar además el transporte de fármacos a través de la barrera hematoencefálica. Véase la Solicitud de Patente de los Estados Unidos de Norteamérica Número 20040161738 publicada el 19 de agosto de 2004. Estas características, combinadas con la baja antigenicidad para los seres humanos, indican un gran potencial terapéutico. Además, estas moléculas se pueden expresar completamente en las células procarióticas, tales como las de *E. coli*, y se expresan como proteínas de fusión con bacteriófagos, y son funcionales.

De conformidad con lo anterior, una característica de la presente invención es un anticuerpo o nanocuerpo de camélido que tiene una alta afinidad para C5. En ciertas modalidades de la

presente, el anticuerpo o nanocuerpo de camélido se produce naturalmente en el animal camélido, es decir, es producido por el camélido en seguida de la inmunización con C5 o un fragmento peptídico del mismo, empleando las técnicas descritas en la presente para otros anticuerpos. De una manera alternativa, el nanocuerpo de camélido de enlace de C5 se diseña, es decir, se produce, mediante selección, por ejemplo, a partir de una biblioteca de fagos que exhiban las proteínas de nanocuerpo de camélido apropiadamente mutadas, utilizando procedimientos de paneo, con C5 como el objetivo, como se describe en los Ejemplos de la presente. Los nanocuerpos diseñados se pueden hacer además a la medida mediante ingeniería genética, para tener una vida media en un sujeto receptor de 45 minutos a dos semanas. En una modalidad específica, el anticuerpo o nanocuerpo de camélido se obtiene mediante el injerto de las secuencias de las regiones determinantes de complementariedad de la cadena pesada o ligera de los anticuerpos humanos de la invención en las secuencias de estructura del nanocuerpo o del anticuerpo de un solo dominio, como se describe, por ejemplo, en la Publicación Internacional del TCP Número PCT/EP93/02214.

Moléculas Biespecíficas y Anticuerpos Multivalentes.

En otro aspecto, la presente invención proporciona moléculas biespecíficas o multiespecíficas que comprenden un anticuerpo de enlace de C5, o un fragmento del mismo, de la invención. Un anticuerpo de la invención, o las regiones de enlace de antígeno del

mismo, se pueden derivar o enlazar a otra molécula funcional, por ejemplo, a otro péptido o proteína (por ejemplo, otro anticuerpo o ligando para un receptor), con el fin de generar una molécula biespecífica que se enlace con cuando menos dos sitios de enlace o moléculas objetivo diferentes. El anticuerpo de la invención, de hecho, se puede derivar o enlazar a más de una molécula funcional diferente para generar moléculas multiespecíficas que se enlacen a más de dos sitios de enlace y/o moléculas objetivo diferentes; estas moléculas multiespecíficas también pretenden ser abarcadas por el término "molécula biespecífica", como se utiliza en la presente. Para crear una molécula biespecífica de la invención, un anticuerpo de la invención se puede enlazar funcionalmente (por ejemplo, mediante acoplamiento químico, fusión genética, asociación no covalente, o de otra manera) a una o más moléculas de enlace diferentes, tales como otro anticuerpo, fragmento de anticuerpo, péptido o mimético de enlace, de tal manera que resulte una molécula biespecífica.

De conformidad con lo anterior, la presente invención incluye moléculas biespecíficas que comprenden cuando menos una primera especificidad de enlace para C5, y una segunda especificidad de enlace para un segundo epítopo objetivo. Por ejemplo, el segundo epítopo objetivo es otro epítopo de C5 diferente del primer epítopo objetivo.

Adicionalmente, para la invención en donde la molécula biespecífica es multiespecífica, la molécula puede incluir además una tercera especificidad de enlace, en adición al primero y segundo

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epítopos objetivo.

En una modalidad, las moléculas biespecíficas de la invención comprenden, como una especificidad de enlace, cuando menos un anticuerpo, o un fragmento de anticuerpo, incluyendo, por ejemplo, un Fab, Fab', $F(ab')_2$, Fv, o un Fv de una sola cadena. El anticuerpo también puede ser un dímero de cadena ligera o de cadena pesada, o cualquier fragmento mínimo del mismo, tal como un Fv, o una construcción de una sola cadena, como se describe en Ladner y colaboradores, Patente de los Estados Unidos de Norteamérica Número 4,946,778.

Los diacuerpos son moléculas biespecíficas bivalentes, en donde los dominios VH y VL se expresan sobre una sola cadena de polipéptido, conectados por un enlazador que es demasiado corto para permitir el emparejamiento entre los dos dominios sobre la misma cadena. Los dominios VH y VL se emparejan con dominios de complementariedad de otra cadena, creando de esta manera dos sitios de enlace de antígeno (véanse, por ejemplo, Holliger y colaboradores, 1993 Proc. Natl. Acad. Sci. EUA 90:6444-6448; Poljak y colaboradores, 1994 Structure 2:1121-1123). Los diacuerpos se pueden producir mediante la expresión de dos cadenas de polipéptido con la estructura VHA-VLB y VHB-VLA (configuración VH-VL), o bien VLA-VHB y VLB-VHA (configuración VL-VH) dentro de la misma célula. La mayoría de ellos se pueden expresar en una forma soluble en bacterias. Los diacuerpos de una sola cadena (scDb) se producen mediante la conexión de las dos cadenas del polipéptido

que forman el diacuerpo con un enlazador de aproximadamente 15 residuos de aminoácidos (véanse Holliger y Winter, 1997 Cancer Immunol. Immunother., 45(3-4):128-30; Wu y colaboradores, 1996 Immunotechnology, 2(1):21-36). Los diacuerpos de una sola cadena se pueden expresar en bacterias en una forma monomérica activa soluble (véanse Holliger y Winter, 1997 Cancer Immunol. Immunother., 45(34): 128-30; Wu y colaboradores, 1996 Immunotechnology, 2(1):21-36; Pluckthun y Pack, 1997 Immunotechnology, 3(2): 83-105; Ridgway y colaboradores, 1996 Protein Eng., 9(7):617-21). Un diacuerpo se puede fusionar a Fc para generar un "di-diacuerpo" (véase Lu y colaboradores, 2004 J. Biol. Chem., 279(4):2856-65).

Otros anticuerpos que se pueden emplear en las moléculas biespecíficas de la invención son los anticuerpos monoclonales de murino, quiméricos, y humanizados.

Las moléculas biespecíficas de la presente invención se pueden preparar mediante la conjugación de las especificidades de enlace constituyentes, empleando los métodos conocidos en este campo. Por ejemplo, cada especificidad de enlace de la molécula biespecífica se puede generar por separado, y luego se conjugan unas con otras. Cuando las especificidades de enlace son proteínas o péptidos, se pueden utilizar una variedad de agentes de acoplamiento o reticulación para la conjugación covalente. Los ejemplos de los agentes de reticulación incluyen Proteína A, carbodi-imida, S-acetil-tioacetato de N-succinimidilo (SATA), 5,5'-ditiobis-

(ácido 2-nitro-benzoico) (DTNB), o-fenilen-dimaleimida (oPDM), 3-(2-ditiopiridil)-propionato de N-succinimidilo (SPDP), y 4-(N-maleimido-metil)-ciclohexan-1-carboxilato de sulfo-succinimidilo (sulfo-SMCC) (véanse, por ejemplo, Karpovsky y colaboradores, 1984 J. Exp. Med. 160:1686; Liu, MA y colaboradores, 1985 Proc. Natl. Acad. Sci. EUA 82:8648). Otros métodos incluyen aquéllos descritos en Paulus, 1985 Behring Ins. Mitt. No. 78,118-132; Brennan y colaboradores, 1985 Science 229:81-83; y Glennie y colaboradores, 1987 J. Immunol. 139: 2367-2375). Los agentes de conjugación son SATA y sulfo-SMCC, ambos disponibles en Pierce Chemical Co. (Rockford, IL).

Cuando las especificidades de enlace son anticuerpos, se pueden conjugar mediante enlace de sulfhidrilo de las regiones de articulación del término C de las dos cadenas pesadas. En una modalidad particular, la región de articulación se modifica para contener un número non de residuos de sulfhidrilo, por ejemplo, uno, antes de la conjugación.

De una manera alternativa, ambas especificidades de enlace se pueden codificar en el mismo vector, y se pueden expresar y ensamblar en la misma célula huésped. Este método es particularmente útil cuando la molécula biespecífica es una proteína de fusión de mAb x mAb, mAb x Fab, Fab x $F(ab')_2$, o ligando x Fab. Una molécula biespecífica de la invención puede ser una molécula de una sola cadena que comprenda un anticuerpo de una sola cadena y un determinante de enlace, o una molécula biespecífica de una sola cadena que comprenda dos determinantes de enlace. Las

moléculas biespecíficas pueden comprender cuando menos dos moléculas de una sola cadena. Los métodos para la preparación de las moléculas biespecíficas se describen, por ejemplo, en la Patente de los Estados Unidos de Norteamérica Número 5,260,203; en la Patente de los Estados Unidos de Norteamérica Número 5,455,030; en la Patente de los Estados Unidos de Norteamérica Número 4,881,175; en la Patente de los Estados Unidos de Norteamérica Número 5,132,405; en la Patente de los Estados Unidos de Norteamérica Número 5,091,513; en la Patente de los Estados Unidos de Norteamérica Número 5,476,786; en la Patente de los Estados Unidos de Norteamérica Número 5,013,653; en la Patente de los Estados Unidos de Norteamérica Número 5,258,498; y en la Patente de los Estados Unidos de Norteamérica Número 5,482,858.

El enlace de las moléculas biespecíficas a sus objetivos específicos se puede confirmar, por ejemplo, mediante el ensayo inmunosorbente enlazado con enzimas (ELISA), el radioinmunoensayo (RIA), el análisis FACS, un bioensayo (por ejemplo, inhibición del crecimiento), o ensayo Western blot. Cada uno de estos ensayos detecta en general la presencia de los complejos de proteína-anticuerpo de un interés particular, mediante el empleo de un reactivo marcado (por ejemplo, un anticuerpo) específico para el complejo de interés.

En otro aspecto, la presente invención proporciona compuestos multivalentes que comprenden cuando menos dos porciones de enlace de antígeno idénticas o diferentes de los anticuerpos de la

invención, que se enlazan a C5. Las porciones de enlace de antígeno se pueden enlazar entre sí por medio de fusión de proteína, o de un enlace covalente o no covalente. De una manera alternativa, los métodos de enlace se han descrito para las moléculas biespecíficas. Se pueden obtener compuestos tetravalentes, por ejemplo, mediante la reticulación de los anticuerpos de la invención con un anticuerpo que se enlace a las regiones constantes de los anticuerpos de la invención, por ejemplo, la región Fc o de articulación.

El dominio trimerizante se describe, por ejemplo, en la patente de Borean Número EP 1 012 280B1. Los módulos pentamerizantes se describen, por ejemplo, en la Publicación del TCP Número PCT/EP97/05897.

Anticuerpos con una Vida Media Prolongada.

La presente invención proporciona anticuerpos que se enlazan específicamente a la proteína C5, que tienen una vida media prolongada *in vivo*.

Muchos factores pueden afectar a la vida media de una proteína *in vivo*. Por ejemplo, la filtración del riñón, el metabolismo en el hígado, la degradación mediante las enzimas proteolíticas (proteasas), y las respuestas inmunogénicas (por ejemplo, neutralización de proteína mediante los anticuerpos, y absorción por los macrófagos y las células dendríticas). Se pueden emplear una variedad de estrategias para prolongar la vida media de los anticuerpos de la presente invención. Por ejemplo, mediante enlace químico a polietilenglicol (PEG), reCODE PEG, andamiaje de

anticuerpo, poli-ácido siálico (PSA), almidón de hidroxi-etilo (HES), ligandos de enlace de albúmina, y protectores de carbohidratos; mediante fusión genética a proteínas que se enlacen a las proteínas de suero, tales como albúmina, IgG, FcRn, y transferrina; mediante acoplamiento (genéticamente o químicamente) a otras fracciones de enlace que se enlacen a las proteínas del suero, tales como nanocuerpos, Fabs, DARPins, avímeros, aficuerpos, y anticalinas; mediante fusión genética a rPEG, albúmina, dominio de albúmina, proteínas de enlace de albúmina, y Fc; o mediante incorporación en nanovehículos, formulaciones de liberación lenta, o dispositivos médicos.

Para prolongar la circulación en suero de los anticuerpos *in vivo*, se pueden unir moléculas poliméricas inertes, tales como PEG de alto peso molecular, a los anticuerpos o a un fragmento de los mismos, con o sin un enlazador multifuncional, ya sea a través de conjugación específica del sitio del PEG al término N o C de los anticuerpos, o bien por medio de los grupos épsilon-amino presentes sobre los residuos de lisina. Para pegilar un anticuerpo, el anticuerpo o el fragmento del mismo típicamente se hace reaccionar con polietilenglicol (PEG), tal como un éster reactivo o un derivado de aldehído de PEG, bajo condiciones en donde uno o más grupos PEG lleguen a unirse al anticuerpo o al fragmento de anticuerpo. La pegilación se puede llevar a cabo mediante una reacción de acilación o mediante una reacción de alquilación con una molécula de PEG reactiva (o un polímero soluble en agua reactivo análogo). Como se

utiliza en la presente, el término "polietilenglicol" pretende abarcar cualquiera de las formas de PEG que se han utilizado para derivar otras proteínas, tales como mono-alcoxilo (de 1 a 10 átomos de carbono)- o ariloxi-polietilenglicol, o polietilenglicol-maleimida. En ciertas modalidades, el anticuerpo que se va a pegilar es un anticuerpo aglicosilado. Se empleará la derivación de polímero lineal o ramificado que dé como resultado una pérdida mínima en la actividad biológica. El grado de conjugación se puede monitorear estrechamente mediante SDS-PAGE y espectrometría de masas, para asegurar una conjugación apropiada de las moléculas de PEG a los anticuerpos. El PEG sin reaccionar se puede separar de los conjugados de anticuerpo-PEG mediante cromatografía por exclusión de tamaños o mediante cromatografía de intercambio de iones. Los anticuerpos derivados de PEG se pueden probar para determinar su actividad de enlace, así como para determinar su eficacia *in vivo*, empleando los métodos bien conocidos por los expertos en este campo, por ejemplo, mediante los inmunoensayos descritos en la presente. Los métodos para pegilar proteínas son conocidos en la técnica, y se pueden aplicar a los anticuerpos de la invención. Véanse, por ejemplo, la Patente Europea Número EP 0 154 316 por Nishimura y colaboradores, y la Patente Europea Número EP 0 401 384 por Ishikawa y colaboradores.

Otras tecnologías de pegilación modificada incluyen la tecnología de reconstitución de diseño dirigido químicamente ortogonal (ReCODE PEG), la cual incorpora cadenas laterales

químicamente especificadas en proteínas biosintéticas por medio de un sistema reconstituido que incluye sintetasa de ARNt y ARNt. Esta tecnología hace posible la incorporación de más de 30 nuevos aminoácidos en las proteínas biosintéticas en *E. coli*, levadura, y células de mamífero. El ARNt incorpora un aminoácido no nativo en cualquier lugar en donde se coloque un codón ámbar, convirtiendo el ámbar desde un codón de paro hasta uno que señale la incorporación del aminoácido químicamente especificado.

También se puede emplear la tecnología de pegilación recombinante (rPEG) para prolongar la vida media en suero. Esta tecnología involucra fusionar genéticamente una cola de proteína no estructurada de 300 a 600 aminoácidos con una proteína farmacéutica existente. Debido a que el peso molecular aparente de esta cadena de proteína no estructurada es aproximadamente 15 veces más grande que su peso molecular real, se aumenta mucho la vida media en suero de la proteína. En contraste con la pegilación tradicional, que requiere de conjugación química y re-purificación, el proceso de fabricación se simplifica mucho, y el producto es homogéneo.

La polisialilación es otra tecnología que utiliza el polímero natural de poli-ácido siálico (PSA) para prolongar la vida activa y mejorar la estabilidad de los péptidos y proteínas terapéuticas. El poli-ácido siálico es un polímero de ácido siálico (un azúcar). Cuando se utiliza para el suministro de proteínas y de fármacos peptídicos terapéuticos. El poli-ácido siálico proporciona un micro-

medio ambiente protector después de la conjugación. Esto aumenta la vida activa de la proteína terapéutica en la circulación, e impide que sea reconocida por el sistema inmunitario. El polímero PSA se encuentra naturalmente en el cuerpo humano. Fue adoptado por ciertas bacterias que evolucionaron durante millones de años para recubrir sus paredes con él. Estas bacterias naturalmente poli-sialiladas fueron entonces capaces, en virtud de la imitación molecular, de cubrir el sistema de defensa del cuerpo. El poli-ácido siálico, la tecnología de vaina final de la naturaleza, se puede producir fácilmente a partir de estas bacterias en grandes cantidades y con características físicas previamente determinadas. El poli-ácido siálico bacteriano es completamente no inmunogénico, inclusive cuando se acople a proteínas, debido a que es químicamente idéntico al poli-ácido siálico del cuerpo humano.

Otra tecnología incluye el uso de derivados de almidón de hidroxi-etilo ("HES") enlazados a anticuerpos. El almidón de hidroxi-etilo es un polímero natural modificado derivado a partir del almidón de maíz ceroso, y puede ser metabolizado por las enzimas del cuerpo. Normalmente se administran soluciones de almidón de hidroxi-etilo para sustituir el volumen deficiente de sangre, y para mejorar las propiedades reológicas de la sangre. La hesilación de un anticuerpo hace posible la prolongación de la vida media en circulación, al aumentar la estabilidad de la molécula, así como mediante la reducción de la eliminación renal, dando como resultado una actividad biológica incrementada. Al variar los diferentes

parámetros, tales como el peso molecular de HES, se pueden hacer a la medida un gran número de conjugados de anticuerpos de HES.

También se pueden generar anticuerpos con una mayor vida media *in vivo* mediante la introducción de una o más modificaciones de aminoácidos (es decir, sustituciones, inserciones, o supresiones) en un dominio constante de IgG, o en un fragmento de enlace de FcRn del mismo (de preferencia un fragmento Fc o un fragmento de dominio Fc de articulación). Véanse, por ejemplo, la Publicación Internacional Número WO98/23289; la Publicación Internacional Número WO 97/34631; y Patente de los Estados Unidos de Norteamérica Número 6,277,375.

Además, los anticuerpos se pueden conjugar a albúmina con el objeto de hacer que el anticuerpo o el fragmento de anticuerpo sea más estable *in vivo*, o tenga una vida media más larga *in vivo*. Las técnicas son bien conocidas en este campo; véanse, por ejemplo, las Publicaciones Internacionales Números WO 93/15199, WO 93/15200, y WO 01/77137; y la Patente Europea Número EP 413,622.

Las estrategias para aumentar la vida media son especialmente útiles en los nanocuerpos, enlazadores basados en fibronectina, y otros anticuerpos o proteínas para los cuales se desee una mayor vida *in vivo*.

Conjugados de Anticuerpos.

La presente invención proporciona anticuerpos o fragmentos de los mismos que se enlazan específicamente a una proteína C5 recombinantemente fusionada o químicamente conjugada (incluyendo

conjugaciones tanto covalentes como no covalentes) a una proteína o polipéptido heterólogo (o fragmento del mismo, de preferencia a un polipéptido de cuando menos 10, cuando menos 20, cuando menos 30, cuando menos 40, cuando menos 50, cuando menos 60, cuando menos 70, cuando menos 80, cuando menos 90, o cuando menos 100 aminoácidos), para generar proteínas de fusión. En particular, la invención proporciona proteínas de fusión que comprenden un fragmento de enlace de antígeno de un anticuerpo descrito en la presente (por ejemplo, un fragmento Fab, un fragmento Fd, un fragmento Fv, un fragmento $F(ab)_2$, un dominio VH, una VH CDR, un dominio VL, o una VL CDR), y una proteína, polipéptido, o péptido heterólogos. Los métodos para fusionar o conjugar las proteínas, los polipéptidos, o los péptidos a un anticuerpo o a un fragmento de anticuerpo, son conocidos en la materia. Véanse, por ejemplo, las Patentes de los Estados Unidos de Norteamérica Números 5,336,603, 5,622,929, 5,359,046, 5,349,053, 5,447,851, y 5,112,946; las Patentes Europeas Números EP 307,434 y EP 367,166; las Publicaciones Internacionales Números WO 96/04388 y WO 91/06570; Ashkenazi y colaboradores, 1991, Proc. Natl. Acad. Sci. EUA 88: 10535-10539; Zheng y colaboradores, 1995, J. Immunol. 154:5590-5600; y Vil y colaboradores, 1992, Proc. Natl. Acad. Sci. EUA 89:11337-11341.

Se pueden generar proteínas de fusión adicionales a través de las técnicas de mezcla de genes, mezcla de motivos, mezcla de hexones, y/o mezcla de codones (colectivamente referidas como

"mezcla de ADN"). La mezcla de ADN se puede emplear para alterar las actividades de los anticuerpos de la invención o de los fragmentos de los mismos (por ejemplo, los anticuerpos o fragmentos de los mismos con más altas afinidades y más bajos índices de disociación). Véanse en general las Patentes de los Estados Unidos de Norteamérica Números 5,605,793, 5,811,238, 5,830,721, 5,834,252, y 5,837,458; Patten y colaboradores, 1997, Curr. Opinion Biotechnol. 8:724-33; Harayama, 1998, Trends Biotechnol. 16(2):76-82; Hansson y colaboradores, 1999, J. Mol. Biol. 287:265-76; y Lorenzo y Blasco, 1998, Biotechniques 24(2):308-313 (cada una de estas patentes y publicaciones se incorporan a la presente como referencia en su totalidad). Los anticuerpos o fragmentos de los mismos, o los anticuerpos codificados o fragmentos de los mismos, se pueden alterar al someterse a mutagénesis aleatoria mediante reacción en cadena de la polimerasa susceptible a error, inserción aleatoria de nucleótidos, u otros métodos, antes de la recombinación. Un polinucleótido que codifique un anticuerpo o fragmento del mismo que se enlace específicamente a una proteína C5, se puede recombinar con uno o más componentes, motivos, secciones, partes, dominios, fragmentos, etc., de una o más moléculas heterólogas.

Más aún, los anticuerpos o fragmentos de los mismos se pueden fusionar a secuencias marcadoras, tales como un péptido, para facilitar la purificación. En las modalidades preferidas, la secuencia de aminoácidos marcadora es un péptido de hexa-

histidina, tal como la marca proporcionada en un vector pQE (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), entre otros, muchos de los cuales están comercialmente disponibles. Como se describe en Gentz y colaboradores, 1989, Proc. Natl. Acad. Sci. EUA 86:821-824, por ejemplo, la hexa-histidina proporciona una purificación conveniente de la proteína de fusión. Otras marcas peptídicas útiles para la purificación incluyen, pero no se limitan a, la marca de hemaglutinina ("HA"), la cual corresponde a un epítopo derivado a partir de la proteína de hemaglutinina de influenza (Wilson y colaboradores, 1984, Cell 37:767), y la marca "flag".

En otras modalidades, los anticuerpos de la presente invención o los fragmentos de los mismos, se conjugan a un agente de diagnóstico o detectable. Estos anticuerpos pueden ser útiles para monitorear o pronosticar el establecimiento, desarrollo, progreso, y/o gravedad de una enfermedad o trastorno, como parte de un procedimiento de prueba clínica, tal como la determinación de la eficacia de una terapia particular. Este diagnóstico y detección se puede llevar a cabo mediante el acoplamiento del anticuerpo a sustancias detectables que incluyen, pero no se limitan a, diferentes enzimas, tales como, pero no limitándose a, peroxidasa de radícula roja, fosfatasa alcalina, beta-galactosidasa, o acetil-colinesterasa; los grupos protésicos, tales como, pero no limitándose a, estreptavidina/biotina y avidina/biotina; materiales fluorescentes, tales como, pero no limitándose a, umbeliferona, fluoresceína, isocianato de fluoresceína, rodamina, dicloro-triazinil-

amina/fluoresceína, cloruro de dansilo o ficoeritrina; materiales luminiscentes, tales como, pero no limitándose a, luminol; materiales bioluminiscentes, tales como, pero no limitándose a, luciferasa, luciferina, y ecuorina; materiales radioactivos, tales como, pero no limitándose a, yodo (^{131}I, ^{125}I, ^{123}I, y ^{121}I,), carbono (^{14}C), azufre (^{35}S), tritio (^{3}H), indio (^{115}In, ^{113}In, ^{112}In, y ^{111}In,), tecnecio (^{99}Tc), talio (^{201}Ti), galio (^{68}Ga, ^{67}Ga), paladio (^{103}Pd), molibdeno (^{99}Mo), xenón (^{133}Xe), flúor (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142} Pr, ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, y ^{117}Tin; y los metales emisores de positrones que utilizan diferentes tomografías de emisión de positrones, y los iones de metales paramagnéticos no radioactivos.

La presente invención abarca además los usos de los anticuerpos o fragmentos de los mismos conjugados a una fracción terapéutica. Un anticuerpo o fragmento del mismo se puede conjugar a una fracción terapéutica, tal como una citotoxina, por ejemplo, un agente citostático o citocida, un agente terapéutico, o un ión de metal radioactivo, por ejemplo emisores-alfa. Una citotoxina o un agente citotóxico incluye cualquier agente que sea perjudicial para las células.

Adicionalmente, un anticuerpo o fragmento del mismo se puede conjugar a una fracción terapéutica o a una fracción de fármaco que codifique una respuesta biológica dada. Las fracciones terapéuticas o las fracciones de fármaco no deben interpretarse como limitadas a

los agentes terapéuticos químicos clásicos. Por ejemplo, la fracción de fármaco puede ser una proteína, péptido, o polipéptido que posea una actividad biológica deseada. Estas proteínas pueden incluir, por ejemplo, una toxina, tal como abrina, risina A, exotoxina de *Pseudomonas*, toxina de cólera, o toxina de difteria; una proteína, tal como el factor de necrosis tumoral, interferón-α, interferón-β, factor de crecimiento de nervios, factor de crecimiento derivado de plaquetas, activador de plasminógeno de tejido, un agente apoptótico, un agente anti-angiogénico; o un modificador de la respuesta biológica, tal como, por ejemplo, una linfocina.

Más aún, un anticuerpo se puede conjugar a fracciones terapéuticas, tales como un ión de metal radioactivo, tales como emisores-alfa, tales como ^{213}Bi, o quelantes macrocíclicos útiles para la conjugación de iones de radiometales, incluyendo, pero no limitándose a, ^{131}In, ^{131}LU, ^{131}Y, ^{131}Ho, ^{131}Sm, a los polipéptidos. En ciertas modalidades, el quelante macrocíclico es el ácido 1,4,7,10-tetra-aza-ciclododecan-N,N',N'',N'''-tetra-acético (DOTA), el cual se puede unir al anticuerpo por medio de una molécula enlazadora. Estas moléculas enlazadoras se conocen comúnmente en la técnica, y se describen en Denardo y colaboradores, 1998, Clin. Cancer Res. 4(10):2483-90; Peterson y colaboradores, 1999, Bioconjug. Chem. 10(4):553-7; y Zimmerman y colaboradores, 1999, Nucl. Med. Biol. 26(8):943-50, cada uno incorporado como referencia en su totalidad.

Las técnicas para conjugar las fracciones terapéuticas a los anticuerpos son bien conocidas; véanse, por ejemplo, Arnon y

colaboradores, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", en Monoclonal Antibodies And Cancer Therapy, Reisfeld y colaboradores (Editores), páginas 243-56 (Alan R. Liss, Inc. 1985); Hellstrom y colaboradores, "Antibodies For Drug Delivery", en Controlled Drug Delivery (Segunda Edición), Robinson y colaboradores, (Editores), páginas 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", en Monoclonal Antibodies 84: Biological And Clinical Applications, Pinchera y colaboradores (Editores), páginas 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", en Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin y colaboradores, (Editores), páginas 303-16 (Academic Press 1985), y Thorpe y colaboradores, 1982, Immunol. Rev. 62:119-58.

Los anticuerpos también se pueden unir a soportes sólidos, los cuales son particularmente útiles para los inmunoensayos o para la purificación del antígeno objetivo. Estos soportes sólidos incluyen, pero no se limitan a, vidrio, celulosa, poliacrilamida, nylon, poliestireno, poli-cloruro de vinilo, o polipropileno.

5.2 Métodos para la producción de los anticuerpos de la invención.

5.2.1 Ácidos nucleicos que codifican los anticuerpos.

La invención proporciona moléculas de ácidos nucleicos sustancialmente purificadas que codifican los polipéptidos que comprenden segmentos o dominios de las cadenas de anticuerpo de

enlace de C5 descritas anteriormente. Algunos de los ácidos nucleicos de la invención comprenden la secuencia de nucleótidos que codifica la región variable de cadena pesada mostrada en las SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, ó 281, y/o la secuencia de nucleótidos que codifica la región variable de cadena ligera mostrada en las SEQ ID NOs: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, ó 289. En una modalidad específica, las moléculas de ácidos nucleicos son aquéllas identificadas en la Tabla 1. Algunas otras moléculas de ácidos nucleicos de la invención comprenden secuencias de nucleótidos que son sustancialmente idénticas (por ejemplo, cuando menos el 65 por ciento, el 80 por ciento, el 95 por ciento, o el 99 por ciento idénticas) a las secuencias de nucleótidos identificadas en la Tabla 1. Cuando se expresan a partir de vectores de expresión apropiados, los polipéptidos codificados por estos polinucleótidos son capaces de exhibir una capacidad de enlace de antígeno de C5.

En la invención también se proporcionan polinucleótidos que codifican cuando menos una región determinante de complementariedad, y usualmente las tres regiones determinantes de complementariedad a partir de la cadena pesada o ligera del anticuerpo de enlace de C5 estipulado anteriormente. Algunos otros polinucleótidos codifican todas o sustancialmente todas las secuencias de región variable de la cadena pesada y/o de la cadena

ligera del anticuerpo de enlace de C5 estipulado anteriormente. Debido a la degeneración del código, una variedad de secuencias de ácidos nucleicos codificarán cada una de las secuencias de aminoácidos de inmunoglobulina.

Las moléculas de ácidos nucleicos de la invención pueden codificar tanto una región variable como una región constante del anticuerpo. Algunas secuencias de ácidos nucleicos de la invención comprenden nucleótidos que codifican una secuencia de región variable de cadena pesada madura que es sustancialmente idéntica (por ejemplo, cuando menos el 80 por ciento, el 90 por ciento, o el 99 por ciento idéntica) a la secuencia de región variable de cadena pesada madura estipulada en las SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, ó 281. Algunas otras secuencias de ácidos nucleicos comprenden nucleótidos que codifican una secuencia de región variable de cadena ligera madura que es sustancialmente idéntica (por ejemplo, cuando menos el 80 por ciento, el 90 por ciento, o el 99 por ciento idéntica) a la secuencia de región variable de cadena ligera madura estipulada en las SEQ ID NOs: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, ó 289.

Las secuencias de polinucleótidos se pueden producir mediante la síntesis de ADN en fase sólida *de novo*, o mediante mutagénesis con reacción en cadena de la polimerasa de una secuencia existente (por ejemplo, las secuencias descritas en los Ejemplos que se

encuentran más adelante), que codifique un anticuerpo de enlace de C5 o su fragmento de enlace. La síntesis química directa de los ácidos nucleicos se puede llevar a cabo mediante los métodos conocidos en este campo, tales como el método de fosfotriéster de Narang y colaboradores, 1979, Meth. Enzymol. 68:90; el método de fosfodiéster de Brown y colaboradores, Meth. Enzymol. 68:109, 1979; el método de dietil-fosforamidita de Beaucage y colaboradores, Tetra. Lett., 22:1859, 1981; y el método de soporte sólido de la Patente de los Estados Unidos de Norteamérica Número 4,458,066. La introducción de mutaciones a una secuencia de polinucleótido mediante reacción en cadena de la polimerasa se puede llevar a cabo como se describe, por ejemplo, en PCR Technology: Principles and Applications for DNA Amplification, H. A. Erlich (Editor), Freeman Press, NY, NY, 1992; PCR Protocols: A Guide to Methods and Applications, Innis y colaboradores (Editores), Academic Press, San Diego, CA, 1990; Mattila y colaboradores, Nucleic Acids Res. 19:967, 1991; y Eckert y colaboradores, PCR Methods and Applications 1:17, 1991.

También en la invención se proporcionan vectores de expresión y células huésped para producir los anticuerpos de enlace de C5 descritos anteriormente. Se pueden emplear diferentes vectores de expresión para expresar los polinucleótidos que codifiquen las cadenas de anticuerpo de enlace de C5 o los fragmentos de enlace. Se pueden utilizar vectores de expresión tanto basados en virus como no virales para producir los anticuerpos en una célula huésped

de mamífero. Los vectores y sistemas no virales incluyen plásmidos, vectores episomales, típicamente con un casete de expresión para expresar una proteína o ARN, y cromosomas artificiales humanos (véase, por ejemplo, Harrington y colaboradores, Nat Genet 15:345, 1997). Por ejemplo, los vectores no virales útiles para la expresión de los polinucleótidos y polipéptidos de enlace de C5 en las células de mamífero (por ejemplo, humanas) incluyen los vectores pThioHis A, B, y C, pcDNA3.1/His, pEBVHis A, B, y C, (Invitrogen, San Diego, CA), MPSV, y otros numerosos vectores conocidos en la técnica para expresar otras proteínas. Los vectores virales útiles incluyen los vectores basados en retrovirus, adenovirus, virus adeno-asociados, virus de herpes, vectores basados en SV40, virus de papiloma, virus HBP Epstein Barr, vectores de virus de vacuna, y virus de Semliki Forest (SFV). Véanse, Brent y colaboradores, *supra*; Smith, Annu. Rev. Microbiol. 49:807, 1995; y Rosenfeld y colaboradores, Cell 68:143, 1992.

La elección del vector de expresión depende de las células huésped pretendidas en donde se vaya a expresar el vector. Típicamente, los vectores de expresión contienen un promotor y otras secuencias reguladoras (por ejemplo, potenciadoras), que se enlazan operablemente a los polinucleótidos que codifican la cadena o fragmento de anticuerpo de enlace de C5. En algunas modalidades, se emplea un promotor inducible para impedir la expresión de las secuencias insertadas, excepto bajo condiciones de inducción. Los promotores inducibles incluyen, por ejemplo, arabinosa, lacZ,

promotor de metalotioneína, o un promotor de choque por calor. Los cultivos de los organismos transformados se pueden expandir bajo condiciones no inductoras sin forzar la población para las secuencias de codificación cuyos productos de expresión sean mejor tolerados por las células huésped. En adición a los promotores, también se pueden requerir o desear otros elementos reguladores para la expresión eficiente de una cadena o fragmento de anticuerpo de enlace de C5. Estos elementos típicamente incluyen un codón de inicio de ATG, y un sitio de enlace de ribosoma adyacente, u otras secuencias. En adición, la eficiencia de la expresión se puede mejorar mediante la inclusión de potenciadores apropiados para el sistema celular en uso (véanse, por ejemplo, Scharf y colaboradores, Results Probl. Cell Differ. 20:125, 1994; y Bittner y colaboradores, Meth. Enzymol., 153:516, 1987). Por ejemplo, se puede utilizar el potenciador de SV40 o el potenciador de CMV para aumentar la expresión en las células huésped de mamífero.

Los vectores de expresión también pueden proporcionar una posición de la secuencia de señal de secreción para formar una proteína de fusión con los polipéptidos codificados por las secuencias de anticuerpos de enlace de C5 insertadas. Más frecuentemente, las secuencias de anticuerpos de enlace de C5 insertadas, se enlazan a una secuencia de señal antes de incluirse en el vector. Los vectores que se van a utilizar para recibir a las secuencias que codifiquen los dominios variables de cadena ligera y pesada del anticuerpo de enlace de C5, algunas veces también

codifican las regiones constantes o partes de las mismas. Estos vectores permiten la expresión de las regiones variables como proteínas de fusión con las regiones constantes, conduciendo de esta manera a la producción de anticuerpos intactos o fragmentos de los mismos. Típicamente, estas regiones constantes son humanas.

Las células huésped para alojar y expresar las cadenas de los anticuerpos de enlace de C5 pueden ser procarióticas o eucarióticas. *E. coli* es un huésped procariótico útil para la clonación y expresión de los polinucleótidos de la presente invención. Otros huéspedes microbianos adecuados para utilizarse incluyen bacilos, tales como *Bacillus subtilis*, y otras enterobacteriáceas, tales como las especies de *Salmonella, Serratia,* y diferentes *Pseudomonas*. En estos huéspedes procarióticos, también se pueden hacer vectores de expresión, los cuales típicamente contienen secuencias de control de expresión compatibles con la célula huésped (por ejemplo, un origen de réplica). En adición, estará presente cualquier número de una variedad de promotores bien conocidos, tales como el sistema promotor de lactosa, un sistema promotor de triptófano (trp), un sistema promotor de beta-lactamasa, o un sistema promotor a partir del fago lambda. Los promotores típicamente controlan la expresión, opcionalmente con una secuencia operadora, y tienen secuencias del sitio de enlace de ribosoma y similares, para iniciar y completar la transcripción y la traducción. También se pueden emplear otros microbios, tales como levadura, para expresar los polipéptidos de enlace de C5 de la invención. También se pueden utilizar células de

insecto en combinación con vectores de baculovirus.

En algunas modalidades preferidas, se utilizan células huésped de mamífero para expresar y producir los polipéptidos de enlace de C5 de la presente invención. Por ejemplo, pueden ser ya sea una línea celular de hibridoma que exprese los genes de inmunoglobulina endógenos (por ejemplo, el clon de hibridoma de mieloma 1D6.C9, como se describe en los Ejemplos), o bien una línea celular de mamífero que aloje un vector de expresión exógeno (por ejemplo, las células de mieloma SP2/0 ejemplificadas más adelante). Éstas incluyen cualquier célula animal o humana mortal normal, o normal, o anormal inmortal. Por ejemplo, se han desarrollado un número de líneas celulares huésped adecuadas para secretar las inmunoglobulinas intactas, incluyendo las líneas celulares de CHO, diferentes líneas celulares COS, las células HeLa, las líneas celulares de mieloma, las células-B transformadas, y los hibridomas. El uso del cultivo celular de tejido de mamífero para expresar polipéptidos se discute en general, por ejemplo, en Winnacker, FROM GENES TO CLONES, VCH Publishers, N.Y., N.Y., 1987. Los vectores de expresión para las células huésped de mamífero pueden incluir secuencias de control de expresión, tales como un origen de réplica, un promotor, y un potenciador (véase, por ejemplo, Queen, y colaboradores, Immunol. Rev. 89:49-68, 1986), y los sitios de información de procesamiento necesarios, tales como los sitios de enlace de ribosoma, los sitios de empalme de ARN, los sitios de poliadenilación, y las secuencias terminadoras de transcripción.

Estos vectores de expresión normalmente contienen promotores derivados a partir de los genes de mamífero o a partir de los virus de mamífero. Los promotores adecuados pueden ser constitutivos, específicos del tipo de célula, específicos de la etapa, y/o modulables o regulables. Los promotores útiles incluyen, pero no se limitan a, el promotor de metalotioneína, el promotor tardío mayor de adenovirus constitutivo, el promotor de MMTV inducible por dexametasona, el promotor SV40, el promotor MRP poll-II, el promotor MPSV constitutivo, el promotor CMV inducible por tetraciclina (tal como el promotor CMV inmediato-temprano humano), el promotor CMV constitutivo, y combinaciones de promotores-potenciadores conocidas en este campo.

Los métodos para introducir vectores de expresión que contengan las secuencias de polinucleótidos de interés varían dependiendo del tipo de huésped celular. Por ejemplo, comúnmente se utiliza la transfección con cloruro de calcio para las células procarióticas, mientras que se puede utilizar el tratamiento con fosfato de calcio o electroporación para otros huéspedes celulares. (Véase en general Sambrook y colaboradores, *supra*). Otros métodos incluyen, por ejemplo, electroporación, tratamiento con fosfato de calcio, transformación mediada por liposomas, inyección y microinyección, métodos balísticos, virosomas, inmunoliposomas, conjugados de policatión:ácido nucleico, ADN desnudo, viriones artificiales, fusión con la proteína estructural de virus de herpes VP22 (Elliot y O'Hare, Cell 88:223, 1997), absorción de ADN

mejorada por el agente, y transducción *ex vivo*. Para la producción de alto rendimiento de proteínas recombinantes a largo plazo, con frecuencia se deseará una expresión estable. Por ejemplo, se pueden preparar líneas celulares que expresen establemente las cadenas de anticuerpos de enlace de C5 o los fragmentos de enlace, utilizando los vectores de expresión de la invención que contengan orígenes de réplica virales o elementos de expresión endógenos y un gen marcador seleccionable. En seguida de la introducción del vector, se puede permitir que las células crezcan durante 1 a 2 días en un medio enriquecido, antes de cambiarse al medio selectivo. El propósito del marcador seleccionable es conferir resistencia a la selección, y su presencia permite el crecimiento de las células que expresen con éxito las secuencias introducidas en el medio selectivo. Las células establemente transfectadas, resistentes, se pueden hacer proliferar utilizando técnicas de cultivo de tejido apropiadas para el tipo de célula.

5.2.2 Generación de los anticuerpos monoclonales de la invención.

Los anticuerpos monoclonales (mAbs) se pueden producir mediante una variedad de técnicas, incluyendo la metodología de anticuerpos monoclonales convencional, por ejemplo, la técnica de hibridación de células somáticas convencional de Kohler y Milstein, 1975 Nature 256: 495. Se pueden emplear muchas técnicas para producir anticuerpos monoclonales, por ejemplo, transformación viral u oncogénica de los linfocitos-B.

Un sistema animal para preparar hibridomas es el sistema de murino. La producción de hibridoma en el ratón es un procedimiento bien establecido. Los protocolos y técnicas de inmunización para el aislamiento de los esplenocitos inmunizados para la fusión son conocidos en este campo. También se conocen los componentes de fusión (por ejemplo, células de mieloma de murino), y los procedimientos de fusión.

Los anticuerpos quiméricos o humanizados de la presente invención se pueden preparar basándose en la secuencia de un anticuerpo monoclonal de murino preparado como se describe anteriormente. El ADN que codifica las inmunoglobulinas de cadena pesada y ligera se puede obtener a partir del hibridoma de murino de interés, y se puede diseñar para contener secuencias de inmunoglobulina que no sean de murino (por ejemplo, humanas), empleando técnicas de biología molecular convencionales. Por ejemplo, con el fin de crear un anticuerpo quimérico, las regiones variables de murino se pueden enlazar a las regiones constantes humanas, empleando los métodos conocidos en la materia (véase, por ejemplo, la Patente de los Estados Unidos de Norteamérica Número 4,816,567 a Cabilly y colaboradores). Con el objeto de crear un anticuerpo humanizado, las regiones determinantes de complementariedad de murino se pueden insertar en una estructura humana, empleando los métodos conocidos en este campo. Véanse, por ejemplo, la Patente de los Estados Unidos de Norteamérica Número 5225539 a Winter, y las Patentes de los Estados Unidos de

Norteamérica Números 5530101; 5585089; 5693762 y 6180370 a Queen y colaboradores.

En cierta modalidad, los anticuerpos de la invención son anticuerpos monoclonales humanos. Estos anticuerpos monoclonales humanos dirigidos contra C5, se pueden generar utilizando ratones transgénicos o transcromosómicos que lleven partes del sistema inmunitario humano, en lugar del sistema de ratón. Estos ratones transgénicos y transcromosómicos incluyen los ratones referidos en la presente como ratones HuMAb y ratones KM, respectivamente, y son referidos colectivamente en la presente como "ratones con Ig humana".

El ratón HuMAb® (Medarex, Inc.) contiene mini-*loci* del gen de inmunoglobulina humana, que codifican las secuencias de inmunoglobulina de cadena pesada (μ y γ) y ligera κ humanas no reconfiguradas, junto con las mutaciones dirigidas que inactivan los *loci* de las cadenas μ y κ endógenos (véase, por ejemplo, Lonberg y colaboradores, 1994 Nature 368(6474): 856-859). De conformidad con lo anterior, los ratones exhiben una expresión reducida de la IgM ó κ de ratón, y, en respuesta a la inmunización, los transgenes de cadena pesada y ligera humanos introducidos sufren cambio de clase y mutación somática para generar la IgGκ monoclonal humana de alta afinidad (Lonberg, N. y colaboradores, 1994, *supra*; revisado en Lonberg, N., 1994 Handbook of Experimental Pharmacology 113:49-101; Lonberg, N. y Huszar, D., 1995 Intern. Rev. Immunol.13: 65-93, y Harding, F. y Lonberg, N., 1995 Ann. N. Y. Acad. Sci. 764:536-

546). La preparación y uso de ratones HuMAb, y las modificaciones genómicas llevadas por estos ratones, se describen adicionalmente en Taylor, L. y colaboradores, 1992 Nucleic Acids Research 20:6287-6295; Chen, J. y colaboradores, 1993 International Immunology 5: 647-656; Tuaillon y colaboradores, 1993 Proc. Natl. Acad. Sci. EUA 94:3720-3724; Choi y colaboradores, 1993 Nature Genetics 4:117-123; Chen, J. y colaboradores, 1993 EMBO J. 12: 821-830; Tuaillon y colaboradores, 1994 J. Immunol. 152:2912-2920; Taylor, L. y colaboradores, 1994 International Immunology 579-591; y Fishwild, D. y colaboradores, 1996 Nature Biotechnology 14: 845-851, el contenido de todos los cuales se incorpora específicamente a la presente como referencia en su totalidad. Véanse además las Patentes de los Estados Unidos de Norteamérica Números 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,789,650; 5,877,397; 5,661,016; 5,814,318; 5,874,299; y 5,770,429; todas a Lonberg y Kay; la Patente de los Estados Unidos de Norteamérica Número 5,545,807 a Surani y colaboradores; Las Publicaciones del TCP Números WO 92103918, WO 93/12227, WO 94/25585, WO 97113852, WO 98/24884 y WO 99/45962, todas a Lonberg y Kay; y la Publicación del TCP Número WO 01/14424 a Korman y colaboradores.

En otra modalidad, los anticuerpos humanos de la invención se pueden reproducir utilizando un ratón que lleve secuencias de inmunoglobulina humana sobre transgenes y transcromosomas, tal como un ratón que lleve un transgén de cadena pesada humana y un

transcromosoma de cadena ligera humana. Estos ratones, referidos en la presente como "ratones KM", se describen con detalle en la Publicación del TCP Número WO 02/43478 a Ishida y colaboradores.

Todavía además, en la técnica están disponibles sistemas de animales transgénicos alternativos que expresan genes de inmunoglobulina humana, y se pueden utilizar para reproducir los anticuerpos de enlace de C5 de la invención. Por ejemplo, se puede utilizar un sistema transgénico alternativo referido como el xeno-ratón (Abgenix, Inc.). Estos ratones se describen, por ejemplo, en las Patentes de los Estados Unidos de Norteamérica Números 5,939,598; 6,075,181; 6,114,598; 6,150,584 y 6,162,963 a Kucherlapati y colaboradores.

Más aún, en la técnica están disponibles sistemas de animales transcromosómicos alternativos que expresan genes de inmunoglobulina humana, y se pueden utilizar para reproducir los anticuerpos de enlace de C5 de la invención. Por ejemplo, se pueden utilizar los ratones que llevan tanto un transcromosoma de cadena pesada humana como un transcromosoma de cadena ligera humana, referidos como "ratones TC"; estos ratones se describen en Tomizuka y colaboradores, 2000 Proc. Natl. Acad. Sci. EUA 97:722-727. Adicionalmente, se han descrito en la técnica vacas que llevan transcromosomas de cadena pesada y ligera humanos (Kuroiwa y colaboradores, 2002 Nature Biotechnology 20:889-894), y se pueden utilizar para reproducir los anticuerpos de enlace de C5 de la invención.

Los anticuerpos monoclonales humanos de la invención también se pueden preparar utilizando los métodos de exhibición de fagos para rastrear bibliotecas de genes de inmunoglobulina humana. Estos métodos de exhibición de fagos para aislar los anticuerpos humanos están establecidos en la técnica, o se describen en los Ejemplos que se encuentran más adelante. Véanse, por ejemplo: las Patentes de los Estados Unidos de Norteamérica Números 5,223,409; 5,403,484; y 5,571,698 a Ladner y colaboradores; las Patentes de los Estados Unidos de Norteamérica Números 5,427,908 y 5,580,717 a Dower y colaboradores; las Patentes de los Estados Unidos de Norteamérica Números 5,969,108 y 6,172,197 a McCafferty y colaboradores; y las Patentes de los Estados Unidos de Norteamérica Números 5,885,793; 6,521,404; 6,544,731; 6,555,313; 6,582,915 y 6,593,081 a Griffiths y colaboradores.

Los anticuerpos monoclonales humanos de la invención también se pueden preparar utilizando ratones SCID, en los cuales se han reconstituido células inmunes humanas, de tal manera que se puede generar una respuesta de anticuerpo humano después de la inmunización. Estos ratones se describen, por ejemplo, en las Patentes de los Estados Unidos de Norteamérica Números 5,476,996 y 5,698,767 a Wilson y colaboradores.

5.2.3 Diseño de estructura o Fc.

Los anticuerpos diseñados de la invención incluyen aquéllos en donde se han hecho modificaciones a los residuos de estructura

dentro de la VH y/o VL, por ejemplo, para mejorar las propiedades del anticuerpo. Típicamente, estas modificaciones de estructura se hacen para disminuir la inmunogenicidad del anticuerpo. Por ejemplo, un planteamiento es "retro-mutar" uno o más residuos de estructura hasta la secuencia de la línea germinal correspondiente. De una manera más específica, un anticuerpo que se haya sometido a mutación somática puede contener residuos de estructura que difieran de la secuencia de la línea germinal a partir de la cual se derive el anticuerpo. Estos residuos se pueden identificar mediante la comparación de las secuencias de estructura del anticuerpo con las secuencias de la línea germinal a partir de la cual se deriva el anticuerpo. Para regresar las secuencias de la región de estructura hasta su configuración de la línea germinal, las mutaciones somáticas se pueden "retro-mutar" hasta la secuencia de la línea germinal, por ejemplo, mediante mutagénesis dirigida al sitio. Estos anticuerpos "retro-mutados" también pretenden ser abarcados por la invención.

Otro tipo de modificación de estructura involucra la mutación de uno o más residuos dentro de la región de estructura, o inclusive dentro de una o más regiones determinantes de complementariedad, para remover los epítopos de células-T, con el fin de reducir de esta manera la inmunogenicidad potencial del anticuerpo. Este planteamiento también es referido como "desinmunización", y se describe con mayor detalle en la Publicación de Patente de los Estados Unidos de Norteamérica Número 20030153043 por Carr y

colaboradores.

En adición o de una manera alternativa a las modificaciones hechas dentro de la estructura o de las regiones determinantes de complementariedad, los anticuerpos de la invención se pueden diseñar para incluir modificaciones dentro de la región Fc, típicamente para alterar una o más propiedades funcionales del anticuerpo, tales como la vida media en suero, la fijación del complemento, el enlace del receptor Fc, y/o la citotoxicidad celular dependiente del antígeno. Adicionalmente, un anticuerpo de la invención se puede modificar químicamente (por ejemplo, se pueden unir o más fracciones químicas al anticuerpo), o se puede modificar para alterar su glicosilación, nuevamente con el fin de alterar una o más propiedades funcionales del anticuerpo. Cada una de estas modalidades se describe con mayor detalle más adelante. La numeración de los residuos en la región Fc es aquélla del índice EU de Kabat.

En una modalidad, la región de articulación de CH1 se modifica de tal manera que se altera el número de residuos de cisteína en la región de articulación, por ejemplo, se aumenta o se disminuye. Este planteamiento se describe adicionalmente en la Patente de los Estados Unidos de Norteamérica Número 5,677,425 por Bodmer y colaboradores. El número de residuos de cisteína en la región de articulación de CH1 se altera, por ejemplo, para facilitar el ensamble de las cadenas ligera y pesada, o con el fin de aumentar o disminuir la estabilidad del anticuerpo.

En otra modalidad, se muta la región de articulación de un anticuerpo para disminuir la vida media biológica del anticuerpo. Más específicamente, se introducen una o más mutaciones de aminoácidos en la región de interfase del dominio CH2-CH3 del fragmento de articulación Fc, de tal manera que el anticuerpo tenga el enlace de Proteína A de Estafilocosilo deteriorado (SpA) en relación con el enlace de SpA del dominio de articulación Fc nativo. Este planteamiento se describe con mayor detalle en la Patente de los Estados Unidos de Norteamérica Número 6,165,745 por Ward y colaboradores.

En otra modalidad, el anticuerpo se modifica para aumentar su vida media biológica. Son posibles diferentes planteamientos. Por ejemplo, se pueden introducir una o más de las siguientes mutaciones: T252L, T254S, T256F, como se describe en la Patente de los Estados Unidos de Norteamérica Número 6,277,375 a Ward. De una manera alternativa, con el fin de aumentar la vida media biológica, el anticuerpo se puede alterar dentro de la región CH1 ó CL para contener un epítopo de enlace de receptor de salvamento tomado a partir de dos ciclos de un dominio CH2 de una región Fc de una IgG, como se describe en las Patentes de los Estados Unidos de Norteamérica Números 5,869,046 y 6,121,022 por Presta y colaboradores.

En todavía otras modalidades, se altera la región Fc reemplazando cuando menos un residuo de aminoácido con un residuo de aminoácido diferente, con el fin de alterar las funciones

efectoras del anticuerpo. Por ejemplo, uno o más aminoácidos pueden reemplazados con un residuo de aminoácido diferente, de tal manera que el anticuerpo tenga una afinidad alterada por un ligando efector, pero retenga la capacidad de enlace de antígeno del anticuerpo progenitor. El ligando efector con el cual se altera la afinidad puede ser, por ejemplo, un receptor de Fc, o el componente C1 del complemento. Este planteamiento se describe con mayor detalle en las Patentes de los Estados Unidos de Norteamérica Números 5,624,821 y 5,648,260, ambas por Winter y colaboradores.

En otra modalidad, uno o más aminoácidos seleccionados a partir de los residuos de aminoácidos, pueden ser reemplazados con un residuo de aminoácido diferente, de tal manera que el anticuerpo tenga un enlace de C1q alterado, y/o una citotoxicidad dependiente del complemento (CDC) reducida o abolida. Este planteamiento se describe con mayor detalle en la Patente de los Estados Unidos de Norteamérica Número 6,194,551 por Idusogie y colaboradores.

En otra modalidad, se alteran uno o más residuos de aminoácidos para alterar de esta manera la capacidad del anticuerpo para fijar el complemento. Este planteamiento se describe adicionalmente en la Publicación del TCP Número WO 94/29351 por Bodmer y colaboradores.

En todavía otra modalidad, se modifica la región Fc para aumentar la capacidad del anticuerpo para mediar la citotoxicidad celular dependiente del anticuerpo (ADCC), y/o para aumentar la afinidad del anticuerpo por un receptor de Fcγ, mediante la

modificación de uno o más aminoácidos. Este planteamiento se describe adicionalmente en la Publicación del TCP Número WO00/42072 por Presta. Más aún, los sitios de enlace sobre la IgG1 humana para FcγRI, FcγRII, FcγRIII y FcRn, se han mapeado, y se han descrito las variantes con un mejor enlace (véase Shields, R. L. y colaboradores, 2001 *J. Biol. Chem.* 276:6591-6604).

En todavía otra modalidad, se modifica la glicosilación de un anticuerpo. Por ejemplo, se puede hacer un anticuerpo aglicosilado (es decir, el anticuerpo carece de glicosilación). La glicosilación se puede alterar, por ejemplo, para aumentar la afinidad del anticuerpo por el antígeno. Estas modificaciones de carbohidratos se pueden llevar a cabo mediante, por ejemplo, la alteración de uno o más sitios de glicosilación dentro de la secuencia del anticuerpo. Por ejemplo, se pueden hacer una o más sustituciones de aminoácidos que den como resultado la eliminación de uno o más sitios de glicosilación de estructura de región variable, para eliminar de esta manera la glicosilación en ese sitio. Esta aglicosilación puede aumentar la afinidad del anticuerpo por el antígeno. Este planteamiento se describe con mayor detalle en las Patentes de los Estados Unidos de Norteamérica Números 5,714,350 y 6,350,861 por Co y colaboradores.

Adicionalmente o de una manera alternativa, se puede hacer un anticuerpo que tenga un tipo de glicosilación alterada, tal como un anticuerpo hipofucosilado que tenga cantidades reducidas de residuos de fucosilo, o un anticuerpo que tenga un aumento de

estructuras de GlcNac de bisección. Se ha demostrado que estos patrones de glicosilación alterada aumentan la capacidad de citotoxicidad celular dependiente del anticuerpo de los anticuerpos. Estas modificaciones de carbohidratos se pueden llevar a cabo, por ejemplo, mediante la expresión del anticuerpo en una célula huésped con una maquinaria de glicosilación alterada. Las células con la maquinaria de glicosilación alterada han sido descritas en este campo, y se pueden utilizar como células huésped en donde se expresan los anticuerpos recombinantes de la invención, para producir de esta manera un anticuerpo con una glicosilación alterada. Por ejemplo, la Patente Europea Número EP 1,176,195 por Hang y colaboradores, describe una línea celular con un gen FUT8 funcionalmente interrumpido, el cual codifica una fucosil-transferasa, de tal manera que los anticuerpos expresados en esta línea celular exhiben hipofucosilación. La Publicación del TCP Número WO03/035835 por Presta describe una línea celular de ovario de hámster chino variante, las células Lec13, con una capacidad reducida para unir la fucosa a los carbohidratos enlazados con Asn(297), que también da como resultado una hipofucosilación de los anticuerpos expresados en esa célula huésped (véase también Shields, R. L. y colaboradores, 2002 *J. Biol. Chem.* 277:26733-26740). La Publicación del TCP Número WO 99/54342 por Umana y colaboradores, describe líneas celulares diseñadas para expresar las glicosil-transferasas modificadoras de glicoproteína (por ejemplo, beta(1,4)-N-acetil-glucosaminil-transferasa III (GnTIII)), de tal

manera que los anticuerpos expresados en las líneas celulares diseñadas exhiben un aumento de estructuras de GlcNac de bisección, lo cual da como resultado un aumento en la actividad de la citotoxicidad celular dependiente del anticuerpo de los anticuerpos (véase también Umana y colaboradores, 1999 Nat. Biotech. 17:176-180).

5.2.4 Métodos para el diseño de anticuerpos alterados.

Como se discute anteriormente, los anticuerpos de enlace de C5 que tienen las secuencias VH y VL o las secuencias de cadena pesada y ligera de longitud completa mostradas en la presente, se pueden utilizar para crear nuevos anticuerpos de enlace de C5, mediante la modificación de las secuencias de cadena pesada y/o de cadena ligera de longitud completa. Las secuencias VH y/o VL, o las regiones constantes unidas a las mismas. Por consiguiente, en otro aspecto de la invención, se utilizan las características estructurales de un anticuerpo de enlace de C5 de la invención para crear anticuerpos de enlace de C5 estructuralmente relacionados que retienen cuando menos una propiedad funcional de los anticuerpos de la invención, tal como el enlace a la C5 humana, y también la inhibición de una o más propiedades funcionales de C5 (por ejemplo, inhiben la lisis de los glóbulos rojos sanguíneos en un ensayo hemolítico).

Por ejemplo, una o más regiones determinantes de complementariedad de los anticuerpos de la presente invención, o mutaciones de las mismas, se pueden combinar de una manera

recombinante con las regiones de estructura conocidas y/o con otras regiones determinantes de complementariedad, para crear anticuerpos de enlace de C5 recombinantemente diseñados adicionales de la invención, como se discute anteriormente. Otros tipos de modificaciones incluyen aquéllas descritas en la sección anterior. El material de partida para el método de diseño es una o más de las secuencias VH y/o VL proporcionadas en la presente, o una o más regiones determinantes de complementariedad de las mismas. Con el fin de crear el anticuerpo diseñado, no es necesario preparar realmente (es decir, expresar como una proteína) un anticuerpo que tenga una o más de las secuencias VH y/o VL proporcionadas en la presente, o una o más regiones determinantes de complementariedad de las mismas. En su lugar, se utiliza la información contenida en las secuencias como el material de partida para crear secuencias de una "segunda generación" derivadas a partir de las secuencias originales, y luego se preparan las secuencias de la "segunda generación" y se expresan como una proteína.

De conformidad con lo anterior, en otra modalidad, la invención proporciona un método para preparar un anticuerpo de enlace de C5, el cual consiste en: una secuencia de anticuerpo de región variable de cadena pesada que tiene una secuencia de CDR1 seleccionada a partir del grupo que consiste en las SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, y 235, una secuencia de CDR2 seleccionada a partir del grupo que consiste en las SEQ ID NOs: 2, 18, 34, 49, 62,

77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, y 236, y/o una secuencia de CDR3 seleccionada a partir del grupo que consiste en las SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, y 237; y una secuencia de anticuerpo de región variable de cadena ligera que tiene una secuencia de CDR1 seleccionada a partir del grupo que consiste en las SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, y 238, una secuencia de CDR2 seleccionada a partir del grupo que consiste en las SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, y 239, y/o una secuencia de CDR3 seleccionada a partir del grupo que consiste en las SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, y 240; alterar cuando menos un residuo de aminoácido dentro de la secuencia de anticuerpo de región variable de cadena pesada y/o dentro de la secuencia de anticuerpo de región variable de cadena ligera, para crear cuando menos una secuencia de anticuerpo alterada; y expresar la secuencia de anticuerpo alterada como una proteína.

De conformidad con lo anterior, en otra modalidad, la invención proporciona un método para la preparación de un anticuerpo de enlace de C5 optimizado para su expresión en una célula de mamífero, el cual consiste en: una secuencia de anticuerpo de cadena pesada de longitud completa que tiene una secuencia seleccionada a partir del grupo de las SEQ ID NOs: 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, y 282; y una secuencia de anticuerpo de cadena ligera de longitud completa que tiene una secuencia

seleccionada a partir del grupo de las SEQ ID NOs: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, y 290; alterar cuando menos un residuo de aminoácido dentro de la secuencia de anticuerpo de cadena pesada de longitud completa y/o dentro de la secuencia de anticuerpo de cadena ligera de longitud completa, para crear cuando menos una secuencia de anticuerpo alterada; y expresar la secuencia de anticuerpo alterada como una proteína.

La secuencia de anticuerpo alterada también se puede preparar mediante el rastreo de bibliotecas de anticuerpos que tengan secuencias de CDR3 fijas o determinantes de enlace esencial mínimo, como se describen en la Patente de los Estados Unidos de Norteamérica Número US20050255552, y la diversidad sobre las secuencias de CDR1 y CDR2. El rastreo se puede llevar a cabo de acuerdo con cualquier tecnología de rastreo apropiada para rastrear anticuerpos a partir de bibliotecas de anticuerpos, tal como la tecnología de exhibición de fagos.

Se pueden emplear las técnicas de biología molecular convencionales para preparar y expresar la secuencia de anticuerpo alterada. El anticuerpo codificado por las secuencias de anticuerpo alteradas, es uno que retiene una, algunas, o todas las propiedades funcionales de los anticuerpos de enlace de C5 descritos en la presente, cuyas propiedades funcionales incluyen, pero no se limitan a, enlazarse específicamente a la C5 humana y/o de cinomolgo; y el anticuerpo inhibe la lisis de los glóbulos rojos sanguíneos en un

ensayo hemolítico.

Las propiedades funcionales de los anticuerpos alterados se pueden evaluar empleando ensayos convencionales disponibles en la técnica y/o descritos en la presente, tales como los que se estipulan en los Ejemplos (por ejemplo, ELISAs).

En ciertas modalidades de los métodos del diseño de anticuerpos de la invención, se pueden introducir mutaciones de una manera aleatoria o selectiva a lo largo de toda o parte de una secuencia de codificación de un anticuerpo de enlace de C5, y los anticuerpos de enlace de C5 modificados resultantes se pueden rastrear para determinar la actividad de enlace y/ u otras propiedades funcionales, como se describe en la presente. Los métodos de mutación se han descrito en este campo. Por ejemplo, la Publicación del TCP Número WO 02/092780 por Short, describe métodos para crear y rastrear mutaciones de anticuerpos utilizando mutagénesis de saturación, ensamble de ligamiento sintético, o una combinación de los mismos. De una manera alternativa, la Publicación del TCP Número 03/074679 por Lazar y colaboradores, describe métodos para utilizar los métodos de rastreo de computación con el fin de optimizar las propiedades fisicoquímicas de los anticuerpos.

5.3 Caracterización de los anticuerpos de la invención.

Los anticuerpos de la invención se pueden caracterizar mediante diferentes ensayos funcionales. Por ejemplo, se pueden caracterizar por su capacidad para inhibir la lisis de los glóbulos

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rojos sanguíneos en los ensayos hemolíticos, por su afinidad con una proteína C5 (por ejemplo, C5 humana y/o de cinomolgo), el enlace de epítopo, su resistencia a la proteólisis, y su capacidad para bloquear la cascada de complemento, por ejemplo, su capacidad para inhibir la formación de MAC.

Se pueden emplear diferentes métodos para medir la presencia de las moléculas de la senda de complemento y la activación del sistema de complemento (véanse, por ejemplo, la Patente de los Estados Unidos de Norteamérica Número 6,087,120; y Newell y colaboradores, J. Lab. Clin. Med., 100:437-44, 1982). Por ejemplo, la actividad del complemento se puede monitorear mediante: (i) la medición de la inhibición de la lisis de los glóbulos rojos sanguíneos (hemólisis) mediada por el complemento; (ii) la medición de la capacidad para inhibir la disociación de C3 ó C5; y (iii) la inhibición de la hemólisis mediada por la senda alternativa.

Las dos técnicas más comúnmente empleadas son los ensayos hemolíticos (véase, por ejemplo, Baatrup y colaboradores, Ann. Rheum. Dis., 51:892-7, 1992), y los ensayos inmunológicos (véase, por ejemplo, Auda y colaboradores, Rheumatol Int, 10:185-9, 1990). Las técnicas hemolíticas miden la capacidad funcional de la secuencia entera - ya sea la senda clásica o bien la alternativa. Las técnicas inmunológicas miden la concentración de proteína de un componente de complemento específico o de un producto dividido. Otros ensayos que se pueden emplear para detectar la activación del complemento o para medir las actividades de los componentes de

complemento en los métodos de la presente invención incluyen, por ejemplo, el ensayo de proliferación de células-T (Chain y colaboradores, J. Immunol Methods, 99:221-8, 1987), y el ensayo de híper-sensibilidad de tipo demorado (DTH) (Forstrom y colaboradores, 1983, Nature 303:627-629; Halliday y colaboradores, 1982, en Assessment of Immune Status by the Leukocyte Adherence Inhibition Test, Academic, Nueva York, páginas 1-26; Koppi y colaboradores, 1982, Cell. Immunol. 66:394-406; y Patente de los Estados Unidos de Norteamérica Número 5,843,449).

En las técnicas hemolíticas, todos los componentes de complemento deben estar presentes y deben ser funcionales. Por consiguiente, las técnicas hemolíticas pueden rastrear tanto la integridad funcional como las deficiencias del sistema de complemento (véanse, por ejemplo, Dijk y colaboradores, J. Immunol. Methods 36: 29-39, 1980; Minh y colaboradores, Clin. Lab. Haematol. 5:23-34 1983; y Tanaka y colaboradores, J. Immunol. 86: 161-170, 1986). Con el objeto de medir la capacidad funcional de la senda clásica, se utilizan glóbulos rojos sanguíneos de oveja recubiertos con hemolisina (IgG de conejo para glóbulos rojos sanguíneos de oveja), o glóbulos rojos sanguíneos de pollo que se sensibilizan con anticuerpos de conejo anti-pollo, como las células objetivo (células sensibilizadas). Estos complejos de Ag-Ab activan la senda clásica, y dan como resultado la lisis de las células objetivo cuando los componentes son funcionales y están presentes en una concentración adecuada. Para determinar la capacidad funcional de

la senda alternativa, se utilizan glóbulos rojos sanguíneos de conejo como las células objetivo (véase, por ejemplo, la Patente de los Estados Unidos de Norteamérica Número 6,087,120).

Con el fin de probar la capacidad de un anticuerpo para inhibir la formación de MAC (complejo de ataque de membrana), se puede llevar a cabo un ensayo de depósito de MAC. Dicho de una manera breve, se puede utilizar zymosan para activar la senda alternativa, y se puede utilizar IgM para activar la senda clásica. Los Fabs se incuban previamente son suero humano, y se agregan a las placas recubiertas con zymosan o IgM. Se puede calcular el porcentaje de inhibición de depósito de MAC para cada muestra en relación con la línea base (suero humano tratado con EDTA) y con un control positivo (suero humano).

La capacidad de un anticuerpo para enlazarse a C5 se puede detectar marcando el anticuerpo de interés directamente, o el anticuerpo puede no estar marcado, y se detecta el enlace de una manera indirecta, utilizando diferentes formatos de ensayo de emparedado conocidos en este campo.

En algunas modalidades, los anticuerpos de enlace de C5 de la invención bloquean o compiten con el enlace de un anticuerpo de enlace de C5 de referencia para un polipéptido de C5. Éstos pueden ser los anticuerpos de enlace de C5 humanos descritos anteriormente. También pueden ser otros anticuerpos de enlace de C5 de ratón, quiméricos, o humanizados, que se enlacen al mismo epítopo que el anticuerpo de referencia. La capacidad para bloquear

o competir con el enlace del anticuerpo de referencia, indica que un anticuerpo de enlace de C5 bajo prueba se enlaza al mismo epítopo o un epítopo similar al definido por el anticuerpo de referencia, o a un epítopo que está suficientemente proximal al epítopo enlazado por el anticuerpo de enlace de C5 de referencia. Estos anticuerpos tienen especialmente probabilidades de compartir las propiedades convenientes identificadas para el anticuerpo de referencia. La capacidad para bloquear o competir con el anticuerpo de referencia se puede determinar, por ejemplo, mediante un ensayo de enlace de competencia. Con un ensayo de enlace de competencia, el anticuerpo bajo prueba se examina para determinar su capacidad para inhibir el enlace específico del anticuerpo de referencia a un antígeno común, tal como un polipéptido de C5. Un anticuerpo de prueba compite con el anticuerpo de referencia por el enlace específico al antígeno si un exceso del anticuerpo de prueba inhibe sustancialmente el enlace del anticuerpo de referencia. La inhibición sustancial significa que el anticuerpo de prueba reduce el enlace específico del anticuerpo de referencia usualmente por cuando menos el 10 por ciento, el 25 por ciento, el 50 por ciento, el 75 por ciento, o el 90 por ciento.

Existen un número de ensayos de enlace de competencia conocidos que se pueden utilizar para evaluar la competencia de un anticuerpo de enlace de C5 con el anticuerpo de enlace de C5 de referencia, por el enlace con una proteína C5. Éstos incluyen, por ejemplo, radioinmunoensayo directo o indirecto en fase sólida (RIA),

inmunoensayo enzimático directo o indirecto en fase sólida (EIA), ensayo de competencia de emparedado (véase Stahli y colaboradores, Methods in Enzymology 9:242-253, 1983); EIA de biotina-avidina directo en fase sólida (véase Kirkland y colaboradores, J. Immunol. 137:3614-3619, 1986); ensayo marcado directo en fase sólida, ensayo de emparedado marcado directo en fase sólida (véase Harlow & Lane, *supra*); RIA de marca directo en fase sólida utilizando una marca de I-125 (véase Morel y colaboradores, Molec. Immunol. 25:7-15, 1988); EIA de biotina-avidina directo en fase sólida (Cheung y colaboradores, Virology 176:546-552, 1990); y RIA marcado directo (Moldenhauer y colaboradores, Scand. J. Immunol. 32:77-82, 1990). Típicamente, este ensayo involucra el uso del antígeno purificado enlazado a una superficie sólida o a células que lleven cualquiera de los mismos, un anticuerpo de enlace de C5 de prueba no marcado, y un anticuerpo de referencia marcado. La inhibición competitiva se mide mediante la determinación de la cantidad de marca enlazada a la superficie sólida o a las células en la presencia del anticuerpo de prueba. Usualmente, el anticuerpo de prueba está presente en un exceso. Los anticuerpos identificados mediante el ensayo de competencia (anticuerpos competidores) incluyen los anticuerpos que se enlacen al mismo epítopo que el anticuerpo de referencia, y los anticuerpos que se enlacen a un epítopo adyacente suficientemente proximal al epítopo enlazado por el anticuerpo de referencia, para evitar que ocurra el impedimento estérico.

Con el objeto de determinar si los anticuerpos monoclonales de enlace de C5 seleccionados se enlazan a epítopos únicos, cada anticuerpo se puede biotinilar utilizando reactivos comercialmente disponibles (por ejemplo, los reactivos de Pierce, Rockford, IL). Se pueden llevar a cabo estudios de competencia utilizando anticuerpos monoclonales no marcados y anticuerpos monoclonales biotinilados, utilizando placas ELISA recubiertas con un polipéptido de C5. El enlace del anticuerpo monoclonal biotinilado se puede detectar con una sonda de estreptavidina-fosfatasa alcalina. Para determinar el isotipo de un anticuerpo de enlace de C5 purificado, se pueden llevar a cabo ELISAs de isotipos. Por ejemplo, los pozos de las placas de microtitulación se pueden recubrir con 1 microgramo/mililitro de IgG anti-humano durante la noche a 4°C. Después del bloqueo con albúmina de suero bovino al 1 por ciento, las placas se hacen reaccionar con 1 microgramo/mililitro o menos del anticuerpo de enlace de C5 monoclonal, o de controles de isotipos purificados, a temperatura ambiente, durante 1 a 2 horas. Entonces los pozos se pueden hacer reaccionar ya sea con la IgG1 humana o con las sondas conjugadas con fosfatasa alcalina específicas de la IgM humana. Luego se desarrollan las placas y se analizan, de tal manera que se puede determinar el isotipo del anticuerpo purificado.

Para demostrar el enlace de los anticuerpos de enlace de C5 monoclonales a las células vivas que expresan un polipéptido de C5, se puede utilizar citometría de flujo. Dicho de una manera breve, las líneas celulares que expresen C5 (cultivadas bajo condiciones de

cultivo convencionales) se pueden mezclar con diferentes concentraciones de un anticuerpo de enlace de C5 en suero regulado con fosfato conteniendo albúmina de suero bovino al 0.1 por ciento y suero fetal de becerro al 10 por ciento, y se incuban a 37°C durante 1 hora. Después de lavarse, las células se hacen reaccionar con el anticuerpo de IgG anti-humano marcado con fluoresceína bajo las mismas condiciones que el teñido del anticuerpo primario. Las muestras se pueden analizar mediante el instrumento FACScan utilizando las propiedades de dispersión de luz y laterales para la compuerta sobre las células individuales. Se puede utilizar un ensayo alternativo utilizando el microscopio de fluorescencia (en adición a, o en lugar de) el ensayo de citometría de flujo. Las células se pueden teñir exactamente como se describe anteriormente, y se examinan mediante el microscopio de fluorescencia. Este método permite la visualización de las células individuales, pero puede tener una sensibilidad disminuida, dependiendo de la densidad del antígeno.

Los anticuerpos de enlace de C5 de la invención se pueden probar adicionalmente para determinar su reactividad con un polipéptido de C5 o fragmento antigénico, mediante Western blot. Brevemente, se pueden preparar polipéptidos de C5 purificados o proteínas de fusión, o extractos celulares a partir de las células que expresen C5, y se pueden someter a electroforesis en gel de poliacrilamida-dodecil-sulfato de sodio. Después de la electroforesis, los antígenos separados se transfieren a las membranas de

nitrocelulosa, se bloquean con suero fetal de becerro al 10 por ciento, y se sondean con los anticuerpos monoclonales que se van a probar. El enlace de IgG humana se puede detectar utilizando una fosfatasa alcalina de IgG anti-humana, y se desarrolla con tabletas de sustrato de BCIP/NBT (Sigma Chem. Co., St. Louis, MO).

Los ejemplos de los ensayos funcionales también se describen en la sección de Ejemplos que se encuentra más adelante.

5.4 Usos profilácticos y terapéuticos.

La presente invención proporciona métodos para el tratamiento de una enfermedad o trastorno asociado con un aumento en la actividad del complemento, mediante la administración a un sujeto que lo necesite, de una cantidad efectiva de los anticuerpos de la invención. En una modalidad específica, la presente invención proporciona un método para el tratamiento de degeneración macular relacionada con la edad (AMD), mediante la administración a un sujeto que lo necesite, de una cantidad efectiva de los anticuerpos de la invención.

Los anticuerpos de la invención se pueden utilizar, entre otras cosas, para prevenir el progreso de la degeneración macular relacionada con la edad seca hasta la degeneración macular relacionada con la edad húmeda, para hacer más lento y/o prevenir el progreso de la atrofia geográfica, y para mejorar la pérdida de visión debido al progreso de la degeneración macular relacionada con la edad seca. También se pueden utilizar en combinación con terapias anti-VEGF, para el tratamiento de los pacientes con

degeneración macular relacionada con la edad húmeda.

En algunas modalidades, la presente invención proporciona métodos para el tratamiento de una enfermedad o trastorno relacionado con el complemento, mediante la administración a un sujeto que lo necesite, de una cantidad efectiva de los anticuerpos de la invención. Los ejemplos de las enfermedades o trastornos relacionados con el complemento incluyen: trastornos neurológicos, esclerosis múltiple, embolia, Síndrome de Guillain-Barre, lesión cerebral traumática, enfermedad de Parkinson, trastornos de una activación inapropiada o indeseable del complemento, complicaciones de hemodiálisis, rechazo de alo-injerto híper-agudo, rechazo de xeno-injerto, toxicidad inducida por interleucina-2 durante la terapia con IL-2, trastornos inflamatorios, enfermedades de inflamación o autoinmunes, enfermedad de Crohn, síndrome de insuficiencia respiratoria de adultos, lesión térmica, incluyendo quemaduras o congelaciones, condiciones posteriores a reperfusión isquémica, infarto de miocardio, angioplastía de globo, síndrome posterior a la bomba en la derivación cardiopulmonar o en la derivación renal, hemodiálisis, isquemia renal, reperfusión arterial mesentérica después de reconstrucción aórtica, enfermedad infecciosa o sepsis, trastornos del complejo inmune y enfermedades auto-inmunes, artritis reumatoide, lupus eritematoso sistémico (SLE), nefritis por lupus eritematoso sistémico, nefritis proliferativa, anemia hemolítica, y miastenia gravis. En adición, otras enfermedades relacionadas con el complemento conocidas son enfermedades

pulmonares y trastornos tales como dispnea, hemoptisis, síndrome de insuficiencia respiratoria de adultos, asma, enfermedad pulmonar obstructiva crónica (COPD), enfisema, embolias e infartos pulmonares, neumonía, enfermedades de polvo fibrogénico, polvos y minerales inertes (por ejemplo, silicio, polvo de carbón, berilio, y asbesto), fibrosis pulmonar, enfermedades por polvos orgánicos, lesión química (debido a gases y productos químicos irritantes, por ejemplo cloro, fosgeno, dióxido de azufre, sulfuro de hidrógeno, dióxido de nitrógeno, amoniaco, y ácido clorhídrico), lesión por humo, lesión térmica (por ejemplo, quemadura, congelación), asma, alergia, broncoconstricción, neumonitis por hipersensibilidad, enfermedades parasitarias, Síndrome de Goodpasture, vasculitis pulmonar, e inflamación asociada con el complejo inmune.

En una modalidad específica, la presente invención proporciona métodos para el tratamiento de una enfermedad o trastorno relacionado con el complemento, mediante la administración a un sujeto que lo necesite, de una cantidad efectiva de los anticuerpos de la invención, en donde esta enfermedad o trastorno es asma, artritis (por ejemplo, artritis reumatoide), enfermedad cardíaca autoinmune, esclerosis múltiple, enfermedad inflamatoria del intestino, lesiones por isquemia-reperfusión, Síndrome de Barraquer-Simons, hemodiálisis, lupus sistémico, lupus eritematoso, soriasis, esclerosis múltiple, trasplante, enfermedades del sistema nervioso central, tales como enfermedad de Alzheimer y otras condiciones neurodegenerativas, aHUS, glomerulonefritis,

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penfigoide buloso, o MPGN II.

En una modalidad específica, la presente invención proporciona métodos para el tratamiento de glomerulonefritis, mediante la administración a un sujeto que lo necesite, de una cantidad efectiva de una composición que comprenda un anticuerpo de la presente invención. Los síntomas de la glomerulonefritis incluyen, pero no se limitan a, proteinuria; índice reducido de filtración glomerular (GFR); cambios de electrolitos en suero, incluyendo azotemia (uremia, nitrógeno de urea excesivo en sangre - BUN), y retención de sal, que conducen a retención de agua, dando como resultado hipertensión y edema; hematuria y sedimentos urinarios anormales, incluyendo vaciados de glóbulos rojos; hipoalbuminemia; hiperlipidemia; y lipiduria. En una modalidad específica, la presente invención proporciona métodos para el tratamiento de hemoglobinuria nocturna paroxismal (PNH), mediante la administración a un sujeto que lo necesite, de una cantidad efectiva de una composición que comprenda un anticuerpo de la presente invención.

En una modalidad específica, la presente invención proporciona métodos para reducir la disfunción de los sistemas inmunitario y hemostático asociada con la circulación extracorpórea, mediante la administración a un sujeto que lo necesite, de una cantidad efectiva de una composición que comprenda un anticuerpo de la presente invención. Los anticuerpos de la presente invención se pueden utilizar en cualquier procedimiento que involucre la

circulación de la sangre del paciente desde un vaso sanguíneo del paciente, a través de un conducto, y de regreso hasta un vaso sanguíneo del paciente, teniendo el conducto una superficie luminal que comprenda un material capaz de provocar cuando menos una de la activación del complemento, la activación de las plaquetas, la activación de los leucocitos, o la adhesión de plaquetas-leucocitos. Estos procedimientos incluyen, pero no se limitan a, todas las formas de SC, así como los procedimientos que involucran la introducción de un órgano, tejido, o vaso artificial o extraño en el circuito sanguíneo de un paciente.

A los sujetos que se van a tratar con los agentes terapéuticos de la presente invención también se les puede administrar otros agentes terapéuticos con los métodos conocidos para el tratamiento de las condiciones asociadas con degeneración macular, tales como tratamientos con antibióticos, como se describen en la Patente de los Estados Unidos de Norteamérica Número 6,218,368. En otros tratamientos, los agentes inmunosupresores, tales como la ciclosporina, son agentes capaces de suprimir las respuestas inmunes. Estos agentes incluyen fármacos citotóxicos, corticosteroides, fármacos anti-inflamatorios no esteroideos (NSAIDs), inmunosupresores de linfocitos-T específicos, y anticuerpos o fragmentos de los mismos (véase el Physicians' Desk Reference, 53ª Edición, Medical Economics Company Inc., Montvale, N. J. (1999)). El tratamiento inmunosupresor típicamente se continúa a intervalos durante un período de una semana, un mes, tres meses,

seis meses, o un año. En algunos pacientes, el tratamiento se administra durante hasta el resto de la vida del paciente.

Cuando los agentes terapéuticos de la presente invención se administran junto con otro agente, los dos se pueden administrar en secuencia en cualquier orden, o de una manera simultánea. En algunos aspectos, un anticuerpo de la presente invención se administra a un sujeto que también esté recibiendo terapia con un segundo agente (por ejemplo, verteporfina). En otros aspectos, la molécula de enlace se administra en conjunto con tratamientos quirúrgicos.

Los agentes adecuados para el tratamiento de combinación con los anticuerpos de enlace de C5 incluyen los agentes conocidos en la técnica que sean capaces de modular las actividades de los componentes de complemento (véase, por ejemplo, la Patente de los Estados Unidos de Norteamérica Número 5,808,109). Se ha reportado que otros agentes disminuyen la actividad mediada por el complemento. Estos agentes incluyen: aminoácidos (Takada, Y. y colaboradores, Immunology 1978, 34, 509); ésteres de fosfonato (Becker, L. Biochem. Biophy. Acta 1967, 147, 289); sustancias polianiónicas (Conrow, R. B. y colaboradores, J. Med. Chem. 1980, 23, 242); fluoruros de sulfonilo (Hansch, C.; Yoshimoto, M. J. Med. Chem. 1974, 17, 1160, y las referencias citadas en el mismo); polinucleótidos (DeClercq, P. F. y colaboradores, Biochem. Biophys. Res. Commun. 1975, 67, 255); ácidos primarios (Glovsky, M. M. y colaboradores, J. Immunol. 1969, 102, 1); porfinas (Lapidus, M. y

Tomasco, J. Immunopharmacol. 1981, 3, 137); varios productos anti-inflamatorios (Burge, J. J. y colaboradores, J. Immunol. 1978, 120, 1625); fenoles (Muller-Eberhard, H. J. 1978, en Molecular Basis of Biological Degradative Processes, Berlin, R. D. y colaboradores, Editores, Academic Press, Nueva York, página 65); y benzamidinas (Vogt, W. y colaboradores, Immunology 1979, 36, 138). Algunos de estos agentes funcionan mediante la inhibición general de las proteasas y las esterasas. Otros no son específicos para cualquier paso intermedio particular en la senda de complemento, sino que más bien inhiben más de un paso de la activación del complemento. Los ejemplos de los últimos compuestos incluyen las benzamidinas, que bloquean la utilización de C1, C4, y C5 (véase, por ejemplo, Vogt y colaboradores, Immunol. 1979, 36, 138).

Los agentes adicionales conocidos en este campo que pueden inhibir la actividad de los componentes de complemento incluyen K-76, un metabolito fúngico a partir de *Stachybotrys* (Corey y colaboradores, J. Amer. Chem. Soc. 104: 5551, 1982). Se ha demostrado que tanto K-76 como K-76 COOH, inhiben al complemento principalmente en el paso C5 (Hong y colaboradores, J. Immunol. 122: 2418, 1979; Miyazaki y colaboradores, Microbiol. Immunol. 24: 1091, 1980), e impiden la generación de un factor quimiotáctico a partir del complemento humano normal (Bumpers y colaboradores, Lab. Clinc. Med. 102: 421, 1983). En altas concentraciones de K-76 o de K-76 COOH, se exhibe alguna inhibición de las reacciones de C2, C3, C6, C7, y C9 con sus

intermediarios precedentes respectivos. También se ha reportado que K-76 o que K-76 COOH inhibe el sistema inactivador de C3b del complemento (Hong y colaboradores, J. Immunol. 127: 104-108, 1981). Otros agentes adecuados para practicar los métodos de la presente invención incluyen griseofulvina (Weinberg, en Principles of Medicinal Chemistry, Segunda Edición, Foye, W. O., Editores, Lea & Febiger, Filadelfia, Pa., página 813, 1981), isopanarina (Djura y colaboradores, Aust. J. Chem. 36: 1057, 1983),y los metabolitos del fago de *Siphonodictyon coralli* (Sullivan y colaboradores, Tetrahedron 37: 979, 1981).

Un régimen de terapia de combinación puede ser aditivo, o puede producir resultados sinérgicos (por ejemplo, reducciones en la actividad de la senda de complemento mayores que las esperadas para el uso combinado de los dos agentes). En algunas modalidades, la presente invención proporciona una terapia de combinación para prevenir y/o tratar la degeneración macular relacionada con la edad, u otra enfermedad relacionada con el complemento, como se describe anteriormente, con un anticuerpo de enlace de C5 de la invención, y un agente anti-angiogénico, tal como un agente anti-VEGF.

5.5 Usos de diagnóstico.

En un aspecto, la invención abarca ensayos de diagnóstico para determinar la expresión de la proteína y/o ácido nucleico de C5, así como la función de la proteína C5, en el contexto de una muestra biológica (por ejemplo, sangre, suero, células, tejido), o a partir de

un individuo que esté afligido con una enfermedad o trastorno, o que esté en riesgo de desarrollar un trastorno asociado con la degeneración macular relacionada con la edad.

Los ensayos de diagnóstico, tales como los ensayos competitivos, se apoyan en la capacidad de un análogo marcado (el "rastreador") para competir con el analito de muestra de prueba, por un número limitado de sitios de enlace, sobre un componente de enlace común. El componente de enlace generalmente está insolubilizado antes o después de la competencia, y entonces el rastreador y el analito enlazados al componente de enlace, se separan del rastreador no enlazado y del analito. Esta separación se lleva a cabo mediante decantación (en donde el componente de enlace fue previamente insolubilizado), o mediante centrifugación (en donde se precipitó el componente de enlace después de la reacción competitiva). La cantidad de analito de muestra de prueba es inversamente proporcional a la cantidad de rastreador enlazado, como se mide mediante la cantidad de sustancia marcadora. Se preparan curvas de respuesta a la dosis con cantidades conocidas del analito, y se comparan con los resultados de la prueba, con el objeto de determinar cuantitativamente la cantidad de analito presente en la muestra de prueba. Estos ensayos se denominan como sistemas ELISA, cuando se utilizan enzimas como los marcadores detectables. En un ensayo de esta forma, el enlace competitivo entre los anticuerpos y los anticuerpos de enlace de C5 da como resultado la proteína C5 enlazada, de preferencia los

epítopos C5 de la invención, que es una medida de los anticuerpos en la muestra de suero, más particularmente los anticuerpos neutralizantes en la muestra de suero.

Una ventaja significativa del ensayo, es que se hace la medición de los anticuerpos neutralizantes directamente (es decir, aquéllos que interfieren con el enlace de la proteína C5, específicamente los epítopos). Este ensayo, en particular en la forma de una prueba ELISA, tiene aplicaciones considerables en el medio ambiente clínico, y en el rastreo de sangre de rutina.

Las técnicas inmunológicas emplean anticuerpos policlonales o monoclonales contra los diferentes epítopos de los distintos componentes de complemento (por ejemplo, C3, C4, C5), para detectar, por ejemplo, los productos divididos de los componentes de complemento (véanse, por ejemplo, Hugli y colaboradores, Immunoassays Clinical Laboratory Techniques 443-460, 1980; Gorski y colaboradores, J. Immunol. Meth. 47: 61-73, 1981; Linder y colaboradores, J. Immunol. Meth. 47: 49-59, 1981; y Burger y colaboradores, J. Immunol. 141: 553-558, 1988). Entonces se podría medir el enlace del anticuerpo con el producto dividido en competencia con una concentración conocida del producto dividido marcado. Están disponibles varios ensayos, tales como radioinmunoensayos, ELISAs, y ensayos de difusión radial, para detectar los productos divididos del complemento.

Las técnicas inmunológicas proporcionan una alta sensibilidad para detectar la activación del complemento, debido a que permiten

hacer la medición de la formación del producto dividido en la sangre a partir de un sujeto de prueba y de los sujetos de control con o sin trastornos relacionados con la degeneración macular. De conformidad con lo anterior, en algunos métodos de la presente invención, se obtiene el diagnóstico de un trastorno asociado con los trastornos oculares mediante la medición de la activación anormal del complemento a través de la cuantificación de los productos divididos solubles de los componentes de complemento en el plasma sanguíneo a partir de un sujeto de prueba. Las mediciones se pueden llevar a cabo como se describe, por ejemplo, en Chenoweth y colaboradores, N. Engl. J. Med. 304: 497-502, 1981; y Bhakdi y colaboradores, Biochim Biophys Acta 737: 343-372, 1983. De una manera preferible, solamente se mide la activación del complemento formada *in vivo*. Esto se puede llevar a cabo mediante la recolección de una muestra biológica a partir del sujeto (por ejemplo, suero) en un medio que contenga los inhibidores del sistema de complemento, y subsiguientemente se mide la activación del complemento (por ejemplo, cuantificación de los productos divididos) en la muestra.

En el diagnóstico clínico o en el monitoreo de los pacientes con trastornos asociados con las enfermedades o trastornos oculares, la detección de las proteínas de complemento, en comparación con los niveles en una muestra biológica correspondiente de un sujeto normal, indica un paciente con trastornos asociados con degeneración macular.

El diagnóstico o la toma de imágenes *in vivo* se describe en la

Patente de los Estados Unidos de Norteamérica Número US2006/0067935. Brevemente, estos métodos comprenden en general la administración o la introducción a un paciente, de una cantidad diagnosticamente efectiva de una molécula de enlace de C5 que esté unida operativamente a un marcador o marca que sea detectable mediante métodos no invasivos. Se permite que el conjugado de anticuerpo-marcador tenga suficiente tiempo para localizar y enlazarse a las proteínas de complemento dentro del ojo. Luego se expone al paciente a un dispositivo de detección para identificar el marcador detectable, formando de esta manera una imagen de la localización de las moléculas de enlace de C5 en el ojo de un paciente. La presencia del anticuerpo de enlace de C5 o de un fragmento de enlace de antígeno del mismo, se detecta mediante la determinación de si un anticuerpo-marcador se enlaza a un componente del ojo. La detección de un mayor nivel en las proteínas de complemento seleccionadas, o de una combinación de proteína en comparación con un individuo normal sin la enfermedad de degeneración macular relacionada con la edad, indica una predisposición a, y/o el establecimiento de, los trastornos asociados con la degeneración macular. Estos aspectos de la invención también son preferidos para utilizarse en los métodos de toma de imágenes del ojo, y en los métodos de diagnóstico y tratamiento angiogénicos combinados.

La invención también pertenece al campo de la medicina predictiva,, en donde se utilizan ensayos de diagnóstico, ensayos de

pronóstico, farmacogenómica, y estudios clínicos de monitoreo, para propósitos de pronóstico (predictivos), con el fin de tratar de esta manera a un individuo profilácticamente. La invención también proporciona ensayos de pronóstico (o predictivos) para determinar si un individuo está en riesgo de desarrollar un trastorno asociado con la mala regulación de la actividad de la senda de complemento. Por ejemplo, se pueden ensayar las mutaciones en un gen C5 en una muestra biológica. Estos ensayos se pueden utilizar para propósitos de pronóstico o predictivos, con el fin de tratar de esta manera profilácticamente a un individuo antes del establecimiento de un trastorno caracterizado por, o asociado con, la expresión o actividad del ácido nucleico de la proteína C5.

Otro aspecto de la invención proporciona métodos para determinar la expresión del ácido nucleico de C5 o de la actividad de la proteína C5 en un individuo, para seleccionar de esta manera los agentes terapéuticos o profilácticos apropiados para ese individuo (referidos en la presente como "farmacogenómica"). La farmacogenómica permite hacer la selección de los agentes (por ejemplo, fármacos) para el tratamiento terapéutico o profiláctico de un individuo, basándose en el genotipo del individuo (por ejemplo, el genotipo del individuo examinado para determinar la capacidad del individuo para responder a un agente particular).

Todavía otro aspecto de la invención pertenece al monitoreo de la influenza de los agentes (por ejemplo, fármacos) sobre la expresión o actividad de la proteína C5 en estudios clínicos.

5.6 Composiciones farmacéuticas.

La invención proporciona composiciones farmacéuticas que comprenden los anticuerpos de enlace de C5 (intactos o fragmentos de enlace) formulados junto con un vehículo farmacéuticamente aceptable. Las composiciones pueden contener adicionalmente uno o más agentes terapéuticos adicionales que sean adecuados para el tratamiento o la prevención de una enfermedad asociada con el complemento (por ejemplo, degeneración macular relacionada con la edad). Los vehículos farmacéuticos mejoran o estabilizan la composición, o facilitan la preparación de la composición. Los vehículos farmacéuticamente aceptables incluyen solventes, medios de dispersión, recubrimientos, agentes anti-bacterianos y anti-fúngicos, agentes isotónicos y demoradores de absorción, y similares, que sean fisiológicamente compatibles.

Una composición farmacéutica de la presente invención se puede administrar mediante una variedad de métodos conocidos en este campo. La vía y/o el modo de administración varían dependiendo de los resultados deseados. Se prefiere que la administración sea intravenosa, intramuscular, intraperitoneal, o subcutánea, o se puede administrar proximal al sitio del objetivo. En una modalidad específica, los anticuerpos de la invención se formulan de tal manera que se puedan administrar intravítreamente en el ojo. El vehículo farmacéuticamente aceptable debe ser adecuado para su administración intravenosa, intramuscular, subcutánea, parenteral, espinal, o epidérmica (por ejemplo, mediante

inyección o infusión). Dependiendo de la vía de administración, el compuesto activo, es decir, el anticuerpo, la molécula biespecífica y multiespecífica, se puede recubrir en un material para proteger al compuesto de la acción de los ácidos y de otras condiciones naturales que puedan inactivar al compuesto.

La composición debe ser estéril y fluida. Se puede mantener la fluidez apropiada, por ejemplo, mediante el uso de un recubrimiento, tal como con lecitina, mediante el mantenimiento del tamaño de partículas requerido en el caso de la dispersión, y mediante el uso de tensoactivos. En muchos casos, es preferible incluir agentes isotónicos, por ejemplo, azúcares, poli-alcoholes, tales como manitol o sorbitol, y cloruro de sodio, en la composición. Se puede provocar una absorción de largo plazo de las composiciones inyectables incluyendo en la composición un agente que demore la absorción, por ejemplo, monoestearato de aluminio o gelatina.

Las composiciones farmacéuticas de la invención se pueden preparar de acuerdo con los métodos bien conocidos y rutinariamente practicados en este campo. Véanse, por ejemplo, Remington: The Science and Practice of Pharmacy, Mack Publishing Co., 20ª Edición, 2000; y Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, Editor, Marcel Dekker, Inc., Nueva York, 1978. Las composiciones farmacéuticas se fabrican de preferencia bajo las condiciones de GMP (buenas prácticas de fabricación). Típicamente, se emplea una dosis terapéuticamente efectiva o una dosis eficaz del anticuerpo de enlace de C5 en las

composiciones farmacéuticas de la invención. Los anticuerpos de enlace de C5 se formulan en formas de dosificación farmacéuticamente aceptables mediante los métodos convencionales conocidos por los expertos en este campo. Los regímenes de dosificación se ajustan para proporcionar la respuesta óptima deseada (por ejemplo, una respuesta terapéutica). Por ejemplo, se puede administrar un solo bolo, se pueden administrar varias dosis divididas a través del tiempo, o la dosis se puede reducir o aumentar proporcionalmente, como sea indicado por las exigencias de la situación terapéutica. Es especialmente conveniente formular las composiciones parenterales en una forma unitaria de dosificación para una facilidad de administración y uniformidad de la dosificación. La forma unitaria de dosificación, como se utiliza en la presente, se refiere a unidades físicamente separadas adecuadas como dosificaciones unitarias para los sujetos que se vayan a tratar; cada unidad contiene una cantidad previamente determinada del compuesto activo, calculada para producir el efecto terapéutico deseado, en asociación con el vehículo farmacéutico requerido.

Los niveles de dosificación reales de los ingredientes activos en las composiciones farmacéuticas de la presente invención se pueden variar para obtener una cantidad del ingrediente activo que sea efectiva para lograr la respuesta terapéutica deseada para un paciente, composición, y modo de administración particulares, sin que sea tóxica para el paciente. El nivel de dosificación seleccionado depende de una variedad de factores farmacocinéticos, incluyendo la

actividad de las composiciones particulares de la presente invención empleadas, del éster, sal, o amida de las mismas, de la vía de administración, del tiempo de administración, de la velocidad de excreción del compuesto particular empleado, de la duración del tratamiento, de otros fármacos, compuestos y/o materiales utilizados en combinación con las composiciones particulares empleadas, de la edad, sexo, peso, condición, salud general e historia médica previa del paciente que se esté tratando, y factores similares.

Un médico o veterinario puede iniciar con dosis de los anticuerpos de la invención empleados en la composición farmacéutica en niveles más bajos que los requeridos para lograr el efecto terapéutico deseado, y se aumenta gradualmente la dosificación hasta que se logre el efecto deseado. En general, las dosis efectivas de las composiciones de la presente invención, para el tratamiento de un trastorno inflamatorio alérgico descrito en la presente, varían dependiendo de muchos factores diferentes, incluyendo el medio de administración, el sitio objetivo, el estado fisiológico del paciente, si el paciente es un ser humano o un animal, de otros medicamentos administrados, y si el tratamiento es profiláctico o terapéutico. Las dosificaciones de tratamiento se necesitan titular para optimizar la seguridad y la eficacia. Para la administración sistémica con un anticuerpo, la dosificación está en el intervalo de aproximadamente 0.0001 a 100 miligramos/kilogramo, y más usualmente de 0.01 a 15 miligramos/kilogramo del peso corporal del huésped. Un régimen de tratamiento de ejemplo implica la

administración sistémica una vez cada dos semanas, o una vez al mes, o una vez cada tres a seis meses. Para la administración intravítrea con un anticuerpo, la dosificación está en el intervalo de aproximadamente 0.0001 a aproximadamente 10 miligramos. Un régimen de tratamiento de ejemplo implica la administración sistémica una vez cada dos semanas, o una vez al mes, o una vez cada 3 a 6 meses.

El anticuerpo normalmente se administra en múltiples ocasiones. Los intervalos entre las dosificaciones individuales pueden ser semanales, mensuales, o anuales. Los intervalos también pueden ser irregulares, como sea indicado por la medición de los niveles en sangre del anticuerpo de enlace de C5 en el paciente. En algunos métodos de administración sistémica, la dosificación se ajusta para alcanzar una concentración del anticuerpo en plasma de 1 a 1,000 microgramos/mililitro, y en algunos métodos de 25 a 500 microgramos/mililitro. De una manera alternativa, el anticuerpo se puede administrar como una formulación de liberación sostenida, en cuyo caso, se requiere una administración menos frecuente. La dosificación y la frecuencia varían dependiendo de la vida media del anticuerpo en el paciente. En general, los anticuerpos humanizados muestran una vida media más larga que aquélla de los anticuerpos quiméricos y de los anticuerpos no humanos. La dosificación y frecuencia de administración pueden variar dependiendo de si el tratamiento es profiláctico o terapéutico. En las aplicaciones profilácticas, se administra una dosificación relativamente baja a

intervalos relativamente infrecuentes durante un largo período de tiempo. Algunos pacientes continúan recibiendo el tratamiento por el resto de sus vidas. En las aplicaciones terapéuticas, algunas veces se requiere una dosificación relativamente alta a intervalos relativamente cortos hasta que se reduzca o se termine el progreso de la enfermedad, y de preferencia hasta que el paciente muestre una aminoración parcial o completa de los síntomas de la enfermedad. Posteriormente, se puede administrar al paciente un régimen profiláctico.

6. EJEMPLOS

Los siguientes Ejemplos se proporcionan para ilustrar adicionalmente la invención, pero no para limitar su alcance. Otras variantes de la invención serán fácilmente evidentes para un experto ordinario en la técnica, y están abarcadas por las reivindicaciones adjuntas.

Ejemplo 1: Generación de C5 de cinomolgo y de C5 humana.

1. Generación de C5 de cinomolgo.

Se purificó la C5 de cinomolgo con éxito a partir de suero de cinomolgo mediante cromatografía de afinidad, utilizando la IgG1 hu MOR07086. Se probó la calidad de la C5 de cinomolgo mediante SDS-PAGE, Western blot, espectrometría de masas, y ensayos hemolíticos. Se demostró que la calidad de la C5 de cinomolgo purificada es alta mediante SDS-PAGE y Western blot. La falta de contaminación con C3 se confirmó mediante SDS y Western blot. En adición, se determinó la identidad de la secuencia de C5 de

cinomolgo mediante el análisis espectrométrico de masas, y se probó la actividad de la C5 de cinomolgo purificada en ensayos hemolíticos. En los ensayos hemolíticos, la nueva preparación fue equipotente con la C5 humana (por ejemplo, la Muestra 6, que se utilizó en los paneos de maduración de afinidad, reconstituyó la actividad del complemento del suero agotado en C5 humana al 20 por ciento con una actividad similar a la C5 humana purificada).

2. Control de calidad de las proteínas C5 humana y de cinomolgo biotiniladas y no biotiniladas.

Se caracterizó la bioactividad de la C5 humana purificada, y se confirmó mediante la actividad hemolítica de la senda alternativa. Se salpicó C5 en el suero humano agotado de C5 en diferentes concentraciones para obtener una EC_{50}. Los valores EC_{50} en el intervalo de entre 0.02 y 0.1 nM se consideraron aceptables.

Antes de utilizarse, se probó la bioactividad de cada lote de proteína C5 humana purificada en el ensayo hemolítico. Se hizo el mismo control de calidad para la C5 de cinomolgo después de la purificación a partir de suero de cinomolgo. Después de la biotinilación de la C5 humana y de cinomolgo, también se probó la bioactividad del material en ensayos hemolíticos, con el objeto de analizar si había una pérdida de actividad causada por la biotinilación.

Ejemplo 2. Generación de anticuerpos específicos de C5 a partir de la biblioteca HuCAL GOLD®.

Se generaron anticuerpos de C5 mediante la selección de los

clones que tuvieran altas afinidades de enlace, utilizando como la fuente de las proteínas variantes de anticuerpo, una biblioteca de exhibición de fagos comercialmente disponible, la biblioteca MorphoSys HuCAL GOLD®.

La biblioteca HuCAL GOLD® es una biblioteca de Fab (Knappik y colaboradores, 2000), en donde las seis regiones determinantes de complementariedad están diversificadas mediante mutaciones apropiadas, y la cual emplea la tecnología CysDisplay^{MR} para enlazar el Fab a la superficie del fago (Publicación Internacional Número WO WO01/05950, Löhning y colaboradores, 2001).

1. Selección mediante paneo de anticuerpos específicos de C5 a partir de la biblioteca.

Para la selección de los anticuerpos contra C5, se aplicaron dos estrategias de paneo diferentes. Las seis diferentes reservas se sometieron individualmente a tres rondas de: (a) un paneo en fase sólida, en donde los antígenos (C5 humana y de cinomolgo) se recubrieron directamente sobre placas de microtitulación Maxisorp de 96 pozos (Nunc, Wiesbaden, Alemania); o (b) un paneo en solución con la C5 humana y de cinomolgo biotinilada, en donde se capturó el complejo de fago-antígeno mediante perlas magnéticas de estreptavidina (Dynabeads M-280; Dynal) para cada reserva de paneo.

La biblioteca HuCAL GOLD® se amplificó en un medio 2xYT que contenía 34 microgramos/mililitro de cloranfenicol y glucosa al 1 por ciento (2xYT-CG). Después de la infección con el fago auxiliar

VCSM13 a una OD_{600nm} de 0.5 (30 minutos a 37°C sin agitación; 30 minutos a 37°C con agitación a 250 revoluciones por minuto), las células se centrifugaron (4,120 gramos; 5 minutos; 4°C), se volvieron a suspender en 2xYT/34 microgramos/mililitro de cloranfenicol/50 microgramos/mililitro de canamicina/IPTG 0.25 mM, y se cultivaron durante la noche a 22°C. Los fagos se precipitaron en PEG a partir del sobrenadante, se volvieron a suspender en suero regulado con fosfato/glicerol al 20 por ciento, y se almacenaron a -80°C. La amplificación de fagos entre dos rondas de paneo se condujo como sigue: las células de *E. coli* TG1 en fase mid-log se infectaron con el fago eluido, y se aplicaron sobre ágar-LB complementado con el 1 por ciento de glucosa y 34 microgramos/mililitro de cloranfenicol (placas LB-CG). Después de la incubación durante la noche a 30°C, se rasparon las colonias de TG1 de las placas de ágar, y se utilizaron para inocular el 2xYT-CG hasta que se alcanzó una OD_{600nm} de 0.5. Se agregaron fagos auxiliares VCSM13 para la infección, como se describe anteriormente.

Tomados juntos, se secuenciaron 354 clones derivados a partir de todas las estrategias de paneo, dando como resultado 64 clones únicos con el perfil deseado: que se enlazan con la C5 humana y de cinomolgo y que no se enlazan con los contra-objetivos C3 y C4.

Se seleccionaron 45 clones derivados a partir de los paneos en fase sólida, y 19 clones a partir de los paneos en solución, para la expresión y purificación de la proteína. Cuatro Fabs a partir de los paneos en fase sólida (MOR06525, MOR06756, MOR06757 y

MOR06763) y 6 Fabs a partir de los paneos en solución (MOR07086, MOR07087, MOR07091, MOR07092, MOR07093 y MOR07094) entraron a la maduración de afinidad.

Paneo en fase sólida contra C5 sobre la proteína directamente recubierta

La primera variante de paneo fue el paneo en fase sólida alternando la C5 humana (primera y tercera rondas de selección) y la C5 de cinomolgo (segunda ronda de selección).

Tres pozos de una placa Maxisorp (F96 Nunc-Immunoplate) se recubrieron con 200 microlitros de C5 50 nM cada uno durante la noche a 4°C. Los pozos recubiertos se lavaron dos veces con 400 microlitros de suero regulado con fosfato, y se bloquearon con 350 microlitros de MPBS al 5 por ciento durante 2 horas a temperatura ambiente sobre un agitador de placas de microtitulación. Para cada paneo, se bloquearon aproximadamente 10^{13} fagos-anticuerpos HuCAL GOLD® con un volumen igual de PBST/polvo de leche al 5 por ciento durante 2 horas a temperatura ambiente. Los pozos recubiertos se lavaron dos veces con 400 microlitros de suero regulado con fosfato después del procedimiento de bloqueo. Se agregaron 200 microlitros de fagos-anticuerpos HuCAL GOLD® previamente bloqueados a cada pozo recubierto, y se incubaron durante 2 horas a temperatura ambiente sobre un agitador. El lavado se llevó a cabo mediante la adición de cinco veces 350 microlitros de suero regulado con fosfato/Tween al 0.05 por ciento, seguido por lavado otras cinco veces con suero regulado con fosfato. Para

algunas condiciones de paneo, se aplicó un procedimiento de lavado más restringente.

La elución del fago a partir de la placa se llevó a cabo con 200 microlitros de DTT 20 mM en Tris/HCl 10 mM, pH de 8, por pozo, durante 10 minutos. El eluato de fago-DTT se agregó a 15 mililitros de TG1 de *E. coli*, que se cultivaron a una OD_{600} de 0.6 a 0.8 a 37°C en un medio 2YT, y se incubó en tubos de plástico de 50 mililitros durante 45 minutos a 37°C sin agitación para la infección del fago. Después de la centrifugación durante 5 minutos a 4,120 x g, cada gránulo bacteriano se volvió a suspender en 600 microlitros del medio 2xYT, se aplicó sobre placas de ágar 3xYT-CG, y se incubó durante la noche a 37°C. Las colonias se rasparon de las placas, y se rescataron los fagos y se amplificaron como se describe anteriormente.

Las segunda y terca rondas de paneo en fase sólida se llevaron a cabo de acuerdo con el protocolo de la primera ronda. En la segunda ronda de selección para algunas condiciones de paneo, se utilizó la producción de la primera ronda para las selecciones sobre C5 de cinomolgo, con el objeto de enriquecer los anticuerpos de reacción cruzada de cinomolgo.

Para algunas condiciones de paneo, se aumentó la restringencia de lavado, y se disminuyó la concentración de antígeno dentro de la tercera ronda de selección, con el objeto de generar anticuerpos de alta afinidad.

Se utilizó la biblioteca de fagémidos HuCAL GOLD® para

seleccionar los fragmentos de anticuerpos Fab específicos contra la C5 humana. La primera estrategia fue un paneo en fase sólida sobre la proteína C5 humana directamente recubierta (procedimiento de paneo descrito anteriormente).

Después de la tercera ronda de paneo, las reservas de fagos enriquecidas se subclonaron a partir del vector de la biblioteca pMORPH®23 (que permite la exhibición eficiente del anticuerpo sobre la superficie del fago (en el vector de expresión pMORPH®x9_Fab_MH, que media la expresión periplásmica de los Fabs solubles. Se recogieron los clones individuales, y los Fabs solubles se expresaron a partir de estos clones individuales.

En total, se analizaron 6,624 clones en el rastreo primario, el cual se llevó a cabo mediante el enlace de los Fabs directamente a partir de los lisados bacterianos a la C5 humana inmovilizada sobre placas de microtitulación Maxisorp. Se obtuvieron 1,660 impactos a partir del rastreo primario sobre la C5 humana, con señales >5 veces sobre el fondo. Además se analizaron 384 impactos en un rastreo secundario para confirmar el enlace sobre la C5 humana, y para rastrear el enlace a los contra-objetivos de C3 y C4 humanas.

Se pudieron confirmar muchos impactos primarios sobre la C5 humana, y no mostraron reactividad cruzada con las C3 y C4 humanas, sino que solamente seis Fabs tuvieron una débil reactividad cruzada con la C5 de cinomolgo.

Como una primera consecuencia, se llevaron a cabo nuevos paneos en fase sólida, alternando sobre la C5 humana y de

cinomolgo. En paralelo, los controles de calidad del lote de C5 de cinomolgo purificado revelaron una alta cantidad de C3 de cinomolgo con el lote de C5 de cinomolgo. Considerando estos resultados, se aplicó un nuevo método para rastrear los anticuerpos que reaccionan cruzadamente con cinomolgo. Se capturó la C5 de cinomolgo a partir de suero de cinomolgo, utilizando un anticuerpo policlonal de enlace de C5 (véase el Ejemplo 3, sección 3). Empleando este método, los impactos primarios iniciales se rastrearon nuevamente sobre la C5 de cinomolgo, y se confirmaron 56 clones para el enlace con la C5 de cinomolgo.

Para los paneos en fase sólida alternados, se utilizó la producción de la primera ronda de los doce paneos en fase sólida humanos de más éxito, para las secciones sobre C5 de cinomolgo (lote de proteína contaminado con C3 de cinomolgo; no se sabía durante los paneos). Se confirmaron 376 clones en un rastreo secundario para determinar el enlace con la C5 humana, y 365 clones para determinar el enlace con la C5 de cinomolgo capturada a partir del suero de cinomolgo.

Paneo en solución sobre la proteína C biotinilada

La segunda variante de paneo fue el paneo en solución contra la C5 humana biotinilada y la C5 de cinomolgo biotinilada biológicamente activas (en ensayos hemolíticos).

Para este paneo, se lavaron 200 microlitros de perlas magnéticas de estreptavidina (Dynabeads M-280; Dynal) una vez con suero regulado con fosfato, y se bloquearon con el Chemiblocker

durante 2 horas a temperatura ambiente. Se bloquearon 300 microlitros de los fagos diluidos en suero regulado con fosfato, también con el Chemiblocker, durante 1 a 2 horas a temperatura ambiente sobre un rotador. Los fagos bloqueados se pre-adsorbieron dos veces contra 50 microlitros de perlas magnéticas de estreptavidina bloqueadas durante 30 minutos. El sobrenadante de fagos se transfirió a un nuevo tubo de reacción de 2 mililitros bloqueado, y se agregó la C5 biotinilada humana, y se incubó durante 1 hora a temperatura ambiente sobre un rotador. Se agregaron 100 microlitros de las perlas magnéticas de estreptavidina bloqueadas a cada reserva de paneo, y se incubaron durante 10 minutos sobre un rotador. Las perlas se recolectaron con un separador de partículas (Dynal MPC-E) durante aproximadamente 2.5 minutos, y la solución se removió cuidadosamente.

Luego las perlas se lavaron siete veces en suero regulado con fosfato/Tween al 0.05 por ciento, utilizando un rotador, seguido por lavado otras tres veces con suero regulado con fosfato. La elución de los fagos a partir de las Dynabeads se llevó a cabo mediante la adición de 200 microlitros de DTT 20 mM en Tris/HCl 10 mM, pH de 8, a cada tubo, y la incubación durante 10 minutos. Las Dynabeads se removieron mediante el separador de partículas magnéticas, y se agregó el sobrenadante a 15 mililitros de un cultivo de TG-1 de *E. coli* cultivado a una OD_{600nm} de 0.6 a 0.8. Luego las perlas se lavaron una vez con 200 microlitros de suero regulado con fosfato, y, junto con los fagos adicionalmente removidos, se agregó el suero regulado

con fosfato a los 15 mililitros de TG-1 de *E. coli*. Para la infección de los fagos, el cultivo se incubó en tubos de plástico de 50 mililitros durante 45 minutos a 37°C sin agitación. Después de la centrifugación durante 5 minutos a 4,120 x g, los gránulos bacterianos se volvieron a suspender cada uno en 600 microlitros del medio 2xYT, se aplicaron sobre placas de ágar 3xYT-CG, y se incubaron durante la noche a 37°C. Las colonias se rasparon de las placas, y los fagos se rescataron y se amplificaron como se describe anteriormente. Las segunda y tercera rondas de selección se llevaron a cabo de una manera idéntica a la primera ronda de selección.

Una estrategia de paneo adicional fue el paneo en solución utilizando la C5 humana, y alternando la C5 humana y de cinomolgo (lote de proteína contaminado con C3 de cinomolgo; no se sabía durante los paneos). Por consiguiente, las proteínas se biotinilaron, y se confirmó la bifuncionalidad retenida después del procedimiento de biotinilación en los bioensayos hemolíticos.

El complejo de fago-antígeno se capturó sobre perlas magnéticas de estreptavidina por medio de la fracción de biotina del antígeno. Después del lavado, solamente se eluyeron los fagos enlazados específicos (procedimiento de paneo descrito anteriormente).

El primer rastreo se hizo sobre las proteínas directamente recubiertas (véase el Ejemplo 3, sección 1), y solamente se pudieron confirmar 80 clones sobre la C5 humana. Debido al hecho de que,

durante los paneos, el antígeno se mantuvo en solución, se desarrolló un nuevo método de rastreo. En un ELISA en solución, los Fabs se incubaron con el antígeno biotinilado sobre una placa de NeutrAvidin. Utilizando este procedimiento de rastreo en solución, se pudo seleccionar una cantidad significativamente más alta de clones específicos de C5 humana y de cinomolgo. Estos resultados confirmaron que muchos Fabs derivados a partir de los paneos en solución reconocen la C5 solamente en solución, o cuando se captura (por ejemplo, por medio de un anticuerpo de enlace de C5 policlonal).

2. Subclonación y expresión de los fragmentos Fab seleccionados.

Para facilitar la expresión rápida de los Fabs solubles, los insertos que codificaban Fab de los fagos HuCAL GOLD® seleccionados, se subclonaron por medio de XbaI y EcoRI en el vector de expresión de *E. coli* pMORPH®x9_MH. Los fragmentos Fab llevan una marca Myc C-terminal, y como una segunda marca C-terminal, la marca-His 6x (Chen y colaboradores, Gene 139:73-75 (1994)). Después de la transformación de los plásmidos de expresión en las células TG1 F de *E. coli*, se recogieron los clones individuales resistentes al cloranfenicol en los pozos de una placa de microtitulación estéril de 384 pozos previamente llenada con 600 microlitros del medio 2xYT-CG, y se cultivaron durante la noche a 30°C. Se transfirieron 5 microlitros de cada cultivo nocturno de TG-1 de *E. coli* a una placa de microtitulación fresca estéril de 96 pozos

previamente llenada con 40 microlitros del medio 2xYT complementados con 34 microlitros/mililitro de cloranfenicol por pozo. Las placas de microtitulación se incubaron a 30°C, agitando a 400 revoluciones por minuto sobre un agitador de microplacas, hasta que los cultivos estuvieron ligeramente turbios (de aproximadamente 2 a 4 horas) con una OD_{600nm} de aproximadamente 0.5. A estas placas de expresión, se les agregaron 10 microlitros del medio 2xYT complementado con 34 microgramos/mililitro de cloranfenicol e IPTG 3 mM (isopropil-β-D-tiogalactopiranosida) por pozo (concentración final de IPTG 0.5 mM). Las placas de microtitulación se sellaron con una cinta permeable al gas, y se incubaron durante la noche a 30°C, agitando a 400 revoluciones por minuto. A cada pozo de las placas de expresión, se le agregaron 15 microlitros del regulador BEL que contenía 2.5 miligramos/mililitro de lisozima, EDTA 4 mM, y 10 unidades/microlitro de benzonasa, y se incubaron durante 1 hora a 22°C sobre un agitador de placas de microtitulación (400 revoluciones por minuto), seguido por un paso de congelación opcional durante cuando menos 2 horas a -80°C. Los extractos de BEL se utilizaron para los análisis de enlace mediante ELISA o rastreo de Fab SET después de la maduración de afinidad.

La expresión de los fragmentos Fab codificados por pMORPH®x9_Fab_MH en las células TG-1, se levó a cabo en cultivos en matraces de agitación, utilizando 750 mililitros del medio 2xYT complementado con 34 microgramos/mililitro de cloranfenicol. Los cultivos se agitaron a 30°C hasta que la OD_{600nm} alcanzó 0.5. La

expresión se indujo mediante la adición de IPTG 0.75 mM durante 20 horas a 30°C. Las células se alteraron utilizando la lisozima y los fragmentos Fab aislados mediante cromatografía de Ni-NTA (Qiagen, Hilden, Alemania). El intercambio de regulador hasta el suero regulado con fosfato de Dulbecco 1x (pH de 7.2) se llevó a cabo utilizando las columnas PD10. Las muestras se filtraron estériles (0.2 micras, Millipore). La pureza de las muestras se determinó en un estado reducido y desnaturalizado mediante SDS-PAGE (Criterion Gels al 15 por ciento, BioRad), y en el estado nativo mediante cromatografía por exclusión de tamaños (HP-SEC). Las concentraciones de proteína se determinaron mediante espectrofotometría ultravioleta (Krebs y colaboradores, J. Immunol. Methods 254:67-84 (2001)).

Al nivel del Fab, los índices de expresión globales y los porcentajes de fracción monomérica en la SEC (Cromatografía por Exclusión de Tamaños), estuvieron en un intervalo desde aceptable hasta bueno para la mayor parte de los fragmentos de anticuerpo identificados. Se expresaron 64 Fabs progenitores, y se pudieron purificar 61 Fabs. Se purificaron 60 Fabs madurados por afinidad en la escala de miligramos. La mayoría de los Fabs fueron buenos expresadores y no tuvieron tendencia a la acumulación.

Ejemplo 3: Identificación de los anticuerpos específicos de C5 a partir de la biblioteca HuCAL GOLD®.

En seguida, cuatro diferentes métodos de ensayo inmunosorbente enlazado con enzimas (ELISA) describen el rastreo

de los anticuerpos de enlace de C5 (como los lisados BEL bacterianos o los Fabs purificados) sobre antígenos específicos y contra-antígenos.

1. Rastreo sobre la proteína directamente recubierta.

Las placas Maxisorp (Nunc, Rochester, NY, EUA) de 384 pozos, se recubrieron con 20 microlitros por pozo de 2.5 microgramos/mililitro de antígeno (C5 humana, y las contra-proteínas de C3 y C4 humanas) en suero regulado con fosfato, pH de 7.4, durante la noche a 4°C. En paralelo, las placas se recubrieron con 20 microlitros por pozo de 5 microgramos/mililitro de IgG de oveja anti-humano, específica del fragmento Fd (The Binding Site, Birmingham, Reino Unido), diluido en suero regulado con fosfato, pH de 7.4, para verificar el nivel de expresión de Fab.

Las placas se bloquearon con suero regulado con fosfato/Tween 20 al 0.05 por ciento (PBST) conteniendo polvo de leche al 5 por ciento, durante 1 a 2 horas a temperatura ambiente. Después de lavar los pozos con PBST, se agregaron extractos de BEL, Fabs HuCAL GOLD® purificados, o Fabs de control diluidos en suero regulado con fosfato, y se incubaron durante 1 hora a temperatura ambiente. Para detectar el enlace de Fab, se aplicó el anticuerpo anti-HIS6 acoplado con peroxidasa (Roche).

Para la detección de los conjugados de POD, se utilizó el sustrato fluorogénico QuantaBlu (Pierce), de acuerdo con las instrucciones del fabricante. Entre todos los pasos de incubación, los pozos de las placas de microtitulación se lavaron tres veces y cinco

veces con PBST después de la incubación final con el anticuerpo secundario. La fluorescencia se midió en un lector de placas Tecan GENios Pro.

2. Rastreo en solución con las proteínas biotiniladas.

El método ELISA descrito más adelante se utilizó para el rastreo de los Fabs HuCAL GOLD®, después de los paneos en solución, utilizando proteínas de complemento biotiniladas.

Las placas NeutrAvidin se bloquearon con el Chemiblocker 1x (Chemicon) diluido en suero regulado con fosfato durante la noche a 4°C. Estas placas se utilizaron para rastrear el enlace a la C5 humana y a los contra-objetivos de C3 y C4. En paralelo, las placas Maxisorp de 384 pozos (Nunc, Rochester, NY, EUA) se recubrieron con 20 microlitros por pozo de 5 microgramos/mililitro de IgG de oveja anti-humano, específica del fragmento Fd (The Binding Site, Birmingham, Reino Unido), diluida en suero regulado con fosfato, pH de 7.4. Estas placas se utilizaron para verificar los niveles de expresión de Fab y el enlace de biotina no específico. Al día siguiente, las placas Maxisorp recubiertas se lavaron dos veces con PBST, y se bloquearon con albúmina de suero bovino al 3 por ciento en PBS durante 1 a 2 horas a temperatura ambiente. Los extractos de BEL periplásmicos que contenían los Fabs, o los Fabs HuCAL GOLD® purificados, se agregaron a las placas tanto de NeutrAvidin bloqueadas como Maxisorp.

Subsiguientemente, se agregaron 20 microlitros por pozo de la C5 humana biotinilada (para detectar el enlace específico), y en

paralelo, se agregaron la C3 y la C4 humanas biotiniladas (para detectar el enlace indeseado) a los pozos de las placas NeutrAvidin. Los antígenos biotinilados se incubaron con los Fabs HuCAL GOLD® durante 1 a 2 horas a temperatura ambiente. Luego se agregó la transferrina de antígeno no relacionado biotinilado a las placas Maxisorp, para verificar los Fabs que se enlazan con biotina (en este caso, los fragmentos Fab HuCAL® se capturaron previamente mediante el anticuerpo anti-Fd).

En seguida de que se aplicaron los anticuerpos secundarios para la detección: se agregó el fragmento $F(ab')_2$ de cabra anti-humano AffiniPure de Estreptavidina-AP conjugado con fosfatasa alcalina 8AP), a las placas de expresión Maxisorp; se agregó el anticuerpo de ratón conjugado con peroxidasa anti-HIS6, Roche a las placas NeutrAvidin, y se agregó Estreptavidina-Fosfatasa Alcalina, ZYMED, a las placas Maxisorp con la transferrina biotinilada.

Para la detección de los conjugados-AP, se utilizó el sustrato AttoPhos (Roche Diagnostics, Mannheim, Alemania), y para la detección de los conjugados-POD, se utilizó el sustrato fluorogénico QuantaBlu (Pierce), de acuerdo con las instrucciones del fabricante. La fluorescencia se midió en un lector de placas Tecan GENios Pro.

Empleando este método, fue posible rastrear los Fabs de C5 anti-humanos que reconocen la C5 humana en solución, y excluir los anticuerpos que se enlazaban a la fracción de biotina de los antígenos objetivo.

3. Determinación de la reactividad cruzada con la C5 de

cinomolgo.

Se utilizó un anticuerpo de enlace de C5 policlonal (US Biological Cat. #C7650-24) para capturar la C5 de cinomolgo a partir de suero de cinomolgo.

Las placas Maxisorp de 384 pozos se recubrieron con 20 microlitros/pozo de 5 microgramos/mililitro de anticuerpo de enlace de C5 policlonal en suero regulado con fosfato, y se incubaron durante la noche a 4°C. Al día siguiente, las placas se lavaron tres veces con PBST, y se bloquearon con 100 microlitros/pozo de diluyente (albúmina de suero bovino al 4 por ciento/Tween 20 al 0.1 por ciento/Triton-X 100 al 0.1 por ciento/suero regulado con fosfato) durante 2 horas a temperatura ambiente. El suero de cinomolgo se diluyó a 1:20 en diluyente (albúmina de suero bovino al 4 por ciento/Tween 20 al 0.1 por ciento/Triton-X 100 al 0.1 por ciento/suero regulado con fosfato) (concentración aproximada de C5 de cinomolgo de 4 microgramos/mililitro), y se agregaron 20 microlitros/pozo a las placas Maxisorp lavadas con PBST dos veces. Después de 1 hora de incubación a temperatura ambiente, las placas se lavaron tres veces con PBST, y se agregaron los lisados BEL que contenían los fragmentos Fab o los Fabs purificados, y se incubaron durante 1 hora a temperatura ambiente. Las placas se lavaron nuevamente, y se agregó el anticuerpo de detección anti-HIS6-POD (Roche #1965085). Se agregó el sustrato POD, BM Blue, soluble (Roche Applied Science), y la reacción se detuvo con H_2SO_4 1M. La absorbencia se leyó a 450 nanómetros, utilizando el dispositivo BMG Reader.

Ejemplo 4: Maduración de afinidad.

1. Construcción de bibliotecas de maduración de afinidad de los Fabs de enlace de C5 seleccionados.

Con el objeto de aumentar la afinidad y la actividad biológica de los fragmentos de anticuerpo seleccionados, se optimizaron las regiones L-CDR3 y H-CDR2 en paralelo mediante mutagénesis de casete, utilizando mutagénesis dirigida al trinucleótido (véase, por ejemplo, Virnekas y colaboradores, Nucleic Acids Res. 22:5600-5607 (1994)), mientras que las regiones de estructura se mantuvieron constantes. Antes de la clonación para la maduración de afinidad, todos los fragmentos Fab progenitores se transfirieron desde el vector de expresión correspondiente (pMORPH®x9_MH) hasta el vector pMORPH®25 CysDisplay^{MR} por medio de XbaI/EcoRI. pMORPH®25 se creó a partir del vector pMORPH®23 de exhibición de HuCAL GOLD® mediante la remoción de un sitio BssHII que interfería con la clonación de la biblioteca, para la optimización de la H-CDR2. Para la optimización de la L-CDR3 de los Fabs progenitores, se removieron la L-CDR3, la estructura 4, y la región constante de las cadenas ligeras (405 pares de bases) de los enlazadores mediante BpiI/SphI, y fueron reemplazadas por un repertorio de L-CDR3s diversificadas, junto con la estructura 4 y el dominio constante.

Diez Fabs de enlace de C5 progenitores se dividieron en siete reservas de acuerdo con diferentes criterios de selección, y solamente se pusieron juntos los Fabs con la misma estructura: (1)

MOR07086; (2) MOR06525 + 6756 (la misma estructura); (3) MOR06757; (4) MOR06763; (5) MOR07087; (6) MOR07091 + 7092 (la misma estructura); (7) MOR07093 + 7094 (la misma estructura).

Aproximadamente 1.5 microgramos del fragmento del vector de Fab individual y de la reserva de Fab se ligaron con un exceso molar de 3 a 5 veces del fragmento de inserto que llevaba las L-CDR3s diversificadas. En un segundo establecimiento de la biblioteca, la H-CDR2 (XhoI/BssHII) se diversificó mientras que las regiones de estructura de conexión se mantuvieron constantes. Con el objeto de monitorear la eficiencia de la clonación, la H-CDR2 progenitora fue reemplazada por una falsa, antes de clonar el casete de H-CDR2 diversificado.

Las mezclas de ligamiento de las diferentes bibliotecas de electroporaron en células TOP10 F' de *E. coli* (Invitrogen), proporcionando de $2x10^7$ a $2x10^8$ colonias independientes. Las bibliotecas se amplificaron. Para el control de calidad, se recogieron al azar varios clones individuales por biblioteca, y se secuenciaron utilizando los cebadores CFR84 (VL) y OCAL_Seq_Hp (VH).

Como se describe anteriormente, se generaron siete sub-reservas de maduración, y se mantuvieron separadas durante el siguiente proceso de selección.

Se generaron 14 bibliotecas de maduración de afinidad diferentes (una biblioteca de LCDR3 y una biblioteca de HCDR3 para cada reserva) mediante procedimientos de clonación convencionales y la transformación de los clones diversificados en células TOP10 F'

de *E. coli* electro-competentes (Invitrogen). Los tamaños de las bibliotecas fueron buenos, en el intervalo de $2x10^7$ a $5x10^8$. La secuenciación de los clones aleatoriamente recogidos mostró una diversidad del 100 por ciento. No se encontraron enlazadores progenitores sino derivados de todos los enlazadores de entrada progenitores respectivos. Finalmente, se prepararon por separado los fagos de las 14 bibliotecas.

Tabla 2

Panorama de las bibliotecas de maduración

MOR0	Maduración	Tipo de VH/VL	Tamaño de Biblioteca
6757	HCDR2	VH3	3.70X10E7
6763	HCDR2	VH3	4.96X10E7
7086	HCDR2	VH1A	1.58X10E8
7087	HCDR2	VH1A	7.85x10E7
6525 + 6756	HCDR2	VH5	5.22x10E7
7091 + 7092	HCDR2	VH5	3.51x10E7
7093 + 7094	HCDR2	VH2	2.01x10E7
5767	LCDR3	Vkappa1	1.89x10E7
6763	LCDR3	Vlambda2	7.35x10E7

MOR0	Maduración	Tipo de VH/VL	Tamaño de Biblioteca
7086	LCDR3	Vlambda3	7.54x10E7
7087	LCDR3	Vkappa1	5.46x10E7
6525 + 6756	LCDR3	Vlambda2	8.50x10E7
7091 + 7092	LCDR3	Vlambda3	4.93x10E8
7093 + 7094	LCDR3	Vlambda2	1.33x10E8

2. Preparación de anticuerpos-fagos para la maduración de afinidad.

Las bibliotecas de maduración HuCAL® se amplificaron en un medio 2xYT conteniendo 34 microgramos/mililitro de cloranfenicol, y glucosa al 1 por ciento (2xYT-CG). Después de la infección con el fago auxiliar VCSM13 a una OD_{600nm} de 0.5 (30 minutos a 37°C sin agitación; 30 minutos a 37°C agitando a 250 revoluciones por minuto), las células se centrifugaron (4,120 x g; 5 minutos; 4°C), se volvieron a suspender en 2xYT/34 microgramos/mililitro de cloranfenicol/50 microgramos/mililitro de canamicina/IPTG 0.25 mM, y se cultivaron durante la noche a 22°C. Los fagos se precipitaron en PEG dos veces a partir del sobrenadante, se volvieron a suspender en suero regulado con fosfato, y se utilizaron para los paneos de maduración descritos en seguida

3. Paneo de maduración en solución estándar sobre la

proteína C biotinilada.

Aproximadamente 10^{12} fagos rescatados a partir de las bibliotecas de maduración de afinidad generadas, como se describen anteriormente, se sometieron a paneos llevados a cabo bajo condiciones muy restringentes para seleccionar los Fabs específicos de C5 mejorados en afinidad.

Los paneos en solución utilizando las reservas de fagos respectivas se llevaron a cabo ya sea utilizando la C5 humana biotinilada, o bien alternando las proteínas C5 humana y de cinomolgo biotiniladas. Con el objeto de aumentar la restringencia del paneo, y de seleccionar mejores índices, se disminuyó la concentración de antígeno, y se aplicaron períodos de lavado prolongados (las condiciones de lavado se enlistan en la Tabla 3).

Tabla 3

Incremento en las condiciones de lavado dentro de las rondas de selección de los paneos de maduración en solución

Ronda de selección	Condiciones de lavado (modificadas: restringentes)
Primera ronda	• 4x suero regulado con fosfato/Tween al 0.05 por ciento, 5 minutos, sobre un rotador. • 3x suero regulado con fosfato/Tween al 0.05 por ciento, 15 minutos, sobre un rotador → se transfieren las perlas magnéticas con el antígeno y los fagos capturados a un tubo bloqueado

Ronda de selección	Condiciones de lavado (modificadas: restringentes)
	fresco. • 4x suero regulado con fosfato rápido. • 3x suero regulado con fosfato 5 minutos sobre el rotador → se transfieren las perlas magnéticas con el antígeno y los fagos capturados a un tubo bloqueado fresco.
Segunda ronda	• 3x suero regulado con fosfato/Tween al 0.05 por ciento, rápido. • 7x suero regulado con fosfato/Tween al 0.05 por ciento, 15 minutos sobre el rotador → se transfieren las perlas magnéticas con el antígeno y los fagos capturados a un tubo bloqueado fresco. • 3x suero regulado con fosfato rápido. • 7x suero regulado con fosfato, 15 minutos sobre el rotador → se transfieren las perlas magnéticas con el antígeno y los fagos capturados a un tubo bloqueado fresco.
Tercera ronda	• 5x suero regulado con fosfato/Tween al 0.05 por ciento rápido. • 8x suero regulado con fosfato/Tween al 0.05 por

Ronda de selección	Condiciones de lavado (modificadas: restringentes)
	ciento, 15 minutos sobre el rotador. • 1x suero regulado con fosfato/Tween al 0.05 por ciento durante la noche sobre el rotador. • 3x suero regulado con fosfato/Tween al 0.05 por ciento, rápido. • 6x suero regulado con fosfato/Tween al 0.05 por ciento, 15 minutos sobre el rotador → se transfieren las perlas magnéticas con el antígeno y los fagos capturados a un tubo bloqueado fresco. • 5x suero regulado con fosfato, rápido. • 8x suero regulado con fosfato, 15 minutos sobre el rotador → se transfieren las perlas magnéticas con el antígeno y los fagos capturados a un tubo bloqueado fresco.

Los fagos previamente bloqueados (mezcla de 1:2 con Chemiblocker 2x incubada durante 1 hora a temperatura ambiente) se incubaron con una baja concentración de proteína C5 biotinilada durante 1 a 2 horas a temperatura ambiente. La estrategia de paneo es similar al paneo en solución estándar descrito anteriormente. El complejo de fago-antígeno se capturó por medio de la fracción de

biotina de C5 a las perlas magnéticas de estreptavidina previamente bloqueadas durante 30 minutos a temperatura ambiente. Luego las perlas se lavaron más restringentemente, comparándose con un paneo normal. La elución y la amplificación de los fagos se llevó a cabo como se describe anteriormente.

Las segunda y tercera rondas de selección se llevaron a cabo de una manera idéntica a la primera ronda, pero en condiciones de lavado de más alta restringencia y en concentraciones de antígeno más bajas. Para cada reserva de anticuerpos, se llevaron a cabo varios paneos diferentes. Para cada estrategia de paneo, se aplicaron diferentes condiciones de restringencia. Las estrategias de paneo se resumen en la Tabla 4.

Tabla 4

Panorama de los paneos de maduración en solución 1783 y 1784 sobre C5 humana biotinilada y C5 de cinomolgo biotinilada

Paneo #	Biblioteca	Modo de paneo	Antígeno Primera Ronda	Antígeno Segunda Ronda	Antígeno Tercera Ronda	Concentración de antígeno	Lavado
1783.1	MOR06525 + 6756 HCDR2	Perlas de Estrepta-vidina en solución	C5 humano	C5 humano	C5 humano	humano 50nM/5nM humano/ humano 0.25nM	modificado (más restringente)
1783.2	MOR07086 HCDR2						
1783.3	MOR06763 HCDR2						

Paneo #	Biblioteca	Modo de paneo	Antígeno Primera Ronda	Antígeno Segunda Ronda	Antígeno Tercera Ronda	Concentración de antígeno	Lavado
1783.4	MOR07087 HCDR2						
1783.5	MOR06525 + 6756 LCDR3						
1783.6	MOR07086 LCDR3						
1783.7	MOR06763 LCDR3						
1783.8	MOR07087 LCDR3						
1783.9	MOR06525 + 6756 HCDR2	Perlas de Estreptavidina en solución	C5 humano	C5 de cinomolgo	C5 humano	humano 25nM/cinomolgo 5nM/ humano 0.25nM	modificado (más restringente)
1783.10	MOR07086 HCDR2						
1783.11	MOR06763 HCDR2						
1783.12	MOR06525 + 6756 LCDR3						

Paneo #	Biblioteca	Modo de paneo	Antígeno Primera Ronda	Antígeno Segunda Ronda	Antígeno Tercera Ronda	Concentración de antígeno	Lavado
1783.13	MOR07086 LCDR3						
1783.14	MOR06763 LCDR3						
1784.1	MOR06757 HCDR2	Perlas de Estreptavidina en solución	C5 humano	C5 humano	C5 humano	humano 50nM/humano 5nM/humano 0.25nM	modificado (más restringente)
1784.2	MOR07091 + 7092 HCDR2						
1784.3	MOR07093 + 7094 HCDR2						
1784.4	MOR06757 LCDR3						
1784.5	MOR07091 + 7092 LCDR3						
1784.6	MOR07093 + 7094 LCDR3						
1784.7	MOR06757	Perlas de	C5	C5 de	C5	humano	modifi-

Paneo #	Biblioteca	Modo de paneo	Antígeno Primera Ronda	Antígeno Segunda Ronda	Antígeno Tercera Ronda	Concentración de antígeno	Lavado
	HCDR2	Estreptavidina en solución	humano	cinomolgo	humano	25nM/cinomolgo 5nM/humano 0.25nM	cado (más restringente)
1784.8	MOR07091 + 7092 HCDR2						
1784.9	MOR07093 + 7094 HCDR2						
1784.10	MOR07087 HCDR2						
1784.11	MOR06757 LCDR3						
1784.12	MOR07091 + 7092 LCDR3						
1784.13	MOR07093 + 7094 LCDR3						
1784.14	MOR07087 LCDR3						

Después de los paneos de maduración, las reservas de fagémidos enriquecidos se sub-clonaron en el vector de expresión pMORPH®x9_MH.

4. Combinación cruzada de VL optimizada (L-CDR3) con VH optimizada (H-CDR2).

Para una mejora adicional de la afinidad y la potencia, se combinaron las cadenas pesada y ligera independientemente optimizadas a partir de los anticuerpos madurados, derivados a partir del mismo clon progenitor (véanse, por ejemplo, Rauchenberger y colaboradores, J. Biol. Chem. 278:38194-38205 (2003); Chen y colaboradores, J. Mol. Biol. 293:865-881 (1999); y Schier y colaboradores, J. Mol. Biol. 263:551-567 (1996)). Este procedimiento, denominado como clonación cruzada, se aplicó para los enlazadores derivados a partir de los mismos clones progenitores.

5. Rastreo de afinidad y resultado del paneo de maduración.

Se rastreo un total de 2,640 clones derivados a partir de todos los paneos como los lisados bacterianos para determinar las afinidades mejoradas sobre la C5 humana. Las afinidades preliminares se estimaron mediante titulación de equilibrio en solución (SET). Basándose en sus afinidades estimadas, se secuenciaron los clones derivados a partir de cada Fab progenitor o de las reservas de Fab. La Tabla 5 muestra el número de clones secuenciados y el número de secuencias únicas obtenidas para cada condición de paneo.

Tabla 5

Panorama de los clones mejorados en afinidad seleccionados para el análisis de secuencias

Progenitor/Maduración	Antígeno	Clones Secuenciados	Secuencias Únicas	Progenitor de Únicas
MOR06525 + 6756 HCDR2	hu/hu/hu	10	9	6525
MOR07086 HCDR2	hu/hu/hu	10	4	7086
MOR06763 HCDR2	hu/hu/hu	22	10	6763(8x), 7086(2x)
MOR07087 HCDR2	hu/hu/hu	10	4	7087
MOR06757 HCDR2	hu/hu/hu	10	0	
MOR07091 + 7092 HCDR2	hu/hu/hu	24	7	7092
MOR07093 + 7094 HCDR2	hu/hu/hu	10	10	7093
MOR06525 + 6756 LCDR3	hu/hu/hu	20	5	6756
MOR07086 LCDR3	hu/hu/hu	10	5	7086
MOR06763 LCDR3	hu/hu/hu	10	8	7086
MOR07087 LCDR3	hu/hu/hu	6	1	7086
MOR06757 LCDR3	hu/hu/hu	16	0	

Progenitor/Maduración	Antígeno	Clones Secuenciados	Secuencias Únicas	Progenitor de Únicas
MOR07091 + 7092 LCDR3	hu/hu/hu	6	6	7091(1x), 7092(5x)
MOR07093 + 7094 LCDR3	hu/hu/hu	10	9	7094
MOR06525 + 6756 HCDR2	hu/cino/hu	10	8	6525
MOR07086 HCDR2	hu/cino/hu	10	6	7086
MOR06763 HCDR2	hu/cino/hu	22	5	6763
MOR06757 HCDR2	hu/cino/hu	15	2	6757
MOR07091 + 7092 HCDR2	hu/cino/hu	15	6	7091(3x), 7092(3x)
MOR07093 + 7094 HCDR2	hu/cino/hu	10	10	7093
MOR07087 HCDR2	hu/cino/hu	10	6	7087(5x), 7086(1x)
MOR06525 + 6756 LCDR3	hu/cino/hu	15	0	
MOR07086 LCDR3	hu/cino/hu	10	1	7086
MOR06763 LCDR3	hu/cino/hu	10	0	
MOR06757 LCDR3	hu/cino/hu	9	1	7094
MOR07091 + 7092 LCDR3	hu/cino/hu	11	9	7091(6x),

Progenitor/Maduración	Antígeno	Clones Secuenciados	Secuencias Únicas	Progenitor de Únicas
				7092(3x)
MOR07093 + 7094 LCDR3	hu/cino/hu	10	7	7094
MOR07087 LCDR3	hu/cino/hu	10	0	
Total		338	139	

6. Análisis de secuencias y selección de los Fabs optimizados en afinidad para la producción de la proteína.

Se mantuvo una muy buena diversidad durante la recuperación de los derivados de los 10 Fabs progenitores. Se determinaron las secuencias de nucleótidos de la cadena pesada (VH) para los 188 clones mejorados de HCDR2, y de las regiones variables de cadena ligera (VL) para los 150 clones de LCDR3 mejorados. Se seleccionaron 87 secuencias de HCDR2 únicas y 52 secuencias de LCDR3 únicas para un análisis detallado de la diversidad de secuencias dentro de las CDRs maduras. Se omitieron los Fabs que contenían posibles sitios de glicosilación en las CDRs de la otras caracterizaciones.

El análisis de secuencias VH y VL y los datos de afinidad mostraron que los 10 Fabs progenitores produjeron sucesores mejorados en afinidad. Los Fabs progenitores MOR06525,

MOR06757, MOR06763, MOR07087 y MOR07094 proporcionaron solamente clones mejorados de HCDR2, y los progenitores MOR06756 y MOR07093 proporcionaron solamente clones mejorados de LCDR3. MOR07086, MOR07091 y MOR07092 tuvieron clones maduros tanto para VH como VL. Esto último permitió la clonación cruzada de las cadenas maduras VH y VL. A partir de todos los datos, se seleccionaron 60 clones con la mejor afinidad y la más alta diversidad en las CDRs maduras para la expresión de Fab. Las secuencias de aminoácidos VH y VL seleccionadas, así como las secuencias de nucleótidos, se enlistan en la Tabla 1.

Ejemplo 5: Conversión de IgG.

1. Conversión en el formato de IgG2 humana.

Con el objeto de expresar la inmunoglobulina de longitud completa (Ig), se sub-clonaron los fragmentos de dominio variable de las cadenas pesada (VH) y ligera (VL) a partir de los vectores de expresión de Fab pMORPH®x9_MH en la serie del vector pMORPH®2_h_Ig para la IgG2 humana. Se utilizaron las enzimas de restricción MfeI, y BlpI para la sub-clonación del fragmento del dominio VH en pMORPH®2_h_IgG2. La sub-clonación del fragmento del dominio VL en pMORPH®2_h_Igκ se llevó a cabo por medio de los sitios EcoRV y BsiWI, mientras que la sub-clonación en el pMORPH®2_h_Igλ2 se hizo utilizando EcoRV y HpaI.

Los 10 Fabs progenitores (MOR06525, 6756, 6757, 6763, 7086,

7087, MOR07091, 7092, 7093 y 7094) se convirtieron hasta la IgG2 humana. También se expresaron las IgGs.

2. Conversión en el formato de la IgG1AA humana.

Con el objeto de expresar la inmunoglobulina de longitud completa, los fragmentos de dominio variable de las cadenas pesada (VH) y ligera (VL) de Fab se sub-clonaron a partir de los vectores de expresión de Fab en los vectores de expresión de IgG1. Se utilizaron las enzimas de restricción MfeI y BlpI para la sub-clonación del fragmento del dominio VH en pMORPH®2_h_IgG1AA, en donde se mutaron las leucinas en las posiciones 234 y 235 hasta alaninas para abrogar el enlace de FcRγ, y atenuar las funciones efectoras. Se utilizaron las enzimas de restricción EcoRV y HpaI para sub-clonar el fragmento del dominio VL en pMORPH®2_h_Igλ2.

En seguida, los Fabs maduros con el perfil deseado se sub-clonaron en el formato de la IgG1AA humana: MOR07832, 7834, 7872, 7876, 7829, 7871, 7865, 7873, 7830, 7878, 7910. La clonación cruzada al nivel de la IgG se logró mediante la transfección de las células con combinaciones de construcciones de cadena ligera y pesada. Por ejemplo, MOR08114 fue el producto de la cadena pesada de la línea germinal a partir de MOR07829 y la cadena ligera de la línea germinal a partir de MOR07871. La Tabla 6 resume las IgGs de la línea germinal clonadas cruzadamente más relevantes.

Tabla 6

Panorama de las IgG de la línea germinal clonadas cruzadamente más relevantes

MOR0 No.	VH/VL Línea germinal	VH/VL		CDRs maduras		Formato
		VH	VL	VH madura	VL madura	
8114	sí	7829	7871	7091/HCDR2	7091/LCDR3	hulg1AA
8125	sí	7091	7873	-	7091/LCDR3	hulg1AA
8126	sí	7829	7873	7091/HCDR2	7091/LCDR3	hulg1AA
8127	sí	7830	7873	7091/HCDR2	7091/LCDR3	hulg1AA
8128	sí	7092	7878	-	7091/LCDR3	hulg1AA
8129	sí	7909	7092	7091/HCDR2	-	hulg1AA
8130	sí	7909	7878	7091/HCDR2	7091/LCDR3	hulg1AA
8131	sí	7910	7092	7091/HCDR2	-	hulg1AA
8132	sí	7910	7878	7091/HCDR2	7091/LCDR3	hulg1AA

3. Expresión transitoria y purificación de la IgG humana.

Las células eucarióticas HKB11 y HEK293 se transfectaron con una proporción equimolar de ADN del vector de expresión de cadena

pesada y ligera de IgG. El sobrenadante del cultivo celular se cosechó a los 3 o a los 7 días después de la transfección, y se sometió a cromatografía de afinidad de Proteína A estándar (rProteinA FF ó MabSelect SURE, GE Healthcare). Como no se menciona de otra manera, se llevó a cabo el intercambio de regulador hasta suero regulado con fosfato de Dulbecco 1x (pH de 7.2, Invitrogen), y las muestras se filtraron para esterilizarse (7.2 micras). La pureza de la IgG se analizó bajo condiciones desnaturalizantes, reductoras, y no reductoras, en SDS-PAGE, o mediante la utilización del Agilent BioAnalyzer, y en estado nativo mediante HP-SEC.

Ejemplo 6: Línea germinal.

Las construcciones de IgG se llevaron a la línea germinal por medio de mutagénesis dirigida al sitio, utilizando el Kit de Mutagénesis Dirigida al Sitio QuickChange® (Stratagene). La DI N-terminal de MOR08111 Vλ2 se cambió hasta ES para concordar con la secuencia de la línea germinal humana, así como para evitar una Q terminal (la Q N-terminal puede formar piroglutamina). La DI N-terminal DI de MOR08110 Vλ3, MOR08113 Vλ3, y MOR08114 Vλ3 se llevó hasta la línea germinal hasta SY, la secuencia más comúnmente encontrada en los genes λ3 humanos. La QVQ N-terminal de MOR08111 VH2 se llevó a la línea germinal hasta EVT para concordar con un gen λ2 y evitar la Q terminal. La Q N-terminal Q en MOR08109 VH5, MOR08110 VH5, MOR08113 VH5 y MOR08114 VH5 también se mutó hasta E.

Las secuencias de estructura para MOR08109 VΛ3 se sintetizaron para concordar con el gen λ3j humano, y se clonaron e el vector de expresión utilizando los sitios de restricción NheI y HpaI. Las alineaciones de secuencias de los dominios variables de los anticuerpos con sus secuencias de la línea germinal humana relacionadas más cercanas respectivas se muestran en la Figura 1.

Ejemplo 7: Determinación de afinidad.

1. $K_{activado}/K_{desactivado}$ y determinación de K_d de los anticuerpos anti-C5 humana utilizando resonancia de plasmón superficial (Biacore).

Se determinó que los anticuerpos anti-Fab utilizados para inmovilizar los Fabs en el chip Biacore, estaban teniendo una influencia diferente sobre la afinidad de enlace de cada Fab por la C5 humana, haciendo de esta manera difícil la comparación de los Fabs unos con otros. Se llevó a cabo el análisis Biacore sobre los anticuerpos de IgG.

Un chip CM4 se recubrió con 50 miligramos/mililitro de anticuerpo Fc de cabra anti-humano (500-2000 RU) en regulador de acetato 10mM, pH de 4.5, utilizando la química de acoplamiento de amina convencional de EDC-NHS. Cada IgG anti-C5 humana se capturó sobre el chip en regulador HBS-EP a una velocidad de flujo constante de 10 microlitros/minuto, durante un tiempo de contacto que llevó hasta una densidad de ligando de alrededor de 20 RU. Después de la captura de la IgG anti-C5 humana, se inyectaron diferentes concentraciones de C5 humana o de cinomolgo, en el

intervalo de entre 0.156 nM y 2.5 nM. Cada ciclo se realizó con dos pasos de regeneración con ácido fosfórico. Todas las condiciones de ejecución se llevaron a cabo a 25°C en regulador HBS-EP 1x. Las señales resultantes se ajustaron mediante referenciación doble, sustracción de los valores del índice de refracción a partir de la celda de flujo de referencia, y el paso de enlace sin analito. Los datos se recolectaron a 10 Hz, y se analizaron utilizando el Software de Evaluación Biacore T100 Versión 1.1 (GE). Este programa utiliza un método de análisis de ajuste global para la determinación del índice y las constantes de afinidad para cada interacción.

Se midió la especificidad de los anticuerpos. De preferencia, los valores $K_{activado}$ y $K_{desactivado}$ para el enlace con la C5 humana y de cinomolgo son como sigue: $K_{activado} > 1 \times 10^5$, $K_{desactivado} < 1 \times 10^{-4}$. Estas mediciones se llevaron a cabo en Biacore para las IgGs de la línea germinal, y los datos resultantes se enlistan en la Tabla 7.

Tabla 7

Valores K_d, $K_{activada}$, y $K_{desactivada}$ de las IgGs de la línea germinal, determinados en Biacore

IgG final anti-C5	Muestra de C5	ka [1/Ms]	kd [1/s]	KD [pM]
MOR08109	C5 humana	2.13E+06	2.56E-05	12
	C5 de cinomolgo	1.23E+06	4.49E-05	37
MOR08110	C5 humana	4.15E+06	4.69E+05	12

IgG final anti-C5	Muestra de C5	ka [1/Ms]	kd [1/s]	KD [pM]
	C5 de cinomolgo	1.81E+06	9.24E-05	60
MOR08111	C5 humana	1.00E+06	3.07E-05	31
	C5 de cinomolgo	8.91E+05	1.28E-04	144
MOR08113	C5 humana	2.51E+06	6.77E-05	28
	C5 de cinomolgo	1.53E+06	1.27E-04	83
MOR08114	C5 humana	2.09E+06	3.12E-05	15
	C5 de cinomolgo	1.06E+06	3.13E-05	31
5G1.1	C5 humana	1.29E+06	7.22-05	56

2. Determinación de las afinidades picomolares utilizando la titulación de equilibrio en solución (SET) para los Fabs purificados o los lisados bacterianos de Fabs (descubrimiento de meso-escala (MSD)).

Para la determinación de la KD mediante titulación de equilibrio en solución (SET), se utilizaron fracciones de monómeros (cuando menos un contenido del 90 por ciento de monómero, analizado mediante SEC analítica; Superdex75, Amersham Pharmacia) de la proteína de Fab. La determinación de afinidad en solución se llevó a

cabo básicamente como se describe en la literatura (Friguet y colaboradores, J. Immunol Methods 77:305-319 (1985)). Con el objeto de mejorar la sensibilidad y la precisión del método de SET, se transfirió desde el ELISA clásico hasta la tecnología basada en ECL (Haenel y colaboradores, Anal Biochem 339:182-184 (2005)).

Un miligramo/mililitro de anticuerpos específicos del fragmento $(Fab)_2$ de cabra anti-humano (Dianova) se marcaron con el ECL Sulfo-TAGTM NHS-Ester (Meso Scale Discovery, Gaithersburg, MD, EUA) de acuerdo con las instrucciones del fabricante. Los experimentos se llevaron a cabo en placas de microtitulación de polipropileno y suero regulado con fosfato a un pH de 7.4 con albúmina de suero bovino al 0.5 por ciento y Tween 20 al 0.02 por ciento como el regulador de ensayo. El antígeno no marcado se diluyó en 2^n series, empezando con una concentración cuando menos 10 veces más alta que la K_D. Los pozos sin antígeno se utilizaron para determinar los valores B_{max}; los pozos sin antígeno ni Fab se utilizaron para determinar el fondo. Después de la adición, por ejemplo, del Fab 10 pM (concentración final en un volumen final de 60 microlitros), la mezcla se incubó durante la noche a temperatura ambiente. La concentración de Fab aplicada fue similar a, o estuvo debajo de, la K_D esperada.

Las placas MSD de estreptavidina se recubrieron con 0.2 microgramos/mililitro de C5 humana biotinilada (30 microlitros/pozo), y se bloquearon con albúmina de suero bovino al 5 por ciento en suero regulado con fosfato. Subsiguientemente, las muestras

equilibradas se transfirieron a estas placas (30 microlitros por pozo), y se incubaron durante 20 minutos. Después de lavarse, se agregaron 30 microlitros/pozo del anticuerpo de detección marcado con la marca ECL Sulfo ($(Fab)_2$ de cabra anti-humano) en una dilución final de 1:1500 a la placa MSD, y se incubaron durante 30 minutos sobre un agitador Eppendorf (700 revoluciones por minuto).

Después de lavar y de agregar 30 microlitros/pozo de Regulador de Lectura MSD T con el tensoactivo, se detectaron señales de electroquimiluminiscencia utilizando un Sector Imager 6000 (Meso Scale Discovery, Gaithersburg, MD, EUA).

Los datos se evaluaron con el software XLFit (IDBS), aplicando modelos de ajuste a la medida. Para la evaluación de los datos, es decir, la determinación de la KD de las moléculas de Fab, se utilizó el siguiente modelo de ajuste (modelo de Abraham y colaboradores, modificado de acuerdo con 200515): y=Bmax-(Bmax/(2*cFab)*(x +cFab+KD-sqrt((x+cFab+ KD)*(x+cFab+ KD)-4*x*cFab))); cFab: concentración de Fab aplicada; x: concentración de antígeno soluble total aplicada (sitios de enlace); sqrt: raíz cuadrada. Utilizando las condiciones de ensayo descritas anteriormente, se determinaron las afinidades (monoméricas) para los Fabs de enlace de C5 optimizados en la afinidad, en solución.

Fabs progenitores

Con el objeto de caracterizar adicionalmente los anticuerpos de enlace de C5, se determinó la afinidad de los Fabs progenitores con la C5 humana. Debido a que el enfoque de la caracterización fue

sobre la eficacia en los ensayos hemolíticos, se hicieron mediciones de afinidad solamente para los Fabs más relevantes. Para una determinación confiable de las afinidades monovalentes, solamente se utilizaron los lotes de Fab para las mediciones que mostraron una fracción monomérica ≥ 90 por ciento en una cromatografía por exclusión de tamaños cualitativa.

Las afinidades de los 10 Fabs progenitores que entraron en la maduración de afinidad se resumen en la Tabla 8. Las afinidades estuvieron en el intervalo de 72 pM a 3.7 nM.

Tabla 8

Afinidades de los 10 Fabs progenitores determinadas en la SET

	SET
MOR0 No.	**KD [pM]** (n=1)
6525	72
6756	1521
6757	1186
6763	820
7086	108
7087	3793
7091	324

	SET	
MOR0 No.	**KD [pM]**	**(n=1)**
7092	229	
7093	576	
7094	1364	
3207 (control negativo)	ningún enlace	

Fabs maduros

Se midieron las afinidades monovalentes de los Fabs purificados con la C5 humana en la SET. Las afinidades estuvieron en el intervalo de pM bajo, y se obtuvieron las mejores afinidades para los derivados de MOR07086, 7091, 7092 y 7093. Subsiguientemente, las mediciones de afinidad de estos derivados con la C5 de cinomolgo mostraron afinidades en el intervalo de pM medio abajo.

El proceso de maduración de afinidad tuvo mucho éxito, dando como resultado un repertorio de enlazadores con una afinidad notoriamente mejorada. La Tabla 9 resume las afinidades con la C5 humana y de cinomolgo de los mejores enlazadores perfeccionados. Ciertos Fabs tienen una KD para la C5 humana ≤ 30pM, y para la C5 de cinomolgo ≤ 150pM.

Tabla 9

Panorama de afinidades con la C5 humana y de cinomolgo para los Fabs mejorados con la mejor afinidad

MOR	Madurado	SET C5 humana (n=1-2)	SET C5 de cinomolgo (n=1)
6525		**273/29**	
7813	**HCDR2**	**437**	
7814	**HCDR2**	**137**	
7816	**HCDR2**	**116**	
6757		**3650/1245**	
7818	**HCDR2**	**491**	**70**
7907	**HCDR2**	**179**	
6763		**673/962**	
7820	**HCDR2**	**62**	
7086		**12/65**	**10**
7821	**HCDR2**	**7**	**39**

MOR	Madurado	SET C5 humana (n=1-2)	SET C5 de cinomolgo (n=1)
7822	**HCDR2**	**5**	**14**
7823	**HCDR2**	**5**	**15**
7824	**HCDR2**	**55/130**	
7864	LCDR3	**22**	**974**
7865	LCDR3	**10**	**88**
7866	LCDR3	**10**	**191**
7867	LCDR3	**19**	**154**
7868	LCDR3		**384**
7869	LCDR3	**2**	**83**
7870	LCDR3	**12**	**500**
7087		**120**	
7827	**HCDR2**	**361**	
7828	**HCDR2**	**2477/1730**	
7091		**135/138**	**704**

MOR	Madurado	SET C5 humana (n=1-2)	SET C5 de cinomolgo (n=1)
7829	**HCDR2**	**429**	**116**
7830	**HCDR2**	**399**	**75**
7908	**HCDR2**	**15***	**39***
7871	LCDR3	3	4
7872	LCDR3	2	3
7873	LCDR3	13/13	6
7874	LCDR3	35	8
7092		**96**	**481**
7831	**HCDR2**	**10**	**36**
7832	**HCDR2**	**4**	**13**
7909	**HCDR2**	**7**	**18**
7910	**HCDR2**	**27**	**31**
7876	LCDR3	**78**	**60**
7877	LCDR3	**29**	**144**

MOR	Madurado	SET C5 humana (n=1-2)	SET C5 de cinomolgo (n=1)
7878	LCDR3	**33**	**70**
7879	LCDR3	**25**	**122**
7093		**431/992**	**3146**
7833	**HCDR2**	**47**	**107**
7834	**HCDR2**	**4**	**15**
7835	**HCDR2**	**29**	**28**
7836	**HCDR2**	**11**	
7890	**HCDR2**	**46**	
7094			
7880	LCDR3	**13**	**13**
7881	LCDR3	**88**	
7882	LCDR3	**70**	
7883	LCDR3	**49**	
7884	LCDR3	**83**	

MOR	Madurado	SET C5 humana (n=1-2)	SET C5 de cinomolgo (n=1)
7885	LCDR3	**35**	
Criterio: K_D de C5 humana <30 pM; C5 de cinomolgo <150 pM. *Dispersión (no hay una medición confiable).			

3. Determinación de la K_D de las moléculas de IgG utilizando titulación de equilibrio en solución (SET).

Se determinaron las afinidades de las IgGs de la línea germinal (formato de IgG1AA humana) con la C5 humana y de cinomolgo en la SET, como se describe más adelante. Los conjuntos de datos similares entre dos mediciones independientes mostraron afinidades más altas de las IgGs principales con la C5 humana que la IgG 5G1.1 de referencia (véase la Patente de los Estados Unidos de Norteamérica Número 6,355,245). Las IgGs finales tuvieron afinidades por la C5 humana en el intervalo de 1 a 14 pM, y afinidades por la C5 de cinomolgo en el intervalo de 3 a 29 pM.

Tabla 10

Determinación de valor K_D para las IgGs finales (formato de IgG1AA humana) en la SET

		Primera Medición		Segunda Medición	
		C5 humana	**C5 de cinomolgo**	**C5 humana**	**C5 de cinomolgo**
		KD [pM]	KD [pM]	KD [pM]	KD [pM]
Línea germinal de IgG1AA humana	**MOR08109**	**4**	**13**	**2**	**6**
	MOR08110	**7**	**18**	**3**	**8**
	MOR08111	**5**	**14**	**3**	**17**
	MOR08113	**14**	**29**	**8**	**16**
	MOR08114	**1**	**5**	**2**	**4**
IgG2/4 humana (IgG de referencia)	**5G1.1**	**24**	ningún enlace	**19**	ningún enlace

Para la determinación de la K_D mediante titulación de equilibrio en solución (SET), se utilizaron fracciones monoméricas de la proteína IgG (contenido de monómero de cuando menos el 90 por ciento, analizado mediante SEC MALS analítico; Tosoh TSKgel

G3000SWXL, Wyatt Treos miniDAWN). La determinación de afinidad en solución se llevó a cabo básicamente como se describe en la literatura (Friguet y colaboradores, J. Immunol Methods 77:305-319 (1985)). Con el objeto de mejorar la sensibilidad y precisión del método SET, se transfirió desde el ELISA clásico hasta la tecnología basada en ECL (Haenel et al., Anal Biochem 339:182-184 (2005)).

1 miligramo/mililitro de anticuerpos específicos del fragmento $(Fab)_2$ de cabra anti-humano (Dianova) se marcaron con ECL Sulfo-TAGTM NHS-Ester (Meso Scale Discovery, Gaithersburg, MD, EUA) de acuerdo con las instrucciones del fabricante. Los experimentos se llevaron a cabo en placas de microtitulación de polipropileno y suero regulado con fosfato a un pH de 7.4, con albúmina de suero bovino al 0.05 por ciento y Tween 20 al 0.02 por ciento como regulador de ensayo. El antígeno no marcado se diluyó en una serie 2n ó 1.75n, respectivamente, empezando con una concentración cuando menos 10 veces más alta que la K_D. Los pozos sin antígeno se utilizaron para determinar los valores B_{max}; los pozos que no contenían antígeno ni IgG, se utilizaron para determinar el fondo. Después de la adición, por ejemplo, de IgG 10 pM (concentración final en un volumen final de 60 microlitros), la mezcla se incubó durante la noche a temperatura ambiente. La concentración de IgG aplicada fue similar a, o estuvo debajo de, la K_D esperada.

Las placas MSD de estreptavidina se recubrieron con 0.2 microgramos/mililitro de C5 humana biotinilada (30 microlitros/pozo), y se bloquearon con albúmina de suero bovino al 5 por ciento en

suero regulado con fosfato. Subsiguientemente, las muestras equilibradas se transfirieron a estas placas (30 microlitros por pozo), y se incubaron durante 20 minutos. Después de lavarse, se agregaron 30 microlitros/pozo del anticuerpo de detección marcado con la marca ECL Sulfo ($(Fab)_2$ de cabra anti-humano) en una dilución final de 1:1500 a la placa MSD, y se incubaron durante 30 minutos sobre un agitador Eppendorf (700 revoluciones por minuto).

Las señales de electroquimiluminiscencia se detectaron después de lavar y de agregar 30 microlitros/pozo de Regulador de Lectura MSD T con tensoactivo, utilizando un Sector Imager 6000 (Meso Scale Discovery, Gaithersburg, MD, EUA).

Los datos se evaluaron con EL software XLfit (IDBS), aplicando los modelos de ajuste a la medida. Para la evaluación de los datos, es decir, la determinación KD de las moléculas de IgG, se utilizó el siguiente modelo de ajuste para IgG (modificado de acuerdo con Piehler y colaboradores, 199717): y=Bmax/(cIgG/2)*(cIgG/2-((x+cIgG+KD)/2-((x+cIgG+KD)^2/4-x*cIgG^0.5)^2/(2*IgG)); cIgG = concentración de IgG aplicada, molécula completa (ningún sitio de enlace); x = concentración de antígeno soluble total aplicada (sitios de enlace); sqrt: raíz cuadrada.

Ejemplo 8: Caracterización mediante ensayos hemolíticos.

El ensayo hemolítico es un ensayo funcional básico que prueba la activación del complemento, y se ha utilizado para evaluar la capacidad de los anticuerpos monoclonales anti-C5 humana y las moléculas Fab, para bloquear la lisis de los glóbulos rojos

sanguíneos (RBCs), mediante las sendas de complemento (véanse, por ejemplo, Evans y colaboradores, Mol. Immunol. 32: 1183-1195 (1995); Thomas y colaboradores, Mol. Immunol. 33:1389-1401 (1996); Rinder y colaboradores, J. Clin. Invest. 96:1564-1572 (1995)). Dicho de una manera breve, para los ensayos de la senda clásica, los glóbulos rojos sanguíneos sensibilizados se utilizan como objetivos para la lisis mediante las proteínas de complemento presentes en el suero. Este ensayo es de interés para la caracterización y rastreo de los anticuerpos monoclonales anti-C5 humana de alta afinidad.

1. Senda clásica.

El número deseado de glóbulos rojos sanguíneos de pollo se lavó cuatro veces con regulador veronal de gelatina frío (GVB++), y se volvieron a suspender hasta $5x10^7$ células/mililitro. Con el fin de sensibilizar las células, se agregó IgG anti-chRBC de conejo a la suspensión de glóbulos rojos sanguíneos hasta una concentración final de 1 microgramo/mililitro de IgG. Después de 15 minutos de incubación sobre hielo, los chrRBCs sensibilizados se centrifugaron, se lavaron dos veces con GVB++, y se diluyeron hasta $8.33x10^7$ células/mililitro.

Se utilizaron placas de 96 pozos de fondo redondo para el ensayo hemolítico. Los anticuerpos se diluyeron en regulador GVB++, y se agregaron a los pozos (cuando se calculó la concentración requerida de anticuerpos de enlace de C5, se consideró que la muestra se diluirá al doble cuando se agregue el

suero). Se agregaron 50 microlitros de suero humano al 40 por ciento (diluido en GVB++) a 50 microlitros de diluciones de anticuerpo, dando como resultado una concentración del ensayo en suero final del 20 por ciento.

Los pozos de control y de referencia, se prepararon como se describe en la presente: pozos de control: i) 0 por ciento de control de lisis → 100 microlitros de GVB++, ii) 100 por ciento de control de lisis → 100 microlitros de NP-40 al 0.1 por ciento, iii) 20 por ciento de control de suero → 100 microlitros de suero al 20 por ciento (control de anticuerpo al 0 por ciento). Pozos de referencia: i) referencia de suero al 20 por ciento → 100 microlitros de suero al 20 por ciento, ii) referencia de GVB++ → 100 microlitros de GVB++, iii) referencia de NP-40 → 100 microlitros de NP-40 al 0.1 por ciento.

Se agregaron $2.5x10^6$ (30 microlitros) de chRBCs sensibilizados/pozo a todos los pozos de muestra y de control. A los pozos de referencia, se les agregó suero regulado con fosfato en lugar de células. La placa de ensayo se incubó durante 30 minutos a 37°C, se centrifugó (2,000 revoluciones por minuto, 5 minutos), y se transfirieron 85 microlitros del sobrenadante a una nueva placa de 96 pozos de fondo plano. La nueva placa se centrifugó (2,000 revoluciones por minuto, 3 minutos) para deshacerse de cualesquiera burbujas. La liberación de hemoglobina se midió leyendo la absorbencia a 415 nanómetros. El porcentaje de hemólisis se calculó con respecto a los pozos de control y de referencia, utilizando los siguientes algoritmos de cálculo:

$$\% \text{ de hemólisis} = 100 \times \frac{\text{ODmuestra - OD control negativo}}{\text{ODcontrol positivo-ODcontrol negativo}}$$

en donde:

ODmuestra = [$OD_{muestra}$ Promedio]-[$OD_{referencia\ de\ suero\ al\ 20\ por\ ciento}$ Promedio]

ODcontrol negativo = [$OD_{lisis\ del\ 0\%}$ Promedio]-[$OD_{Referencia\ de\ GVB++}$ Promedio]

ODcontrol positivo = [$OD_{lisis\ del\ 100\%}$ Promedio]-[$OD_{Referencia\ de\ NP-40}$ Promedio]

Empleando este procedimiento, se pudieron identificar anticuerpos anti-C5 humana que fueron capaces de inhibir la lisis de los glóbulos rojos sanguíneos. Con el fin de rastrear la reactividad cruzada para la C5 de cinomolgo, se llevó a cabo la senda clásica utilizando suero de cinomolgo al 5 por ciento.

2. Senda alternativa.

Se hicieron ensayos hemolíticos emprendiendo la senda alternativa, de una manera similar a los ensayos hemolíticos de la senda clásica. En la senda alternativa, se utilizaron glóbulos rojos sanguíneos de conejo, y no hubo necesidad de sensibilizar a las células. Los glóbulos rojos sanguíneos de conejo son diferentes de los glóbulos rojos sanguíneos de pollo en que son sensibles a la lisis ocasionada por la senda alternativa del complemento.

El regulador de procesamiento fue GVB++ complementado con EGTA 10 mM y Mg++ 5 mM, debido a que la convertasa de C5 de la senda alternativa depende de Mg++, y la convertasa de C5 de la senda clásica depende de Ca++.

Los ensayos hemolíticos de la senda alternativa se ejecutaron

con: 1) suero humano al 20 por ciento, ii) C5 humana 100 pM agregada al suero agotado de C5 humana al 20 por ciento, iii) suero de cinomolgo al 0.025 por ciento agregado al suero agotado de C5 humana al 20 por ciento, iv) C5 de cinomolgo 100 pM agregada al suero agotado de C5 humana al 20 por ciento, v) suero de cinomolgo al 10 por ciento. Estos establecimientos se utilizaron para rastrear los anticuerpos con una alta afinidad con las proteínas C5 humana y de cinomolgo, que fueron capaces de inhibir muy efectivamente la lisis de los glóbulos rojos sanguíneos inducida por la senda del complemento alternativa.

3. Ensayos hemolíticos con los Fabs progenitores.

Se utilizaron ensayos hemolíticos como un ensayo bifuncional básico para evaluar la capacidad de los anticuerpos monoclonales anti-C5 humana para bloquear la lisis mediada por el complemento de los glóbulos rojos sanguíneos. La convertasa de C5 disocia la C5 en el péptido C5a y el fragmento C5b, que subsiguientemente se incorpora en el complejo de ataque de membrana (MAC), el cual conduce a la lisis celular. La convertasa de C5 de la senda clásica, formada por un complejo de C3bC4bC2a, tiene una estructura diferente de la convertasa de C5 de la senda alternativa, que está formada por un complejo de C3bC3bBb. Los anticuerpos generados con HuCAL GOLD® deben ser inhibidores en la senda tanto clásica como alternativa, pero con un enfoque sobre la senda alternativa, debido a que se implica principalmente la senda alternativa (factor H, factor B, y genes relacionados con el factor H) en la degeneración

macular relacionada con la edad.

Los ensayos de la senda clásica y de la senda alternativa se llevaron a cabo con suero humano al 20 por ciento (C5 en aproximadamente 80 nM). Con el fin de aumentar la sensibilidad de los ensayos de la senda alternativa, se desarrollaron nuevos formatos de ensayo. Se agregaron de 10 a 100 pM de C5 humana purificada, o suero de cinomolgo al 0.025 por ciento (aproximadamente 100 pM de C5 de cinomolgo) al suero agotado de C5 humana (pero que contenía todos los demás componentes del suero y del complemento).

La Figura 2 muestra que se pudo observar una hemólisis considerable entre 10 y 100 pM de la C5 humana purificada agregada al suero agotado de C5 humana. El suero de cinomolgo se agregó al suero agotado de C5 humana para probar la reactividad cruzada. La Figura 3 muestra que el 0.025 por ciento de suero de cinomolgo (aproximadamente 100 pM de C5) agregado al suero agotado de C5 humana, restablece la actividad hemolítica.

Senda clásica

Primero, se hizo la selección de Fab en la senda clásica (suero humano al 20 por ciento). Aproximadamente la mitad de los 61 Fabs progenitores purificados fueron inhibidores débiles a fuertes de la senda clásica. Los valores IC_{50} de los mejores Fabs inhibidores estuvieron entre 35 y 900 nM.

Se hicieron los ensayos mostrando resultados congruentes (como se muestra en la Figura 4). El porcentaje de hemólisis se

calculó con respecto a los pozos de control y de referencia. La inhibición de Fab de la lisis celular se comparó con una lisis máxima provocada por el suero humano al 20 por ciento (= 100 por ciento). Se utilizó un Fab humano irrelevante (enlazador de lisozima de clara de huevo de gallina MOR03207) como un control negativo, y se utilizó el anticuerpo monoclonal de IgG anti-C5 humana (Quidel) como un control positivo. La Figura 4 muestra un ejemplo con los mejores Fabs inhibidores.

Senda alternativa

Los Fabs que mostraron una actividad inhibidora en la senda clásica, se evaluaron adicionalmente en la senda alternativa. Se ejecutaron ensayos hemolíticos con 100 pM de C5 humana purificada, o con suero de cinomolgo al 0.025 por ciento agregado al suero agotado de C5 humana. Los valores IC_{50} para los ensayos alternativos humanos estuvieron entre 0.1 y 90 nM (los ejemplos de los ensayos con los Fabs más relevantes se muestran en la Figura 5).

El control positivo de la senda clásica (anticuerpo anti-C5 humana, Quidel) no fue inhibidor en la senda alternativa. Por consiguiente, se utilizó un anticuerpo anti-factor de complemento P (Quidel) como un control positivo. Como se muestra en la Figura 5, MOR07086 tuvo la mejor actividad inhibidora, y los datos de NBS revelaron una mejor potencia que para el anticuerpo de referencia 5G1.1.

Con el objeto de probar la reactividad cruzada de cinomolgo,

se llevaron a cabo ensayos hemolíticos de la senda alternativa con suero de cinomolgo al 0.025 por ciento agregado al suero agotado de C5 humana. No fue posible hacer una comparación con 5G1.1, debido a que 5G1.1 no reconoce la C5 de cinomolgo. Se utilizó el anticuerpo anti-factor P como el control positivo. Los resultados de los ensayos revelaron valores de IC_{50} entre 0.1 y 400 nM para los mejores Fabs inhibidores. Nuevamente, el MOR07086 mostró la mayor potencia (mostrada en la Figura 6).

Se observó una actividad inhibidora consistente de los Fabs tanto en la senda clásica como alternativa. La siguiente Tabla 11 resume los resultados de los ensayos hemolíticos para los 22 Fabs más relevantes. Para tener una comparación confiable entre diferentes experimentos, la lisis causada por el suero humano al 20 por ciento se normalizó hasta el 100 por ciento.

Tabla 11

Sumario de los ensayos hemolíticos con los Fabs más relevantes

MOR No.	MOR IC_{50} [nM]			NVS IC_{50} [nM]		
	CP [humana] normalizada	AP (C5 0.1 nM) [humana] normalizada	AP (suero de cinomolgo al 0.025 por ciento) [cinomolgo] normalizada	CP [humana] normalizada	AP (C5 0.1 nM) [humana] normalizada	AP (suero de cinomolgo al 0.025 por ciento) [cinomolgo] normalizada
6525	190	15	11	185	7	5

MOR No.	MOR IC_{50} [nM]			NVS IC_{50} [nM]		
	CP [humana] normali-zada	AP (C5 0.1 nM) [humana] normali-zada	AP (suero de cino-molgo al 0.025 por ciento) [ci-nomolgo] norma-lizada	CP [humana] normali-zada	AP (C5 0.1 nM) [humana] normali-zada	AP (suero de cino-molgo al 0.025 por ciento) [ci-nomolgo] norma-lizada
6756	320	80	400	225	70	2500
6757	500	90	30	305	130	25
6763	250	45	110	195	20	360
6764	n.t.	50	n.t.	n.t.	25	30% inh
6776	4000	40		n.t.	20	50% inh
6952	90	20	1000	110	15	200
6961	100	25	600	85	15	30
7081	180	5	40% inh	170	3	10
7082	70	2.5	1	90	1	1
7083	100	30	300	140	10	5
7084	120	10	1.2	160	5	1.5
7086	35	0.2/0.2	0.2-0.4	85	0.1	0.1
7087	4000	50	100	775	10	1

MOR No.	MOR IC_{50} [nM]			NVS IC_{50} [nM]		
	CP [humana] normali-zada	AP (C5 0.1 nM) [humana] normali-zada	AP (suero de cino-molgo al 0.025 por ciento) [ci-nomolgo] norma-lizada	CP [humana] normali-zada	AP (C5 0.1 nM) [humana] normali-zada	AP (suero de cino-molgo al 0.025 por ciento) [ci-nomolgo] norma-lizada
7088	110	15	230	130	5	15
7089	150	75	900	250	20	50
7090	105	20	10	120	10	1
7091	82	7	40	110	3	4
7092	100	1	1.5	90	0.5	1.5
7093	4000	7	190	230	5	15
7094				770	40	190
7095 *	120*	0.5*	1.3*	n.t.		

*No es puro como MH.

**Como pMx9_FS.

4 Ensayos hemolíticos con los Fabs maduros.

Senda clásica

(1) Senda clásica utilizando suero humano al 20 por ciento.

Los Fabs maduros se probaron en la senda clásica con suero humano al 20 por ciento. Los derivados de MOR07086, 7091, 7092 y 7093 mostraron la más alta potencia (valores IC_{50} en el intervalo de nM bajo). Los descendientes de MOR07091, 7092 y 7093, mostraron una potencia fuertemente mejorada. La Figura 7 muestra los ejemplos de los ensayos hemolíticos con los derivados de MOR07086, 7091, 7092 y 7093.

(2) Senda clásica utilizando suero de cinomolgo al 5 por ciento.

También se ejecutaron ensayos de la senda de complemento en la presencia de suero de cinomolgo al 5 por ciento con el objeto de probar la reactividad cruzada. Los derivados de MOR07086, 7091, 7092 y 7093 pudieron inhibir efectivamente la lisis de los glóbulos rojos sanguíneos. El control negativo, MOR03207 (Fab anti-lisozima) no tuvo impacto alguno sobre la senda de complemento. Los resultados de estos ensayos se muestran en la Figura 8.

Senda alternativa

(1) Senda alternativa utilizando C5 humana 100 pM.

Los Fabs maduros se probaron en el ensayo hemolítico de la senda alternativa con C5 humana 100 pM. Algunos derivados de MOR06525, 6757, 6763, y 7087, mostraron una mejor potencia, comparándose con sus progenitores. Los Fabs derivados de MOR07086, 7091, 7092, 7093, y 7094, mostraron la más alta potencia (valores IC_{50} en el intervalo de nM bajo). Los descendientes de MOR07091, 7092, 7093, y 7094 mostraron una potencia altamente mejorada, muchos de los cuales son más potentes que el anticuerpo

de referencia 5G1.1. La Figura 9 muestra los ejemplos de los resultados del ensayo hemolítico para los Fabs madurados en afinidad, y 5G1.1.

(2) Senda alternativa utilizado suero humano al 20 por ciento.

Los Fabs maduros se probaron en el ensayo hemolítico de la senda alternativa, con suero humano al 20 por ciento. Los Fabs derivados de MOR07086, 7091, 7092 y 7093, mostraron la mejor actividad inhibidora. Muchos de estos Fabs tuvieron una mejor actividad inhibidora que el 5G1.1. La Figura 10 muestra los ejemplos de los resultados del ensayo hemolítico para los Fabs madurados en afinidad, y el anticuerpo de referencia 5G1.1.

(3) Senda alternativa utilizando C5 de cinomolgo 100 pM.

Los Fabs maduros se probaron en el ensayo hemolítico de la senda alternativa, utilizando C5 de cinomolgo 100 pM agregada al suero agotado en C5 humana al 20 por ciento. Los Fabs derivados de MOR07091, 7092 y 7093 mostraron la mejor actividad inhibidora; 5G1.1 no reacciona cruzadamente con la C5 de cinomolgo. La Figura 11 muestra los ejemplos de los resultados del ensayo hemolítico para los Fabs madurados en afinidad.

5. Ensayos hemolíticos con las IgGs de la línea germinal (formato de IgG1AA humana).

Senda clásica

(1) Senda clásica utilizando suero humano al 20 por ciento.

Los ensayos de la senda clásica utilizando suero humano al 20 por ciento se ejecutaron en MOR. Los valores IC_{50} de la IgGAA

humana de la línea germinal final - MOR08109, 8110, 8113, 8114 - fueron mejores o similares a la IgG 5G1.1 de referencia (véase la Figura 12).

(2) Senda clásica utilizando suero de cinomolgo al 5 por ciento.

Una comparación con 5G1.1 en la senda clásica utilizando suero de cinomolgo al 5 por ciento no fue aplicable, debido a que este anticuerpo de referencia no reconoce la C5 de cinomolgo. Las IgGs de la línea germinal final pudieron inhibir completamente la lisis de los glóbulos rojos sanguíneos inducida por el suero de cinomolgo, excepto MOR08111. Los datos se muestran en la Figura 13.

Senda alternativa

(1) Senda alternativa utilizando la C5 humana 100 pM.

Las IgGs de la línea germinal se probaron en el ensayo hemolítico de la senda alternativa, utilizando la C5 humana 100 pM. Todos los anticuerpos mostraron una potente actividad inhibidora, con valores IC_{50} entre 28 y 128 pM (con la excepción de MOR08111, véase la Figura 14), todos fueron iguales o mejores a 5G1.1. La Figura 14 muestra los ejemplos de los resultados del ensayo hemolítico para las IgGs.

(2) Senda alternativa utilizando suero humano al 20 por ciento y ELISA de generación de C5a.

Las IgGs de la línea germinal también se probaron en el ensayo hemolítico de la senda alternativa con suero humano al 20 por ciento. La mayoría de los anticuerpos probados lograron una inhibición completa con valor IC_{50} debajo de 80 nM. El anticuerpo de

referencia 5G1.1 no inhibe completamente la hemólisis en el ensayo. La Figura 15 muestra los ejemplos de los resultados del ensayo hemolítico para las IgGs. La inhibición de la generación C5a por parte de las IgGs finales fue similar a la 5G1.1 (valores IC_{50} en el intervalo de nM bajo).

(3) Senda alternativa utilizando la C5 de cinomolgo 100 pM.

Los ensayos hemolíticos de la senda alternativa en suero agotado de C5 humana al 20 por ciento, se reconstituyeron con C5 de cinomolgo 100 pM. La potencia de los candidatos finales de la línea germinal contra la C5 de cinomolgo estuvo dentro de cinco veces aquélla para la C5 humana (valores IC_{50} en el intervalo de pM bajo).

(4) Senda alternativa utilizando suero de cinomolgo al 10 por ciento.

En los ensayos hemolíticos de la senda alternativa utilizando suero de cinomolgo al 10 por ciento ([C5] ~ 40 nM), la potencia de los candidatos de la línea germinal fue similar a la potencia en el suero humano (el criterio de éxito fue tener una potencia no mayor de cinco veces más débil que para el ensayo funcional utilizando C5 humana).

Ejemplo 9: ELISA de generación de C5a.

Se desarrolló el ELISA de C5a-des-Arg para medir la generación de C5a durante la hemólisis, con el fin de confirmar que los anticuerpos que eran inhibidores en el ensayo hemolítico, también inhibían la disociación de C5 en C5a y C5b.

Una placa Maxisorp se recubrió con 100 microlitros/pozo de C5a-des-Arg de ratón anti-humano (US Biologics) a 1 microgramo/mililitro, en regulador de recubrimiento (bicarbonato, pH de 9.5 a 9.8), y se incubaron durante la noche a 4°C. Después de lavar tres veces con PBST, la placa se bloqueó con 300 microlitros/pozo de diluyente (Synblock, AbD Serotec) durante 2 horas a temperatura ambiente. Después de aspirar la solución de bloqueo, se incubaron 100 microlitros de muestras o de referencias diluidas con diluyente, durante 1 hora, a temperatura ambiente. Las referencias se prepararon como sigue: el inicio fue en 20 nanogramos/mililitro de la referencia (rC5a-des-Arg), y se prepararon diluciones en serie de 1:4 para una curva de 7 puntos. Las muestras de los ensayos hemolíticos se diluyeron a 1:5 en diluyente (los sobrenadantes del ensayo hemolítico se deben almacenar a -80°C hasta que se utilicen en el ELISA de C5a). Entre tanto, la placa se lavó tres veces con PBST. Se agregaron 100 microlitros/pozo de 0.4 microgramos/mililitro de anticuerpo de detección (biotina-C5a de cabra anti-humano, R&D Systems) diluidos en el diluyente, y después de 1 hora de incubación a temperatura ambiente, se agregaron 100 microlitros/pozo de Strep-HRP (poli-HRP estreptavidina) diluidos a 1:5000 en diluyente de HRP (diluyente de poli-HRP) durante 30 minutos. Después de lavar cuatro veces con PBST, se agregaron 100 microlitros/pozo de Sustrato TMB (solución de sustrato Ultra TMB) durante 5 a 10 minutos. La reacción se detuvo con 50 microlitros/pozo de solución de paro (H_2SO_4 2N). La

absorbencia se leyó (A450-A570) y los datos se analizaron utilizando el SoftMax Pro.

Los Fabs maduros se probaron para la generación de C5a durante la hemólisis, con el fin de confirmar que la actividad inhibidora se debía al bloqueo de la disociación de C5 en C5a y C5b. Los sobrenadantes de los ensayos hemolíticos en suero humano al 20 por ciento se utilizaron para cuantificar la formación de C5a.

Todos los Fabs probados provocaron niveles de C5a bajando hasta la línea base. La Figura 16 muestra los ejemplos de los resultados del ELISA de C5a.

Ejemplo 10: ELISA de especificidad sobre C3, C4, C5 humanas, y C5 de cinomolgo.

Todos los Fabs purificados se analizaron en un ELISA en solución (el método se describe anteriormente), para enlazarse a C3, C4, y C5 humanas. Los Fabs se incubaron con el antígeno biotinilado sobre una placa de NeutrAvidin, y se detectaron por medio de la marca de histidina.

Se vio un mejor enlace para casi todos los Fabs maduros, comparándose con sus progenitores respectivos. No se detectó enlace alguno con los contra-objetivos de C4 y C3 humanas hasta Fab 100 nM. Estos resultados impactan los criterios de éxito para la especificidad: el enlace con la C5 humana y de cinomolgo, y ningún enlace con las proteínas de complemento humanas C3 y C4. Los ejemplos para los derivados de el Fab progenitor MOR07091 se muestran en la Figura 17.

Ejemplo 11: Ensayos de estabilidad en suero.

Se determinó la actividad de enlace retenida para la C5 humana en un ensayo de enlace, en suero humano al 50 por ciento, de los anticuerpos de enlace de C5, como se describe en seguida.

Los anticuerpos (formato Fab) se incubaron durante hasta 8 horas a 37°C con suero agotado de C5 humana al 100 por ciento, o con PBST/albúmina de suero bovino al 0.5 por ciento (control positivo). Se utilizaron los pozos de una placa de polipropileno bloqueada para la incubación, con el fin de asegurar que no hubiera enlace alguno de los anticuerpos a la superficie durante el largo tiempo de incubación. Las muestras se recolectaron en diferentes puntos del tiempo, y se almacenaron a -20°C.

Las muestras se probaron en un ELISA en solución sobre placas de NeutrAvidin para verificar la capacidad de enlace con la C5 humana. A las placas NeutrAvidin, que se bloquearon durante la noche con el ChemiBlocker-PBST 1x, se les agregaron 20 microlitros de diluciones en serie de las diferentes muestras recolectadas. La primera dilución de las muestras fue de 1:2 (concentración en suero final del 50 por ciento), seguida por los pasos de dilución de 1:3. Después de 1 hora de incubación, la placa se lavó tres veces con PBST, y se aplicaron 20 microlitros de C5 humana biotinilada hasta una concentración de 2.5 microgramos/mililitro. Después de 1 hora, la placa se lavó nuevamente cinco veces con PBST (Tween al 0.05 por ciento), y se agregó el anticuerpo de detección anti-HIS6-POD para los Fabs.

La fluorescencia del sustrato (Quanta Blue ó AttoPhos) se midió después de 5 a 10 minutos, y se calculó la actividad de enlace retenida, comparándose con la señal máxima respectiva (anticuerpo incubado con PBST/albúmina de suero bovino al 0.05 por ciento).

Uno de los criterios obligados para los anticuerpos de enlace de C5 es retener del 75 al 80 por ciento de actividad de enlace en el suero humano i) en un ensayo funcional en suero al 10 por ciento, y ii) en un ensayo de enlace en suero al 50 por ciento. Debido a que los ensayos hemolíticos se ejecutaron en la presencia de suero al 20 por ciento, solamente fue necesario mostrar el enlace retenido en un ensayo de enlace en suero al 50 por ciento.

Por consiguiente, los Fabs finales maduros se incubaron con suero agotado en C5 humana al 100 por ciento a 37°C durante 8 horas. Las muestras se recolectaron en diferentes puntos del tiempo, y se probaron para determinar el enlace a la C5 humana en un ELISA en solución. El Fab + las muestras de suero utilizadas para el ELISA se diluyeron a una concentración+ del 50 por ciento de suero + Fab 10 nM.

La Figura 18 ilustra los resultados de los anticuerpos finales de enlace de C5 en el formato de Fab. Se retuvo del 70 al 93 por ciento de la actividad de enlace después de un tiempo de incubación de 8 horas a 37°C en suero al 50 por ciento, comparándose con la incubación en suero regulado con fosfato.

Ejemplo 12: Caracterización mediante reserva de epítopos.

Este procedimiento se utilizó para agrupar los Fabs anti-C5

humana en diferentes reservas de epítopos que se enlazan al mismo epítopo o a un epítopo traslapado de la proteína C5.

Se probó la competencia de cada anticuerpo anti-C5 humana biotinilado con cada anticuerpo anti-C5 humana no marcado en un exceso de 100 veces en un ELISA (modo de captura). Se comparó con la señal más alta de cada anticuerpo (Fab biotinilado sin competencia).

La C5 humana se capturó por medio de una IgG anti-C5 humana policlonal (US Biological), la cual se recubrió previamente durante la noche a 4°C sobre placas Maxisorp negras de 384 pozos. Al día siguiente, la placa se lavó dos veces con PBST, y se bloqueó durante 2 horas con BSA al 3 por ciento-PBST. Después de lavar tres veces con PBST, se agregaron 20 microlitros de C5 humana, y se incubaron durante 2 horas a temperatura ambiente. La placa se lavó tres veces con PBST antes de agregar los Fabs.

Se agregaron 20 microlitros de Fab no marcado (200 microgramos/mililitro ó 400 microgramos/mililitro) (exceso de 100 veces) a los pozos de una placa Maxisorp, y subsiguientemente se agregaron 20 nanogramos/mililitro ó 40 nanogramos/mililitro del Fab biotinilado. Los Fabs biotinilados y no marcados se incubaron durante 1 hora a temperatura ambiente. La placa se lavó tres veces con PBST, y se agregó Strep-AP Zymax Estreptavidina-Fosfatasa Alcalina, ZYMED, Código: 43-8322, Lote: 50799648, para la detección del enlace del Fab biotinilado por medio de C5 a las placas. Se agregó el sustrato AttoPhos (Roche) a las placas, y se

leyó la fluorescencia después de 5 a 10 minutos.

Fabs progenitores

Se capturó la C5 (por medio de una anticuerpo policlonal), y se aplicó el FabY no marcado en un exceso al FabX biotinilado. Se detectó el enlace del FabX biotinilado a la C5 humana. Se pudieron definir seis grupos de Fabs: Grupo 1: MOR06952, 6961; Grupo 2: MOR06525, 6756, 6757, 6763; Grupo 3: MOR07087; Grupo 4: MOR06764, 6776, 7081; Grupo 5: MOR07089; Grupo 6: MOR07082, 7083, 7084, 7086, 7088, 7090, 7091, 7092, 7093, 7095.

Los Fabs también se dividieron en diferentes grupos de enlace de epítopo utilizando un método diferente: se inmovilizó el FabX, luego se pre-incubó el FabY, y se agregó la C5 biotinilada. Se pudieron definir los siguientes grupos de Fabs: Grupo 1: MOR06952, 6961; Grupo 2: MOR06525,6757, 7083; Grupo 3: MOR07087 ; Group 4: MOR06763; Grupo 5: MOR07081; Grupo 6: MOR07082,7083,7084,7086,7088,7091,7092, 7093 (el 7089 compite con el 7084). Se sacó la conclusión de que, utilizando dos métodos diferentes, se podían obtener resultados similares.

Fabs maduros

Con el objeto de realizar la caracterización del Fab, se midió la competencia del Fab biotinilado con el Fab no marcado (aplicado en un exceso de 100 veces) en un ELISA en solución. Los resultados se compararon con la señal más alta (Fab biotinilado sin competencia).

Como se muestra en la Figura 19, los Fabs biotinilados compiten con los Fabs no marcados idénticos, y todos los Fabs

compiten por el enlace con el mismo epítopo o con un epítopo traslapado. Estos resultados se correlacionan con los datos de reserva de epítopos para los Fabs progenitores.

Ejemplo 13: Rastreo de enlazadores de cadena alfa contra beta de C5, y ensayos de competencia.

Se llevaron a cabo dos experimentos ELISA y ensayos hemolíticos para probar si un Fab era un enlazador de cadena alfa o beta como se describe en seguida.

En el primer experimento, el Fab se recubrió sobre una placa, y se agregó la C5 purificada o el sobrenadante a partir de la preparación de la C5 quimérica (cadena alfa humana, cadena beta de ratón). Como un siguiente paso, se aplicó la 5G1.1, y se hizo la detección por medio de una IgG anti-humano.

En un segundo experimento, se recubrió la 5G1.1 sobre una placa, se agregó la C5 purificada o el sobrenadante a partir de la preparación de la C5 quimérica (cadena alfa humana, cadena beta de ratón), y luego el Fab, que se detectó con un anticuerpo anti-Myc.

La IgG de referencia 5G1.1 reconoce la cadena alfa, y se utilizó para determinar si los Fabs generados por MorhpSys compiten con la 5G1.1 por el enlace. En los ensayos hemolíticos, se agregó el sobrenadante a partir de la preparación de la C5 quimérica al suero agotado en C5 humana, y se probaron los Fabs para determinar la inhibición de la hemólisis.

Fabs progenitores

La Figura 20 muestra los resultados de un experimento ELISA,

en donde los Fabs se recubrieron sobre una placa, se agregó la C5 o el sobrenadante de una preparación de C5 quimérica (cadena alfa humana y cadena beta de ratón), y luego la 5G1.1. La Figura 21 muestra los resultados de un experimento ELISA, en donde se capturaron la C5 purificada y el sobrenadante a partir de la C5 quimérica por medio de la 5G1.1.

MOR06525, 6756, 6763 eran enlazadores de cadena beta (se enlazan a la C5 pero no a la C5 quimérica). La mayoría de los Fabs MOR070XX (derivados a partir de los paneos en solución) son enlazadores de cadena alfa (se enlazan a C5 y a la C5 quimérica). MOR06952 y 6961 compiten con 5G1.1, de tal manera que son negativos tanto para la C5 como para la C5 quimérica, y por lo tanto, son más probablemente enlazadores de cadena alfa como 5G1.1. MOR06757 se comporta como MOR06952 y 6961, es decir, probablemente es un enlazador de cadena alfa. Sin embargo, MOR06757 no inhibe la hemólisis del sobrenadante de la C5 quimérica salpicado en el suero agotado en C5, mientras que todos los otros enlazadores de cadena alfa sí lo hacen (Figura 22).

En el ensayo hemolítico, se agregó el sobrenadante a partir de la preparación de la C5 quimérica al suero agotado en C5 humana, y se probaron los Fabs para determinar la inhibición de la hemólisis. MOR06525, 6756, 6757 y 6763 no inhibieron la hemólisis con la C5 quimérica, y por lo tanto, podrían ser enlazadores de cadena beta. MOR06952, 6961, 7081, 7082, 7083, 7084, 7086, 7087, 7088, 7089, 7090, 7091, 7092, 7093, 7094, 7095 inhibieron la hemólisis, y por lo

tanto, podrían ser enlazadores de cadena alfa.

Ejemplo 14: Resistencia a la proteólisis.

Con el objeto de investigar la rigidez estructural de los Fabs, se llevó a cabo la prueba de resistencia de los Fabs a la proteólisis mediante termolisina (proteasa bacteriana de termolisina, Calbiochem). El Fab se incubó con termolisina (Fab: termolisina = 3:1 (peso/peso), volumen de reacción de 8 microlitros), ya sea a 37°C, o bien a 55°C (la actividad de la termolisina es óptima a 55°C). La reacción se detuvo mediante la adición de 4 microlitros de EDTA 0.5 M y 4 microlitros del regulador de muestreo de LDS 4x (Invitrogen), y las muestras detenidas se ejecutaron sobre SDS-PAGE al 4-12 por ciento en condiciones no reductoras. La proteólisis de los Fabs se analizó mediante el monitoreo de la desaparición de las bandas de Fab que se visualizaron mediante teñido con Coomassie.

Fabs progenitores

Los Fabs progenitores se probaron para determinar su resistencia a la proteólisis de termolisina a 37°C y a 55°C. Se utilizó el Fab de un anticuerpo de IL-1β humanizado como el control. La mayoría de los Fabs probados fueron resistentes a la degradación por la termólisis a 37°C durante hasta 90 minutos. Para diferenciar adicionalmente la rigidez estructural de los Fabs, se llevó a cabo la proteólisis a una temperatura más alta de 55°C. Muchos de los Fabs probados se degradaron rápidamente a 55°C (>90 por ciento del Fab se degradó dentro de 30 minutos), mientras que algunos Fabs

todavía fueron resistentes a la proteólisis después de 90 minutos (por ejemplo, el 7094). Se sugirió que los Fabs resistentes tenían una estructura más rígida, de tal manera que podrían mostrar mejores propiedades farmacocinéticas *in vivo*. Los resultados de estos experimentos se muestran en la Figura 23 y en la Figura 24.

Fabs maduros

Se probaron los Fabs con la más alta potencia en los ensayos hemolíticos para determinar su sensibilidad a la termolisina a 37°C y a 55°C. En la Figura 25 y en la Figura 26, se muestran los experimentos con derivados de MOR07086, 7091, 7092 y 7093.

Los resultados de estas pruebas revelaron que los derivados de los MOR07091, 7092 y 7093 progenitores, eran menos sensibles a la proteólisis, mientras que los derivados de MOR07086 eran más sensibles a la proteólisis.

Ejemplo 15: Ensayo de depósito de MAC.

Debido a que la cascada del complemento terminal finaliza con la formación del MAC, la inhibición de la formación del MAC fue una sugerencia adicional para la capacidad del anticuerpo para bloquear la cascada del complemento. La racionalización fue tener un establecimiento adicional independiente de las células y del comportamiento de las células.

El Zymosan (Sigma), que es un carbohidrato insoluble a partir de la pared celular de la levadura, utilizado especialmente en el inmunoensayo de la senda alternativa, se recubrió para activar la senda alternativa, y se utilizó IgM (Sigma) recubierta para activar la

senda clásica para la determinación del depósito del MAC (complejo de ataque de membrana). Los Fabs se incubaron previamente con suero humano (6 por ciento para AP, 2 por ciento para CP), y se agregaron a la placa. Se calculó el porcentaje (%) de inhibición de depósito de MAC para cada muestra en relación con la línea base (suero humano tratado con EDTA) y con el control positivo (suero humano), y se utilizó para generar la curva de IC_{50} con XLFit.

Fabs progenitores

Se utilizaron los Fabs progenitores en diferentes concentraciones, y se determinó la máxima inhibición (si es aplicable, también los valores IC_{50}) (el ejemplo se muestra en la Figura 27). La mayoría de los Fabs inhibieron completamente el depósito de MAC, indicando el bloqueo de la disociación de la C5. La potencia y clasificación de los Fabs fueron similares a los datos de los ensayos hemolíticos.

REIVINDICACIONES

1. Un anticuerpo aislado o un fragmento de enlace de antígeno del mismo, que se enlaza específicamente a una proteína C5 de complemento, en donde este anticuerpo tiene una constante de afinidad (K_A) de cuando menos $1x10^7$ M^{-1}, 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, ó 10^{11} M^{-1}.

2. El anticuerpo de la reivindicación 1, el cual inhibe la senda de complemento alternativa, como se mide mediante un ensayo hemolítico *in vitro*, con una IC_{50} de 20 a 200 pM.

3. Un anticuerpo o fragmento de enlace de antígeno del mismo, que se enlaza específicamente a la proteína C5 de complemento, y que compite cruzadamente con un anticuerpo descrito en la Tabla 1.

4. Un anticuerpo o fragmento de enlace de antígeno del mismo, que se enlaza al mismo epítopo que un anticuerpo descrito en la Tabla 1.

5. El anticuerpo de la reivindicación 1, 3, ó 4, en donde este anticuerpo es un anticuerpo monoclonal.

6. El anticuerpo de la reivindicación 5, en donde este anticuerpo es un anticuerpo humano o humanizado.

7. El anticuerpo de la reivindicación 5, en donde este anticuerpo es un anticuerpo quimérico.

8. El anticuerpo de la reivindicación 5, en donde este anticuerpo comprende una región constante de cadena pesada

humana y una región constante de cadena ligera humana.

9. El anticuerpo de la reivindicación 5, en donde este anticuerpo es un anticuerpo de una sola cadena.

10. El anticuerpo de la reivindicación 5, en donde este anticuerpo es un fragmento Fab.

11. El anticuerpo de la reivindicación 5, en donde este anticuerpo es un scFv.

12. El anticuerpo de la reivindicación 5, el cual se enlaza tanto a la C5 humana como a la C5 de cinomolgo.

13. El anticuerpo de la reivindicación 5, el cual es un isotipo de IgG.

14. El anticuerpo de la reivindicación 5, en donde este anticuerpo comprende una estructura en donde los aminoácidos han sido sustituidos en la estructura del anticuerpo a partir de las secuencias de la línea germinal VH ó VL humanas respectivas.

15. Un anticuerpo monoclonal aislado, o un fragmento de enlace de antígeno del mismo, el cual comprende cuando menos una secuencia de región determinante de complementariedad (CDR) que tiene una identidad de secuencia de cuando menos el 95 por ciento con las SEQ ID NOs: 1, 2, 3, 4, 5, 6, 17, 18, 19, 20, 21, 22, 33, 34, 35, 36, 37, 38, 49, 50, 61, 62, 63, 64, 65, 66, 77, 78, 89, 95, 101, 107, 113, 119, 120, 131, 132, 133, 134, 135, 136, 145, 146, 147, 148, 149, 150, 159, 160, 161, 162, 163, 164, 173, 174, 175, 176, 177, 178, 195, 196, 197, 198, 199, 200, 209, 226, 235, 236, 237, 238, 239, ó 240, en donde este anticuerpo se enlaza a la proteína C5

humana.

16. Un anticuerpo monoclonal aislado, o un fragmento de enlace de antígeno del mismo, el cual comprende cuando menos una secuencia de la región determinante de complementariedad de cadena pesada, que es idéntica a las SEQ ID NOs: 1, 2, 3, 17, 18, 19, 33, 34, 35, 49, 61, 62, 63, 77, 77, 95, 107, 113, 119, 132, 131, 133, 145, 146, 147, 159, 160, 161, 173, 174, 175, 195, 196, 197, 226, 235, 236, ó 237, en donde este anticuerpo se enlaza a la proteína C5 humana.

17. Un anticuerpo monoclonal aislado, o un fragmento de enlace de antígeno del mismo, el cual comprende cuando menos una secuencia de la región determinante de complementariedad de cadena ligera, que es idéntica a las SEQ ID NOs: 4, 5, 6, 20, 21, 22, 36, 37, 38, 50, 64, 65, 66, 78, 89, 101, 120, 134, 135, 136, 148, 149, 150, 162, 163, 164, 176, 177, 178, 198, 199, 200, 209, 238, 239, ó 240, en donde este anticuerpo se enlaza a la proteína C5 humana.

18. Un anticuerpo monoclonal aislado, o un fragmento de enlace de antígeno del mismo, el cual comprende una CDR1 de cadena pesada seleccionada a partir del grupo que consiste en las SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, y 235; una CDR2 de cadena pesada seleccionada a partir del grupo que consiste en las SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, y 236; y una CDR3 de cadena pesada seleccionada a partir del grupo que consiste en las SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, y 237, en donde este anticuerpo

se enlaza a la proteína C5 humana.

19. Un anticuerpo monoclonal aislado, o un fragmento de enlace de antígeno del mismo, el cual comprende una CDR1 de cadena ligera seleccionada a partir del grupo que consiste en las SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, y 238; una CDR2 de cadena ligera seleccionada a partir del grupo que consiste en las SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, y 239; y una CDR3 de cadena ligera seleccionada a partir del grupo que consiste en las SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, y 240, en donde este anticuerpo se enlaza a la proteína C5 humana.

20. El anticuerpo de la reivindicación 18, o un fragmento de enlace de antígeno del mismo, el cual comprende además una CDR1 de cadena ligera seleccionada a partir del grupo que consiste en las SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, y 238; una CDR2 de cadena ligera seleccionada a partir del grupo que consiste en las SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, y 239; y una CDR3 de cadena ligera seleccionada a partir del grupo que consiste en las SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, y 240.

21. Un anticuerpo monoclonal aislado, o un fragmento de enlace de antígeno del mismo, el cual comprende una región variable de cadena pesada que tiene una identidad de secuencia de cuando menos el 95 por ciento con las SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241,

253, 257, 273, 277, ó 281, en donde este anticuerpo se enlaza a la proteína C5 humana.

22. Un anticuerpo monoclonal aislado, o un fragmento de enlace de antígeno del mismo, el cual comprende una región variable de cadena ligera que tiene una identidad de secuencia de cuando menos el 95 por ciento con las SEQ ID NOs: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, y 289, en donde este anticuerpo se enlaza a la proteína C5 humana.

23. El anticuerpo de la reivindicación 21, o un fragmento de enlace de antígeno del mismo, el cual comprende además una región variable de cadena ligera que tiene una identidad de secuencia de cuando menos el 95 por ciento con las SEQ ID NOs: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, y 289.

24. Un anticuerpo monoclonal aislado, o un fragmento de enlace de antígeno del mismo, el cual comprende una cadena pesada que tiene una identidad de secuencia de cuando menos el 95 por ciento con las SEQ ID NOs: 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, ó 282, en donde este anticuerpo se enlaza a la proteína C5 humana.

25. Un anticuerpo monoclonal aislado, o un fragmento de enlace de antígeno del mismo, el cual comprende una cadena ligera que tiene una identidad de secuencia de cuando menos el 95 por

ciento con las SEQ ID NOs: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, ó 290, en donde este anticuerpo se enlaza a la proteína C5 humana.

26. El anticuerpo de la reivindicación 24, o un fragmento de enlace de antígeno del mismo, el cual comprende además una cadena ligera que tiene una identidad de secuencia de cuando menos el 95 por ciento con las SEQ ID NOs: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, ó 290.

27. Una composición farmacéutica, la cual comprende un anticuerpo seleccionado a partir de las reivindicaciones 1 a 26, y un vehículo farmacéuticamente aceptable.

28. Un ácido nucleico, el cual comprende una secuencia de nucleótidos que codifica un polipéptido que comprende una región variable de cadena pesada que tiene una identidad de secuencia de cuando menos el 95 por ciento con las SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, ó 281.

29. Un ácido nucleico, el cual comprende una secuencia de nucleótidos que codifica un polipéptido que comprende una región variable de cadena ligera que tiene una identidad de secuencia de cuando menos el 95 por ciento con las SEQ ID NOs: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, y 289.

30. Un vector que comprende al ácido nucleico de la reivindicación 28 ó 29.

31. Una célula huésped aislada, la cual comprende: (1) un segmento de ADN recombinante que codifica una cadena pesada del anticuerpo de la reivindicación 18, y (2) un segundo segmento de ADN recombinante que codifica una cadena ligera del anticuerpo; en donde estos segmentos de ADN se enlazan operablemente a un promotor, y son capaces de expresarse en la célula huésped mencionada.

32. La célula huésped de la reivindicación 31, en donde el anticuerpo es un anticuerpo monoclonal humano.

33. La célula huésped de la reivindicación 31, la cual es una línea celular de mamífero no humano.

34. Un método para el tratamiento de la degeneración macular relacionada con la edad, el cual comprende administrar a un sujeto que lo necesite, una cantidad efectiva de una composición que comprende un anticuerpo seleccionado a partir de las reivindicaciones 1 a 26.

35. El método de la reivindicación 34, en donde el sujeto es un ser humano.

36. Un método para el tratamiento de una enfermedad, el cual comprende administrar a un sujeto que lo necesite, una cantidad efectiva de una composición que comprende un anticuerpo seleccionado a partir de las reivindicaciones 1 a 26, en donde esta enfermedad es asma, artritis, enfermedad cardíaca autoinmune,

esclerosis múltiple, enfermedad inflamatoria del intestino, isquemia-lesiones por reperfusión, Síndrome de Barraquer-Simons, hemodiálisis, lupus sistémico, lupus eritematoso, soriasis, esclerosis múltiple, trasplante, enfermedad de Alzheimer, glomerulonefritis, ó MPGN II.

37. El método de la reivindicación 36, en donde la enfermedad mencionada es glomerulonefritis.

38. Un método para el tratamiento de hemoglobinuria nocturna paroxismal (PNH), el cual comprende administrar a un sujeto que lo necesite, una cantidad efectiva de una composición que comprende un anticuerpo seleccionado a partir de las reivindicaciones 1 a 26.

39. Un método para aminorar un síntoma asociado con la circulación extracorpórea, el cual comprende administrar a un sujeto que lo necesite, una cantidad efectiva de una composición que comprende un anticuerpo de las reivindicaciones 1 a 26.

RESUMEN

La presente invención se refiere a anticuerpos que se dirigen a la proteína de complemento C5, y a composiciones y métodos de uso de los mismos.

* * * * *

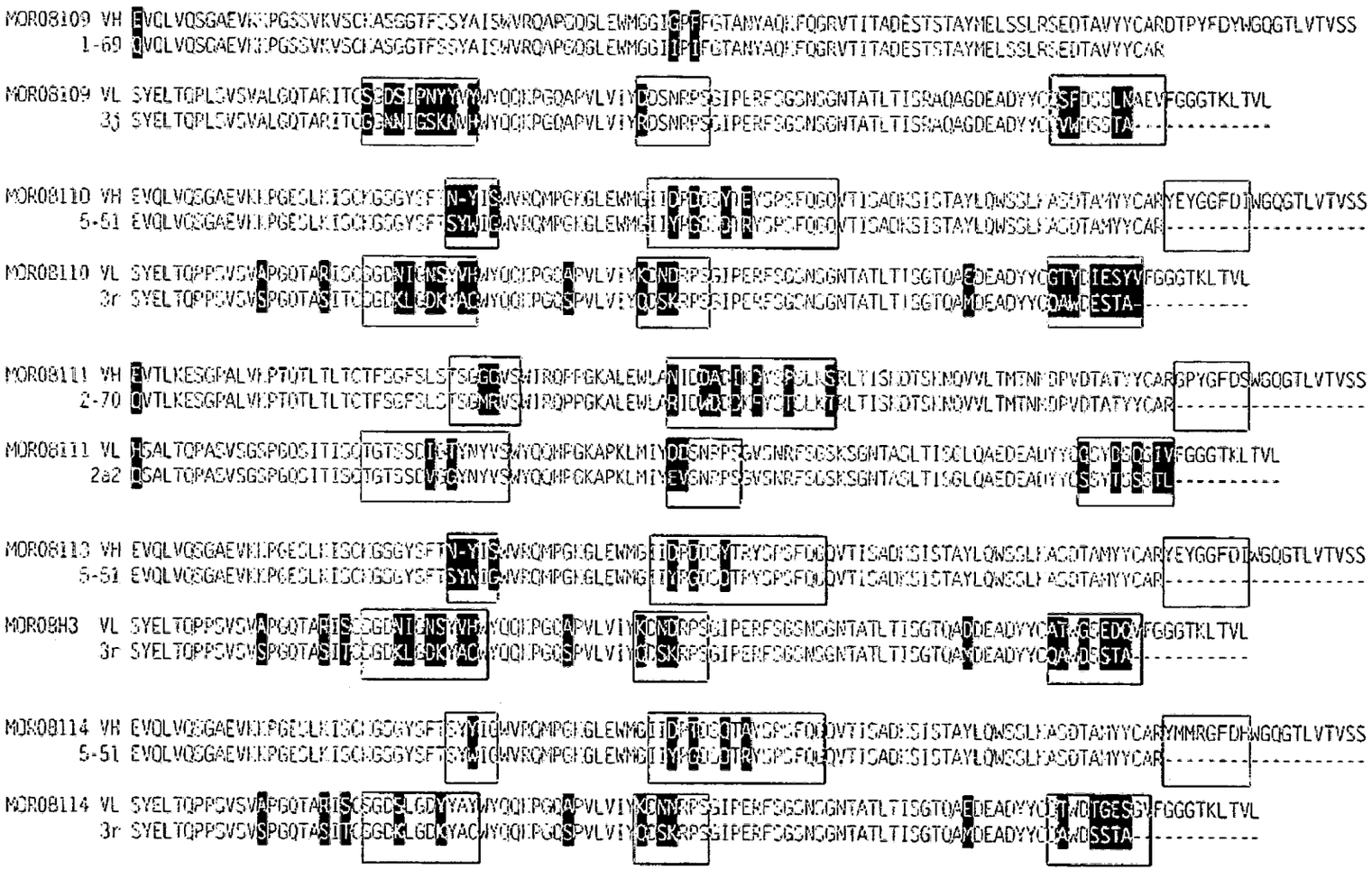


FIG. 1

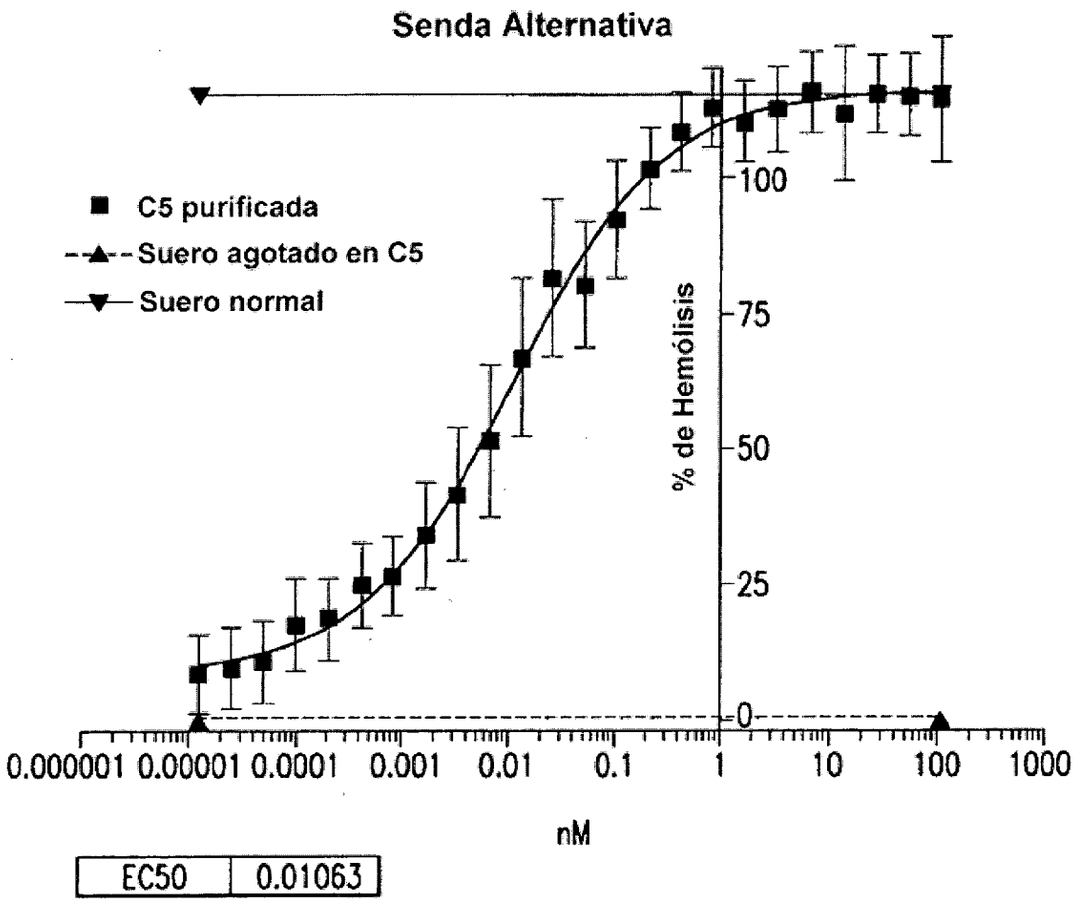

Senda Alternativa
C5 purificada
Suero agotado en C5
Suero normal
% de Hemólisis
100
75
50
25
0
0.000001 0.00001 0.0001 0.001 0.01 0.1 1 10 100 1000
nM
EC50 0.01063

FIG. 2

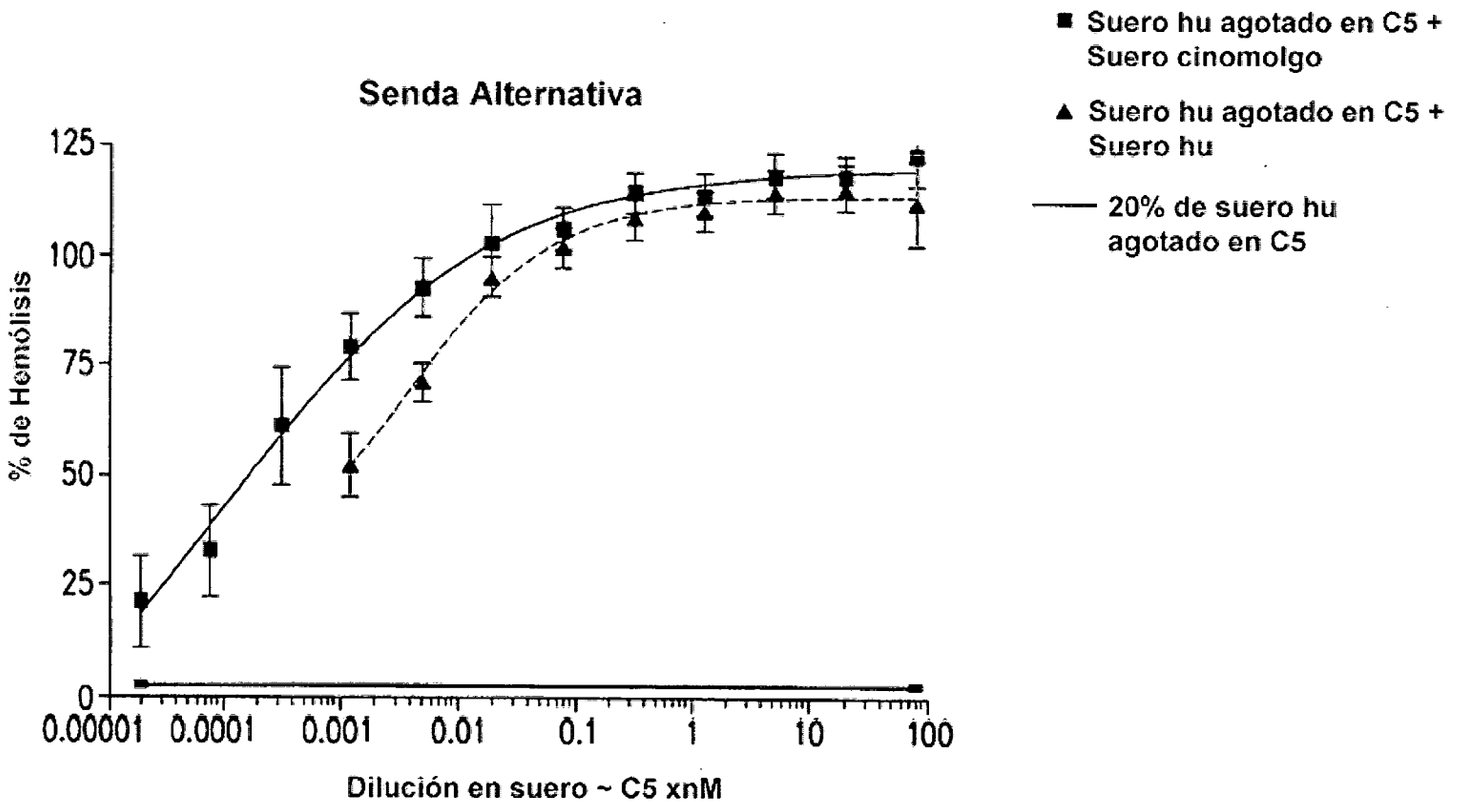

Senda Alternativa
% de Hemólisis
125
100
75
50
25
0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
Dilución en suero ~ C5 xnM
Suero hu agotado en C5 + Suero cinomolgo
Suero hu agotado en C5 + Suero hu
20% de suero hu agotado en C5

FIG. 3

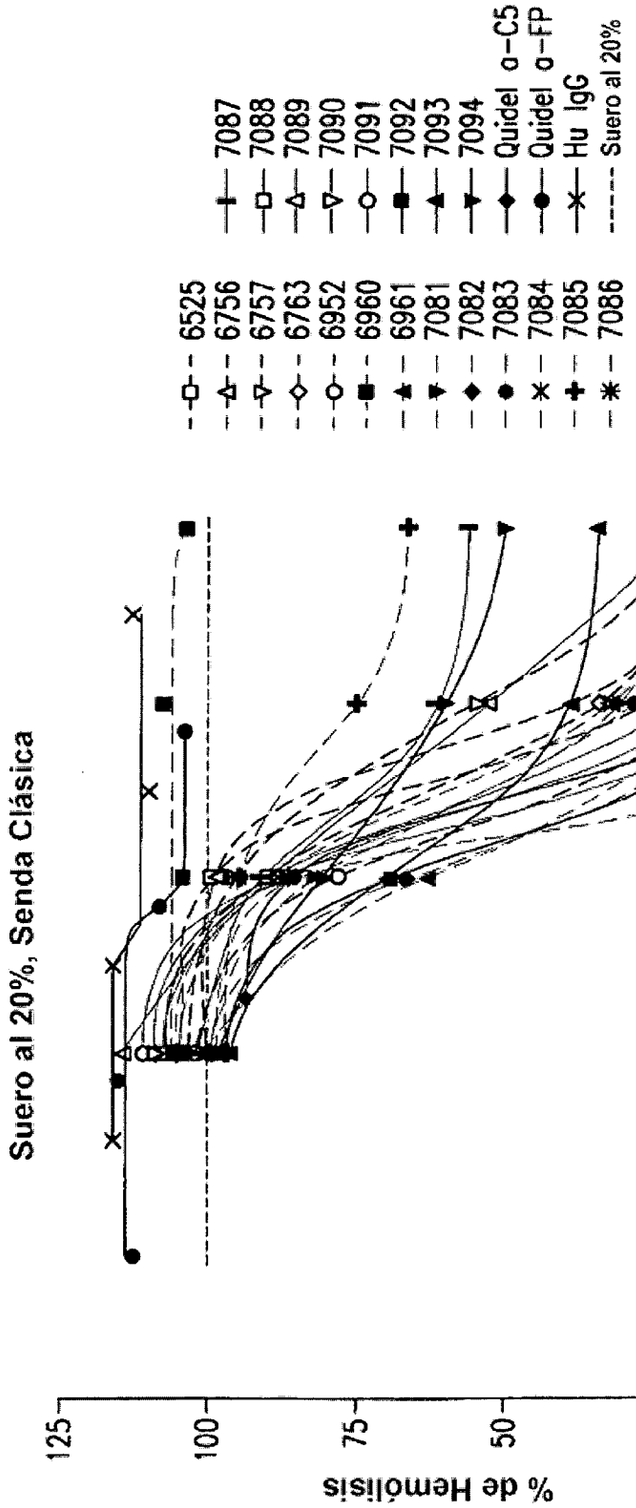

Suero al 20%, Senda Clásica
% de Hemólisis
Fab o Ab nM
0
25
50
75
100
125
1
10
100
1000
6525
6756
6757
6763
6952
6960
6961
7081
7082
7083
7084
7085
7086
7087
7088
7089
7090
7091
7092
7093
7094
Quidel α-C5
Quidel α-FP
Hu IgG
Suero al 20%

FIG. 4

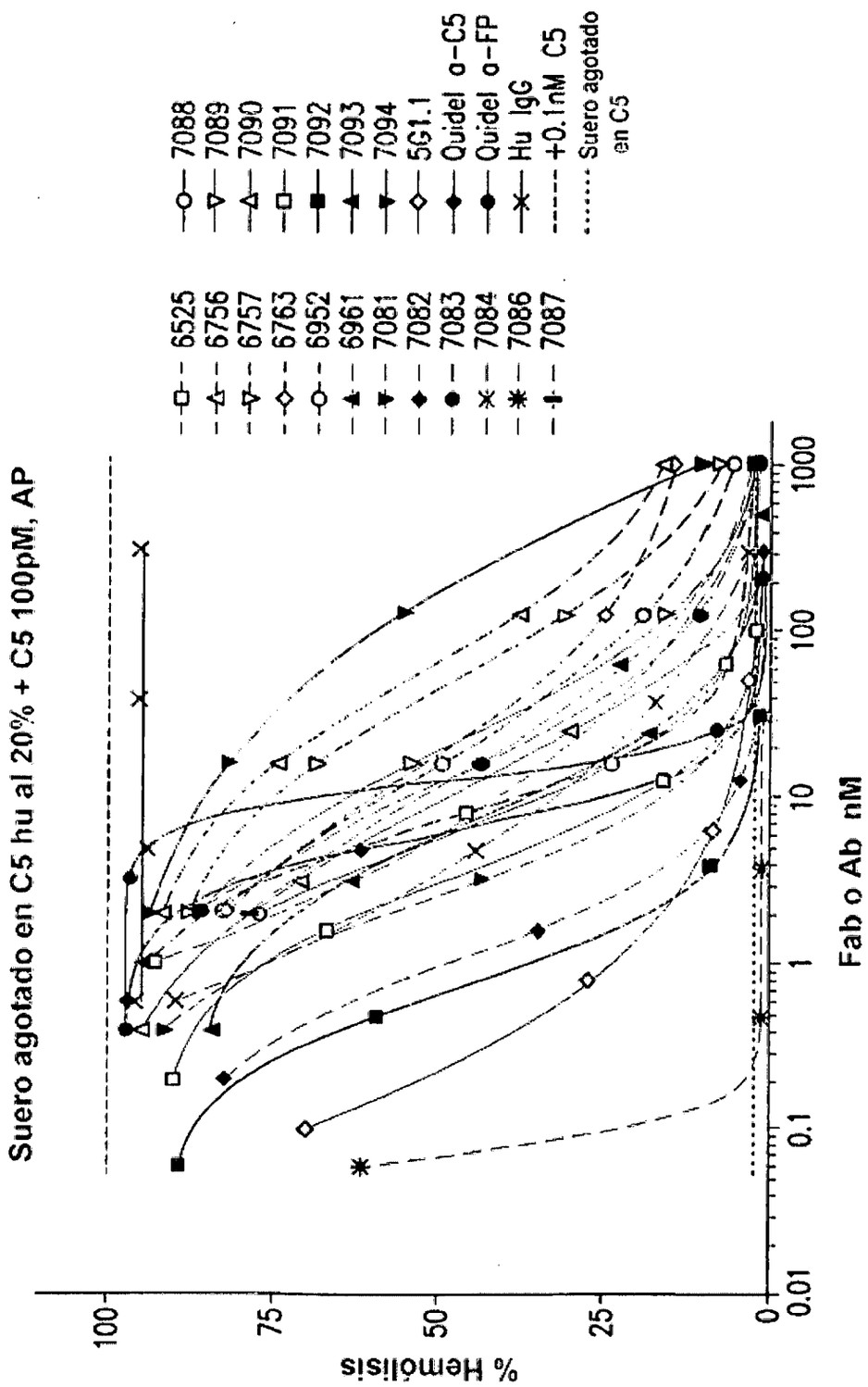

Suero agotado en C5 hu al 20% + C5 100pM, AP
% Hemólisis
Fab o Ab nM
0
25
50
75
100
0.01
0.1
1
10
100
1000
6525
6756
6757
6763
6952
6961
7081
7082
7083
7084
7086
7087
7088
7089
7090
7091
7092
7093
7094
5G1.1
Quidel o-C5
Quidel o-FP
Hu IgG
+0.1nM C5
Suero agotado en C5

FIG. 5

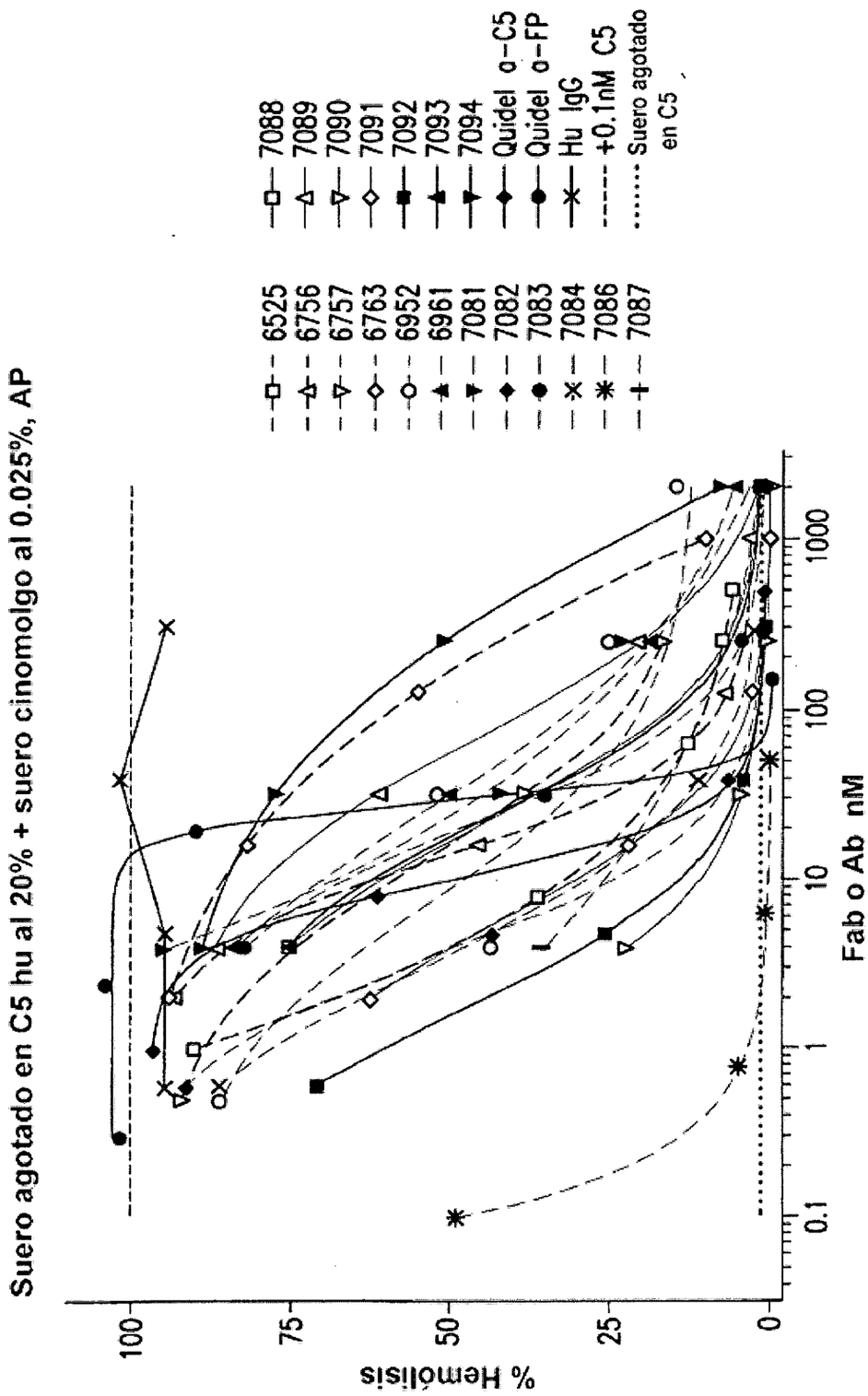
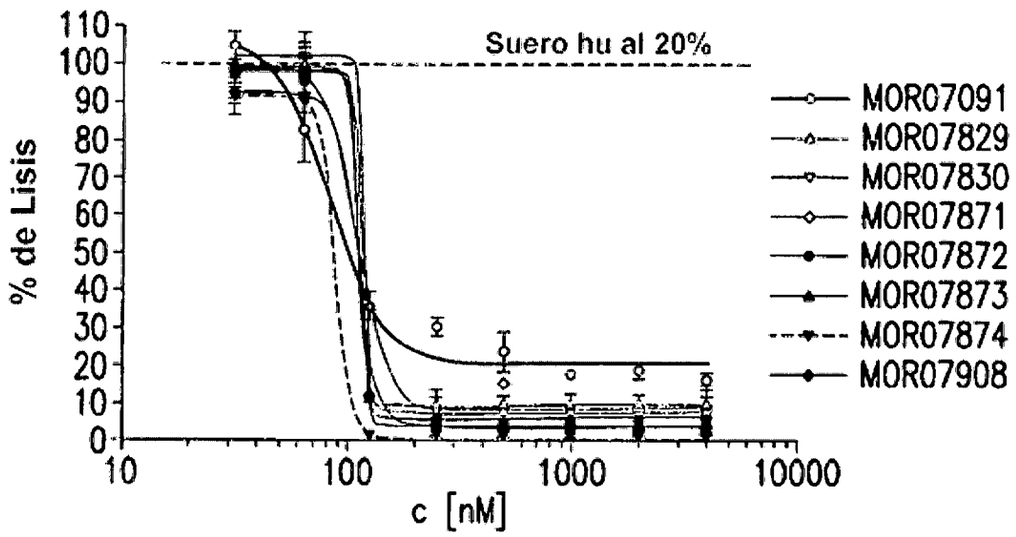

Suero agotado en C5 hu al 20% + suero cinomolgo al 0.025%, AP
% Hemólisis
Fab o Ab nM
0
25
50
75
100
0.1
1
10
100
1000
6525
6756
6757
6763
6952
6961
7081
7082
7083
7084
7086
7087
7088
7089
7090
7091
7092
7093
7094
Quidel α-C5
Quidel α-FP
Hu IgG
+0.1nM C5
Suero agotado en C5

FIG. 6

6GHA23_ensayo hemolítico CP normalizada*



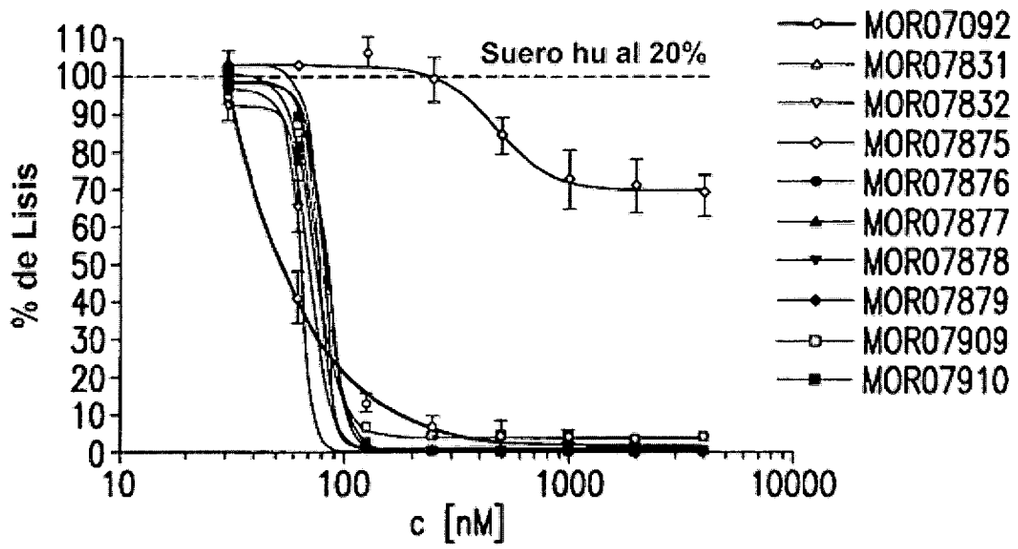
*100% de lisis = lisis en suero al 20%

Máxima Inhibición (%)

MOR07091: 80
MOR07829: 95
MOR07830: 90
MOR07871: 90
MOR07872: 95
MOR07873: 97
MOR07874: 100
MOR07908: 97

FIG. 7-1

6GHA23_ensayo hemolítico CP normalizada*

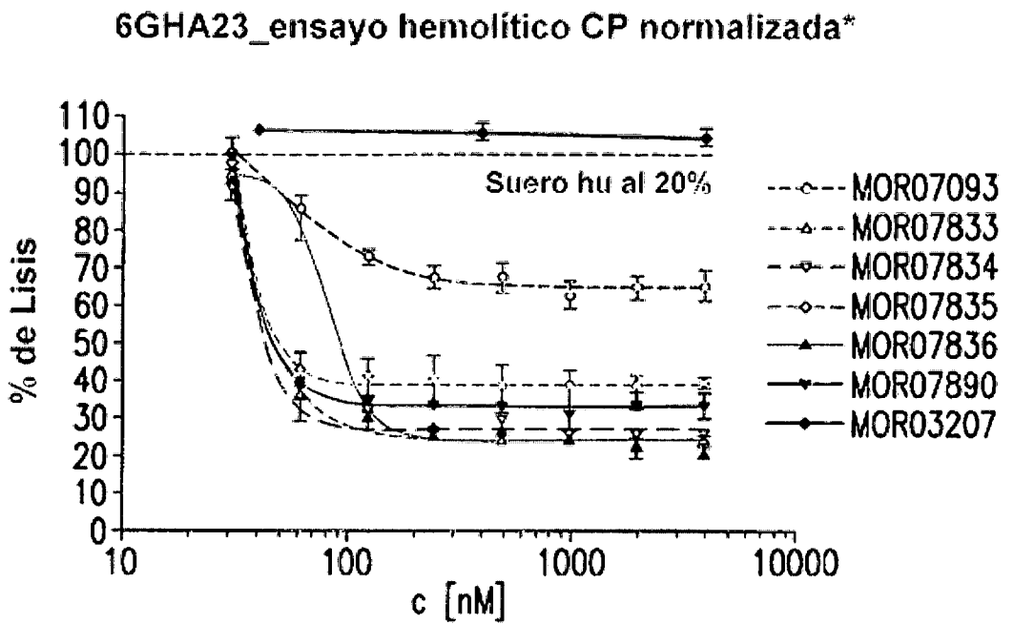


*100% de lisis = lisis en suero al 20%

Máxima Inhibición (%)

MOR07092: 100
MOR07831: 100
MOR07832: 100
MOR07875: 30
MOR07876: 100
MOR07877: 100
MOR07878: 100
MOR07879: 95
MOR07909: 100
MOR07910: 100

FIG. 7-2

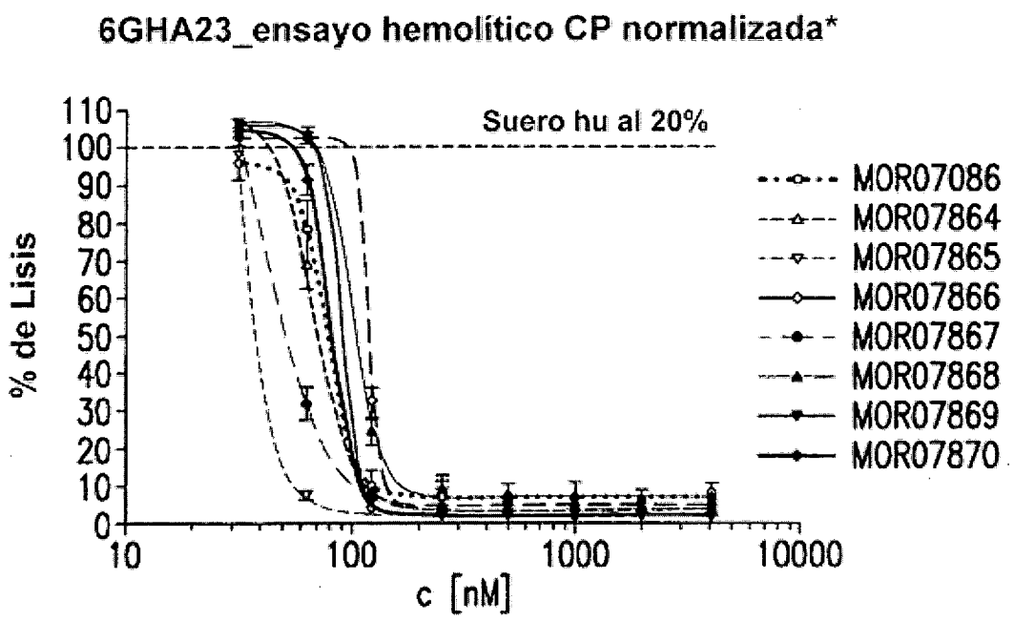


*100% de lisis = lisis en suero al 20%

Máxima Inhibición (%)

MOR07093: 30
MOR07833: 75
MOR07834: 70
MOR07835: 60
MOR07836: 75
MOR07890: 65

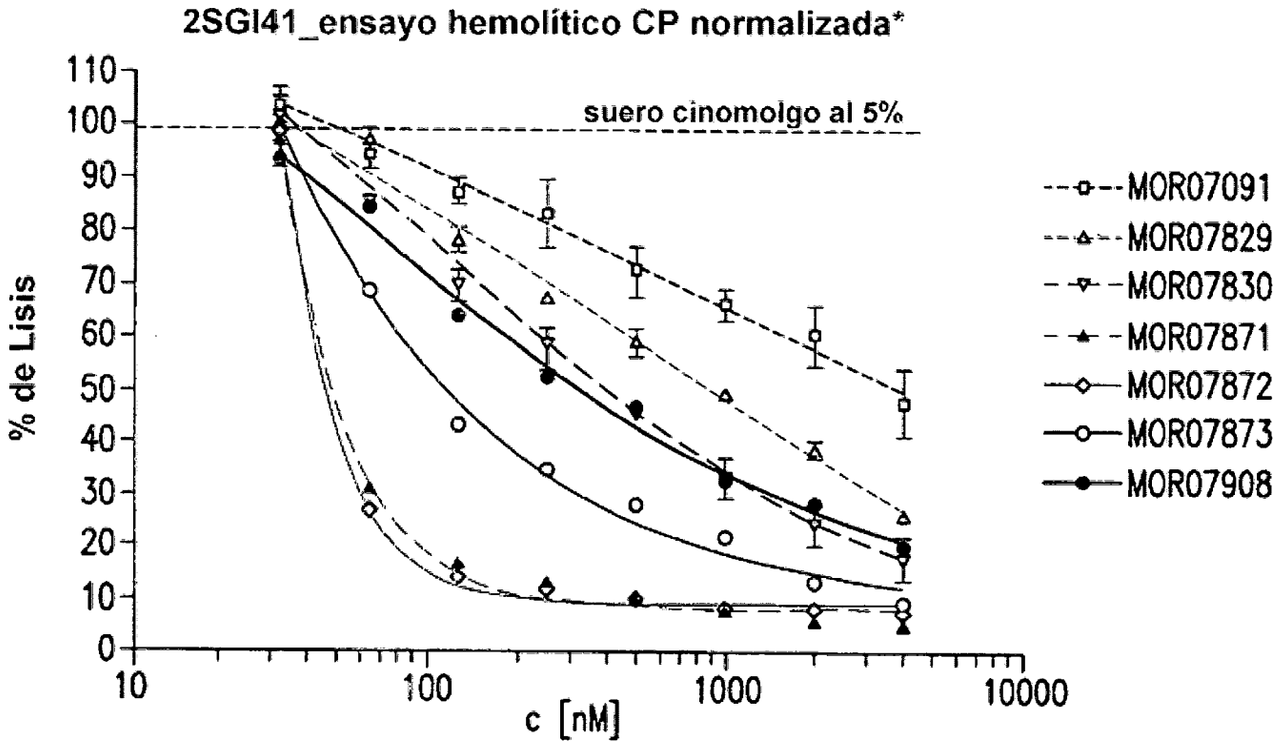
FIG. 7-3



*100% de lisis = lisis en suero al 20%

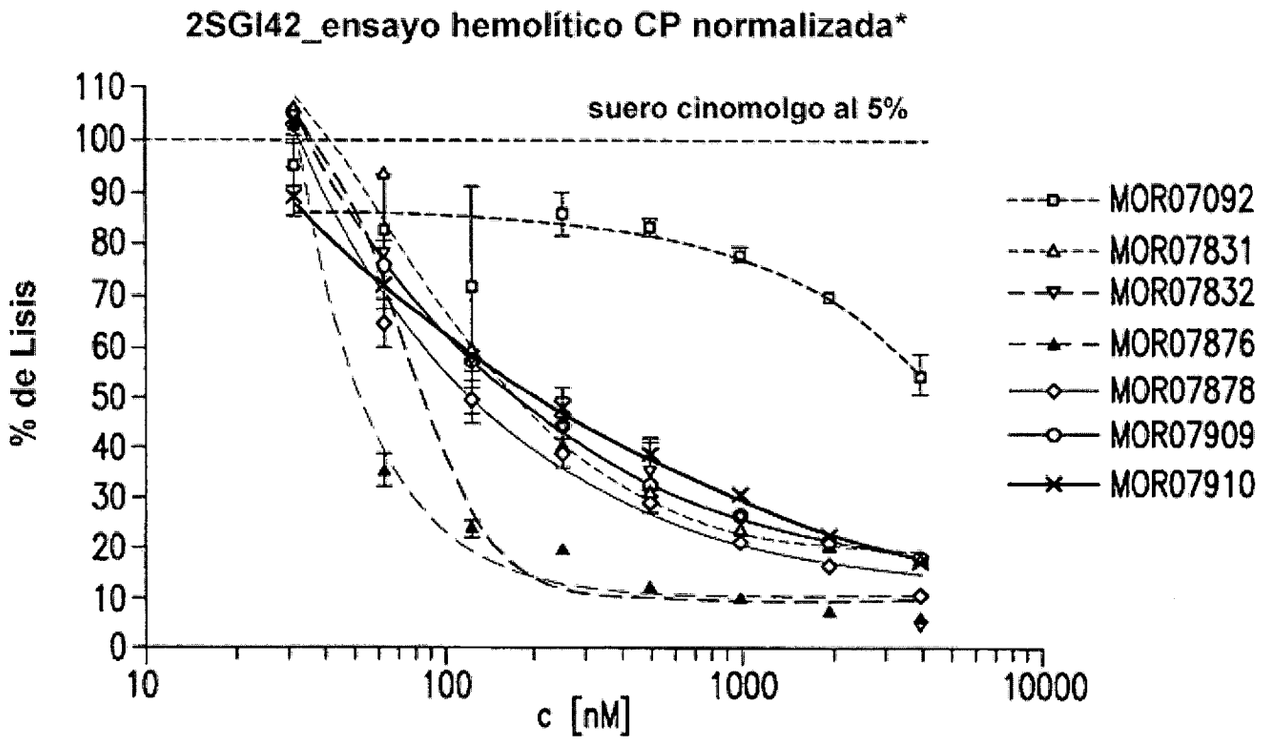
Máxima Inhibición (%)
MOR07086: 95
MOR07864: 100
MOR07865: 100
MOR07866: 100
MOR07867: 100
MOR07868: 95
MOR07869: 100
MOR07870: 97

FIG. 7-4



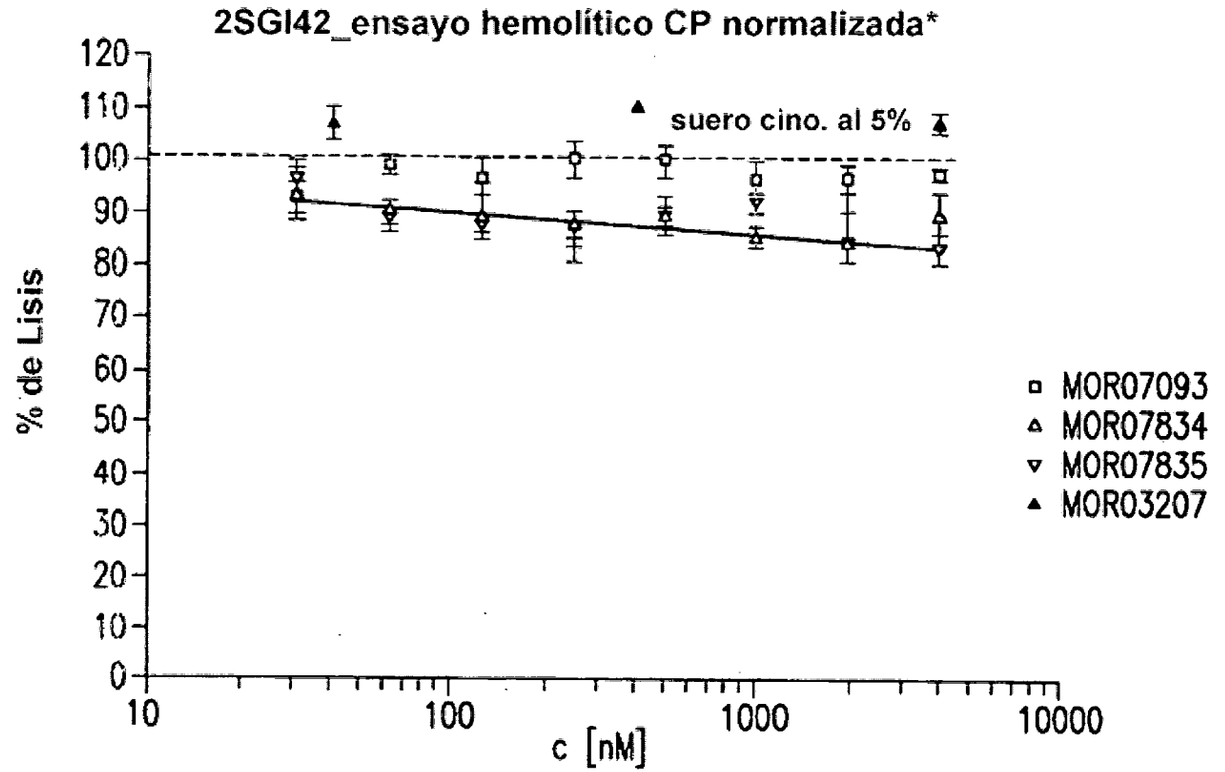
*100% de lisis = lisis en suero cinomolgo al 5%

FIG. 8-1



*100% de lisis = lisis en suero cinomolgo al 5%

FIG. 8-2



*100% de lisis = lisis en suero cinomolgo al 5%

FIG. 8-3

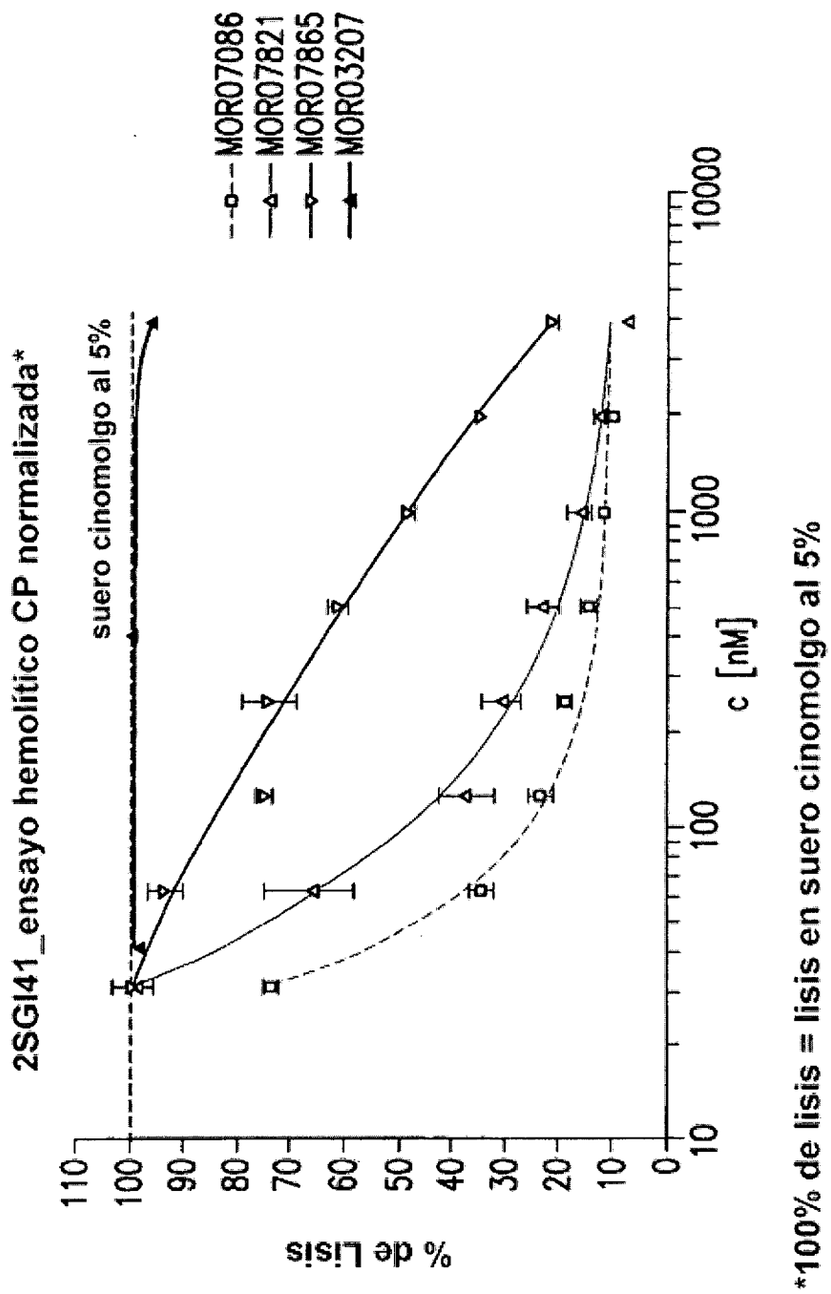
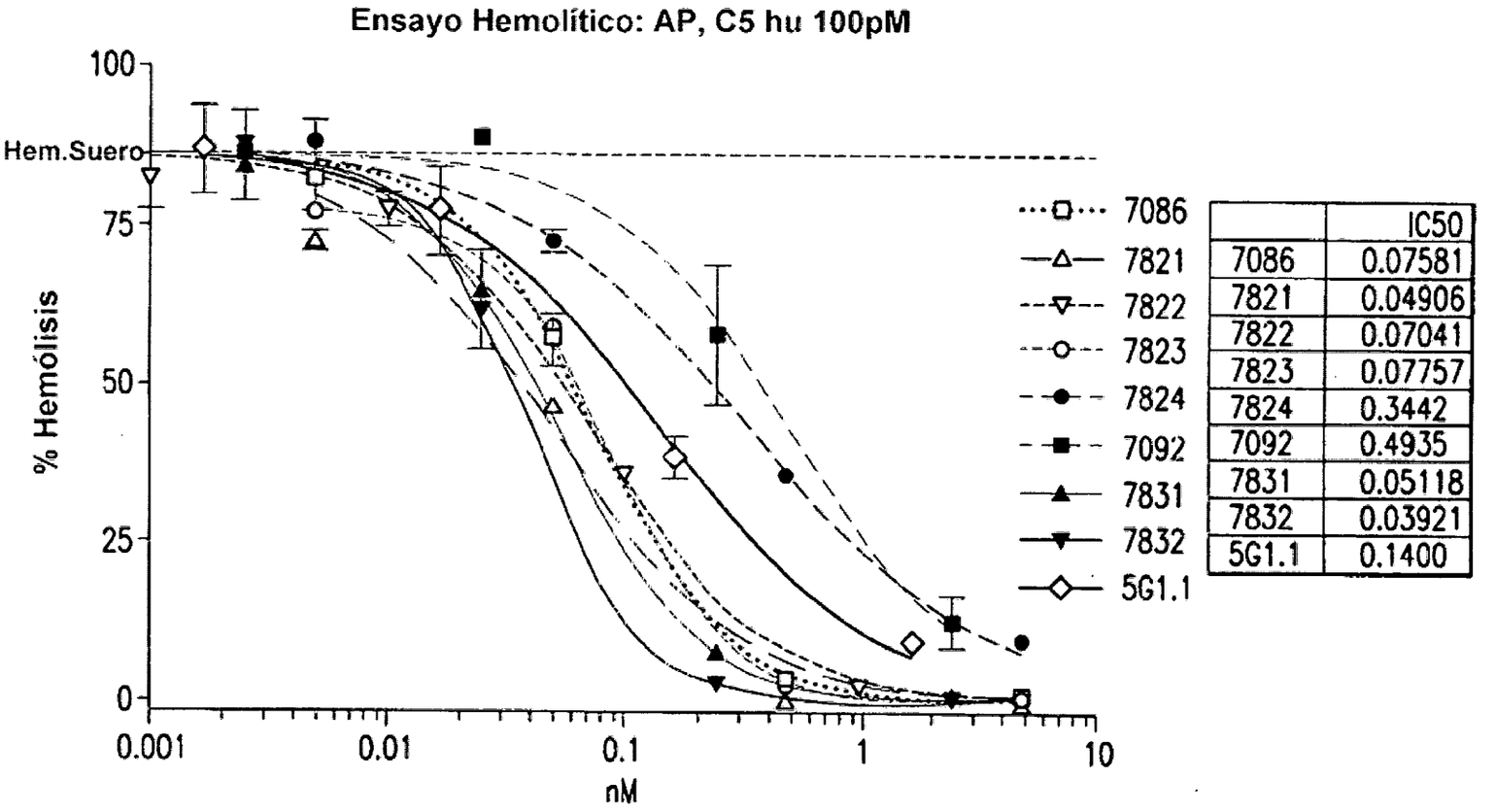
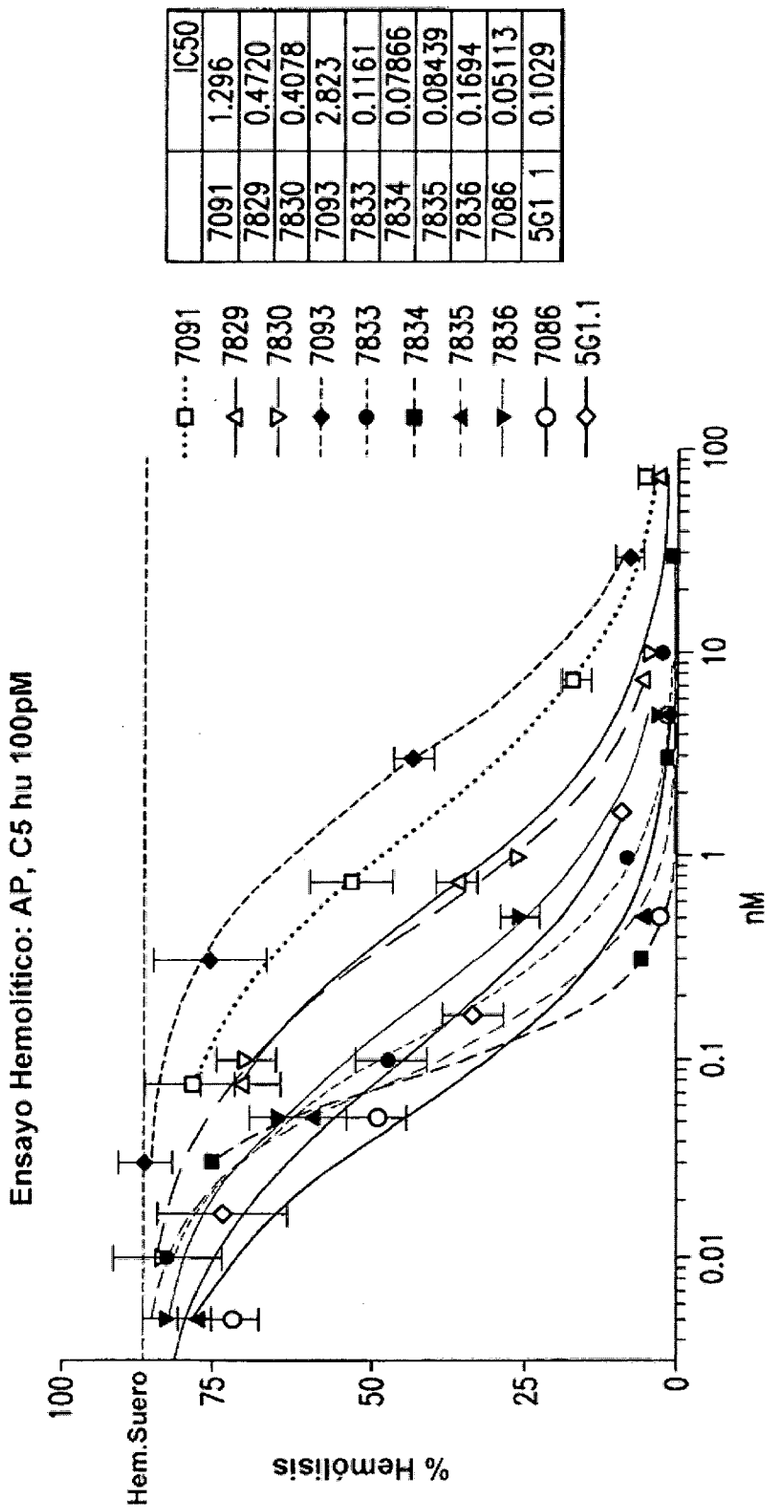

2SGI41_ensayo hemolítico CP normalizada*
suero cinomolgo al 5%
MOR07086
MOR07821
MOR07865
MOR03207
% de Lisis
c [nM]
110
100
90
80
70
60
50
40
30
20
10
0
10
100
1000
10000
*100% de lisis = lisis en suero cinomolgo al 5%

FIG. 8-4



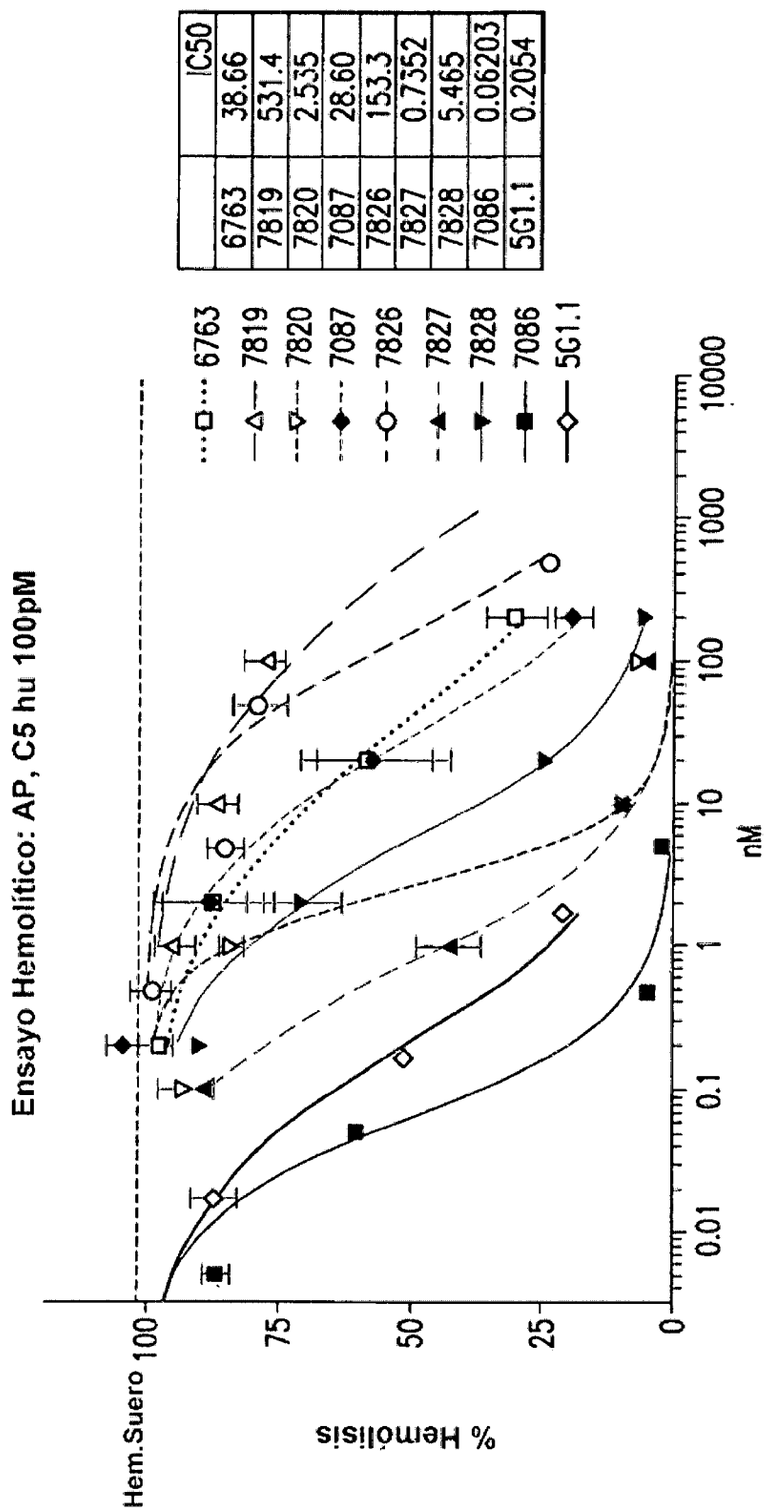
	IC50
7086	0.07581
7821	0.04906
7822	0.07041
7823	0.07757
7824	0.3442
7092	0.4935
7831	0.05118
7832	0.03921
5G1.1	0.1400

FIG. 9a



	IC50
7091	1.296
7829	0.4720
7830	0.4078
7093	2.823
7833	0.1161
7834	0.07866
7835	0.08439
7836	0.1694
7086	0.05113
5G1_1	0.1029

FIG. 9b



	IC50
6763	38.66
7819	531.4
7820	2.535
7087	28.60
7826	153.3
7827	0.7352
7828	5.465
7086	0.06203
5G1.1	0.2054

FIG. 9c

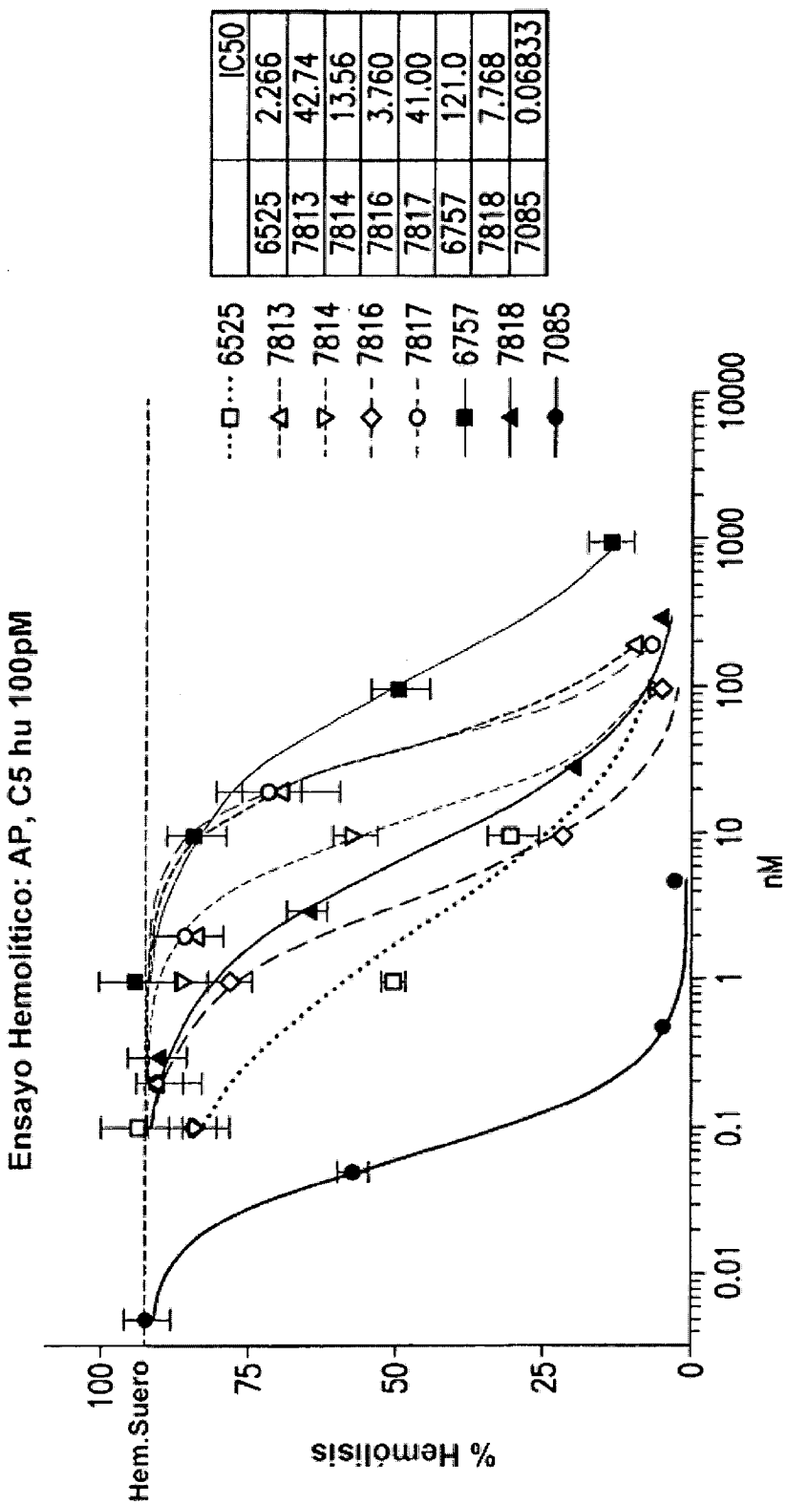
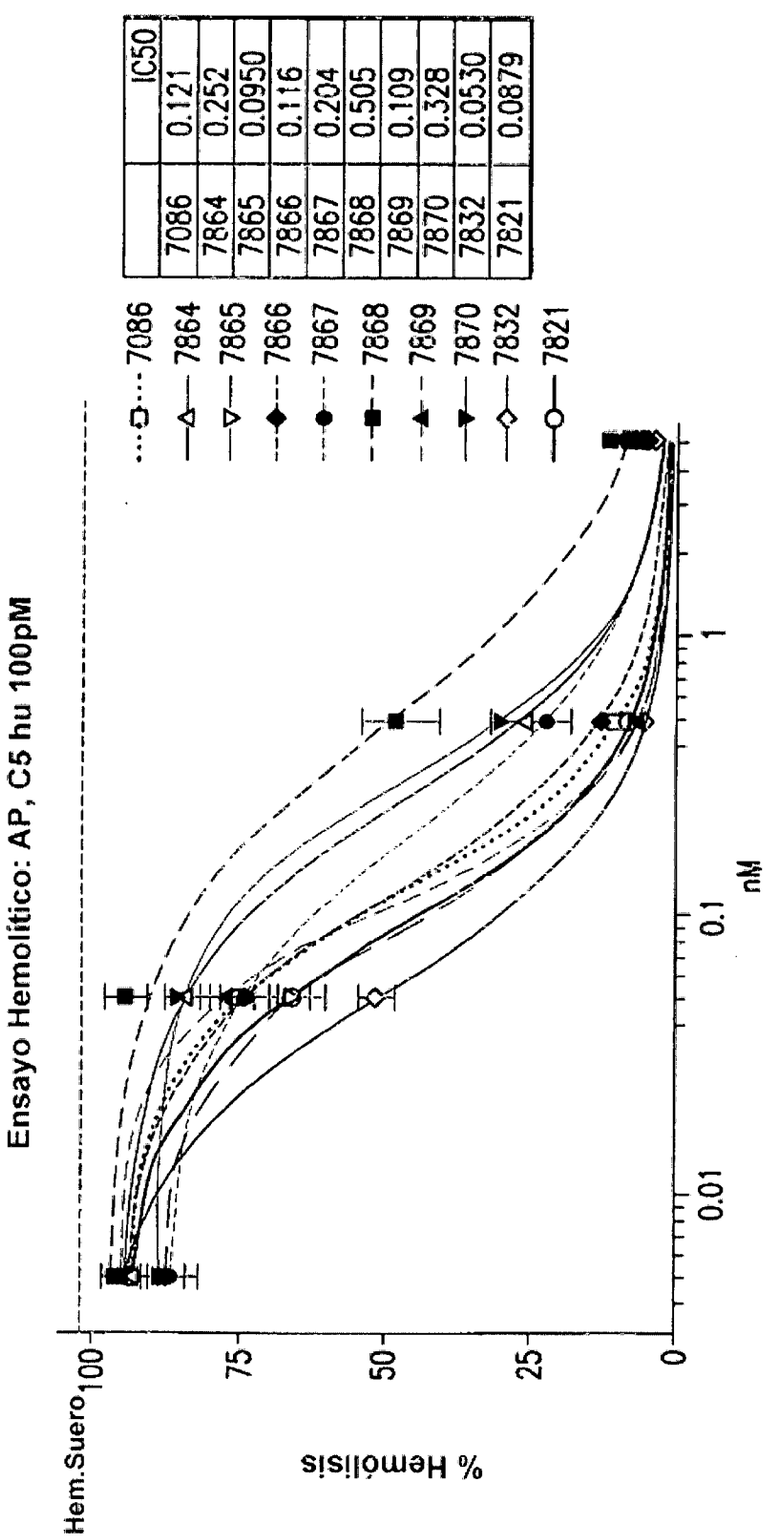

Ensayo Hemolítico: AP, C5 hu 100pM
% Hemólisis
Hem.Suero
100
75
50
25
0
0.01
0.1
1
10
100
1000
10000
nM
6525
7813
7814
7816
7817
6757
7818
7085
IC50
6525 2.266
7813 42.74
7814 13.56
7816 3.760
7817 41.00
6757 121.0
7818 7.768
7085 0.06833

FIG. 9d



	IC50
7086	0.121
7864	0.252
7865	0.0950
7866	0.116
7867	0.204
7868	0.505
7869	0.109
7870	0.328
7832	0.0530
7821	0.0879

FIG. 9e

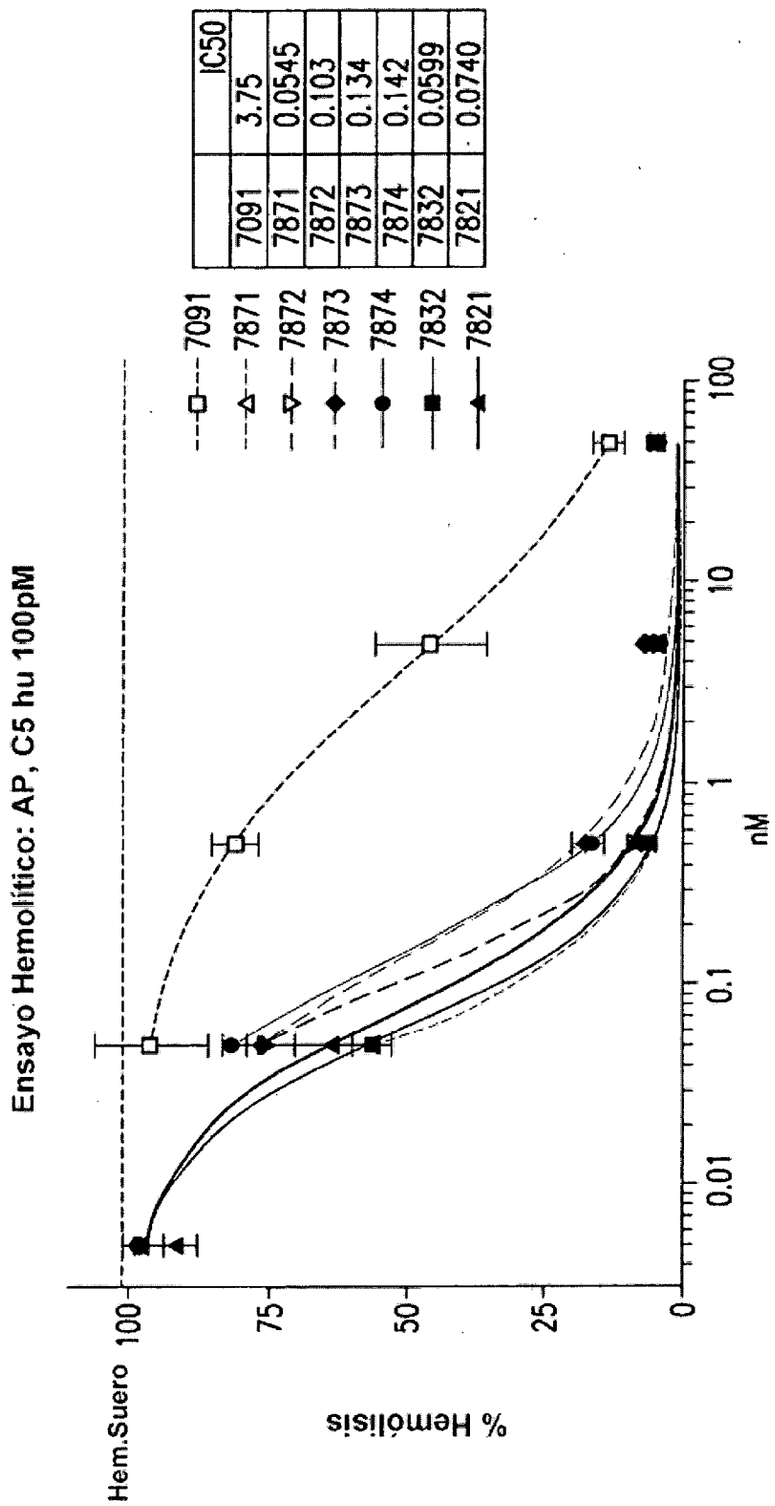

Ensayo Hemolítico: AP, C5 hu 100pM
Hem.Suero
% Hemólisis
nM
0
25
50
75
100
0.01
0.1
1
10
100
7091
7871
7872
7873
7874
7832
7821
IC50
7091 3.75
7871 0.0545
7872 0.103
7873 0.134
7874 0.142
7832 0.0599
7821 0.0740

FIG. 9f

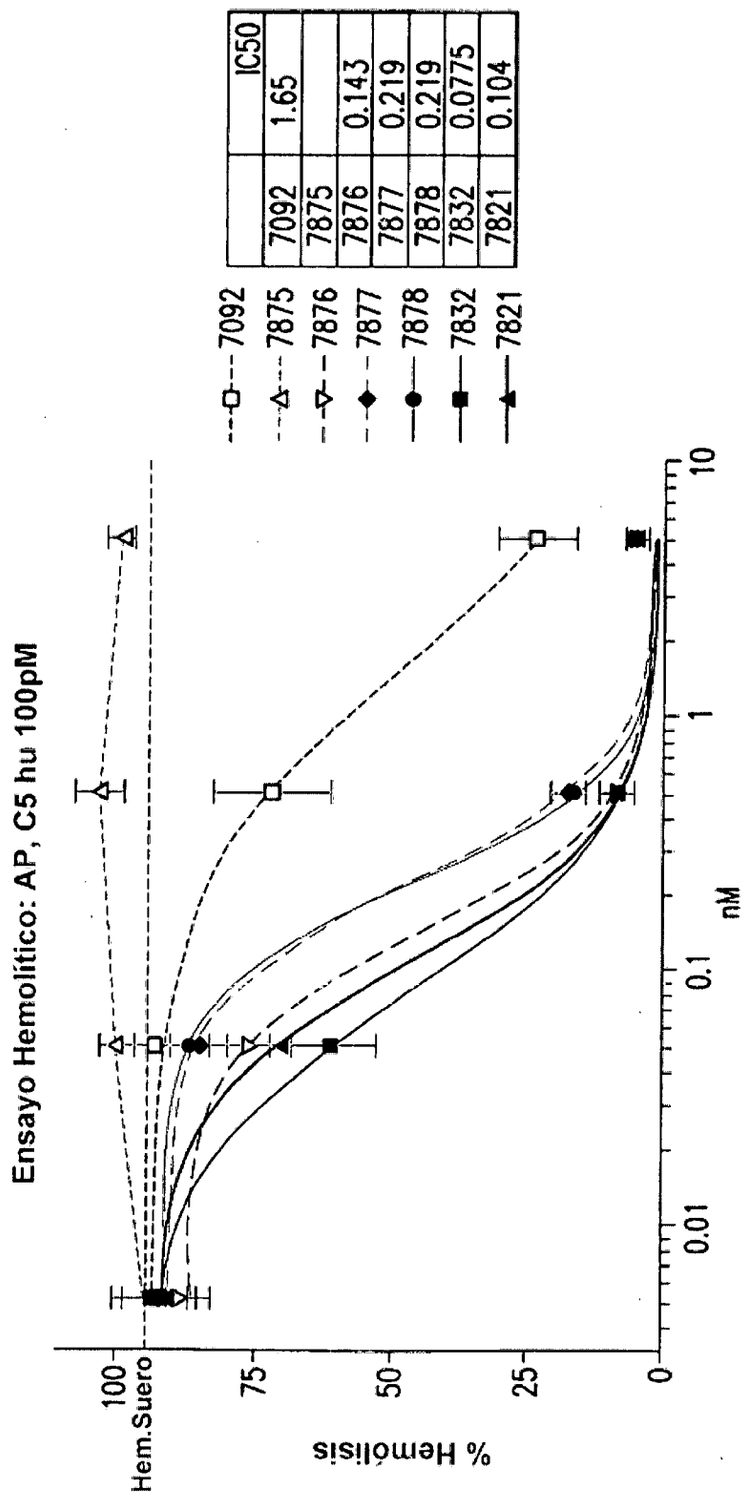
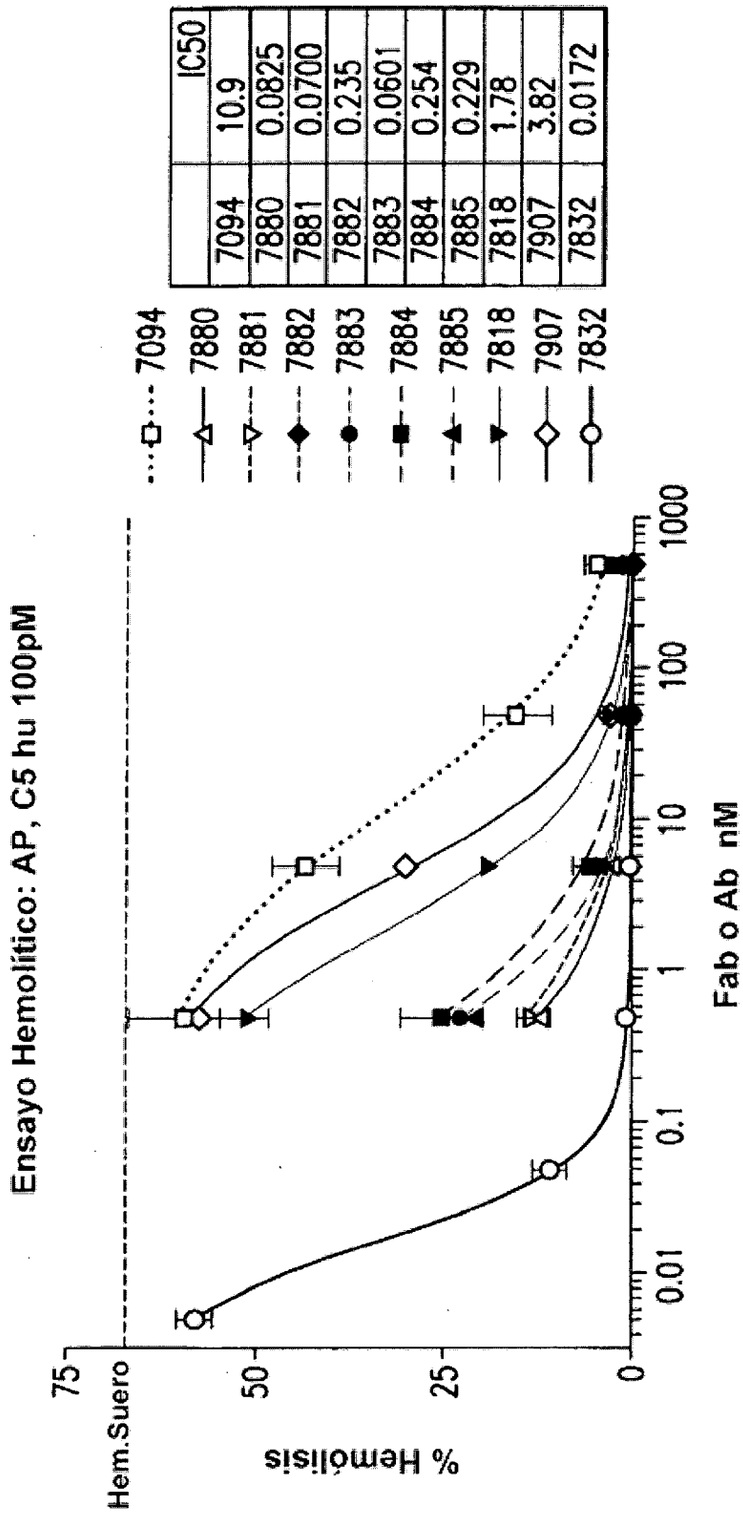
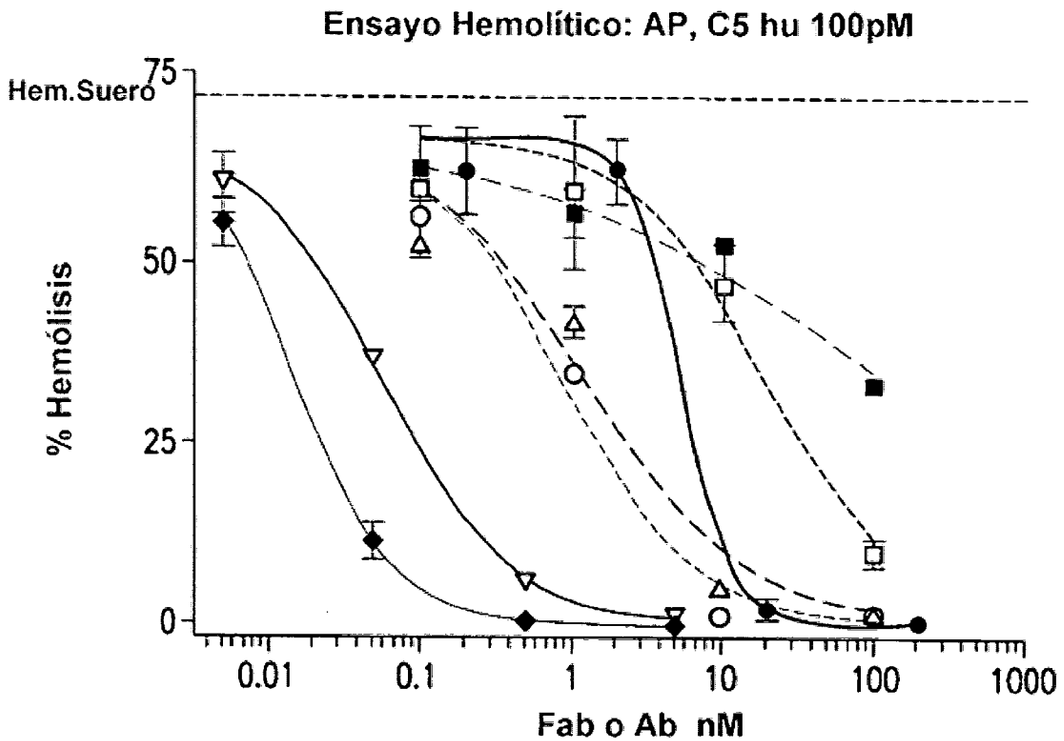

Ensayo Hemolítico: AP, C5 hu 100pM
% Hemólisis
Hem.Suero
100
75
50
25
0
0.01
0.1
1
10
nM
7092
7875
7876
7877
7878
7832
7821
IC50
7092 1.65
7875
7876 0.143
7877 0.219
7878 0.219
7832 0.0775
7821 0.104

FIG. 9g



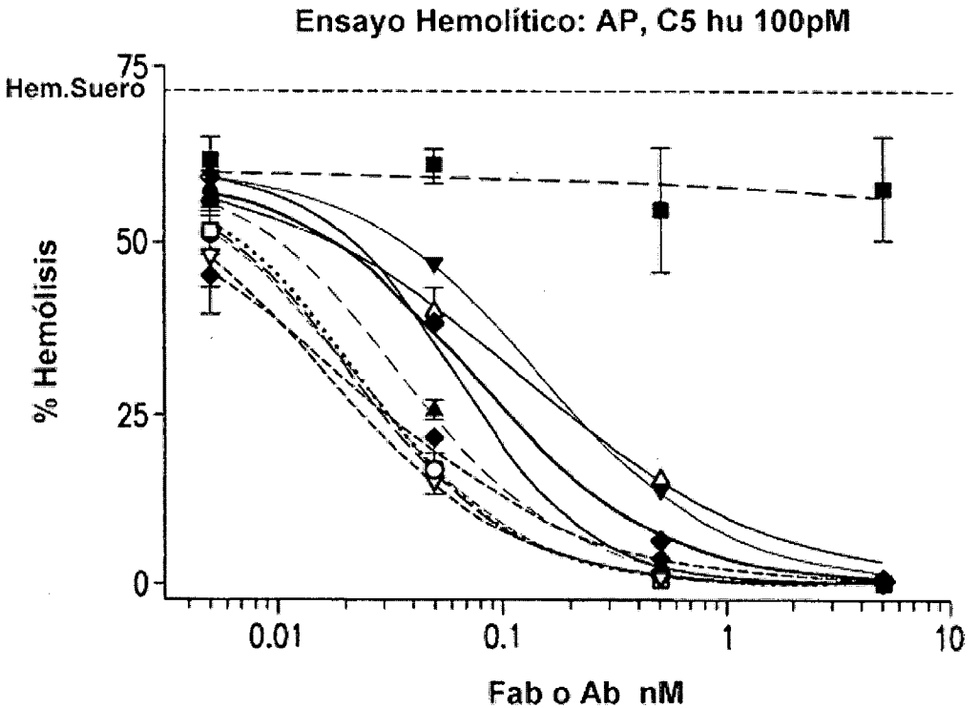
	IC50
7094	10.9
7880	0.0825
7881	0.0700
7882	0.235
7883	0.0601
7884	0.254
7885	0.229
7818	1.78
7907	3.82
7832	0.0172

FIG. 9h



	IC50
7613	19.9
7616	1.24
7620	0.902
7689	120
7832	0.0156
5G1.1	0.0582
A233 (α-FP)	5.45

FIG. 9i



	IC50
7832	0.0234
7879	0.123
7909	0.0167
7910	0.0201
7865	0.0214
7825	343159
7871	0.0366
7908	0.150
7834	0.0622
7890	0.0759

FIG. 9j

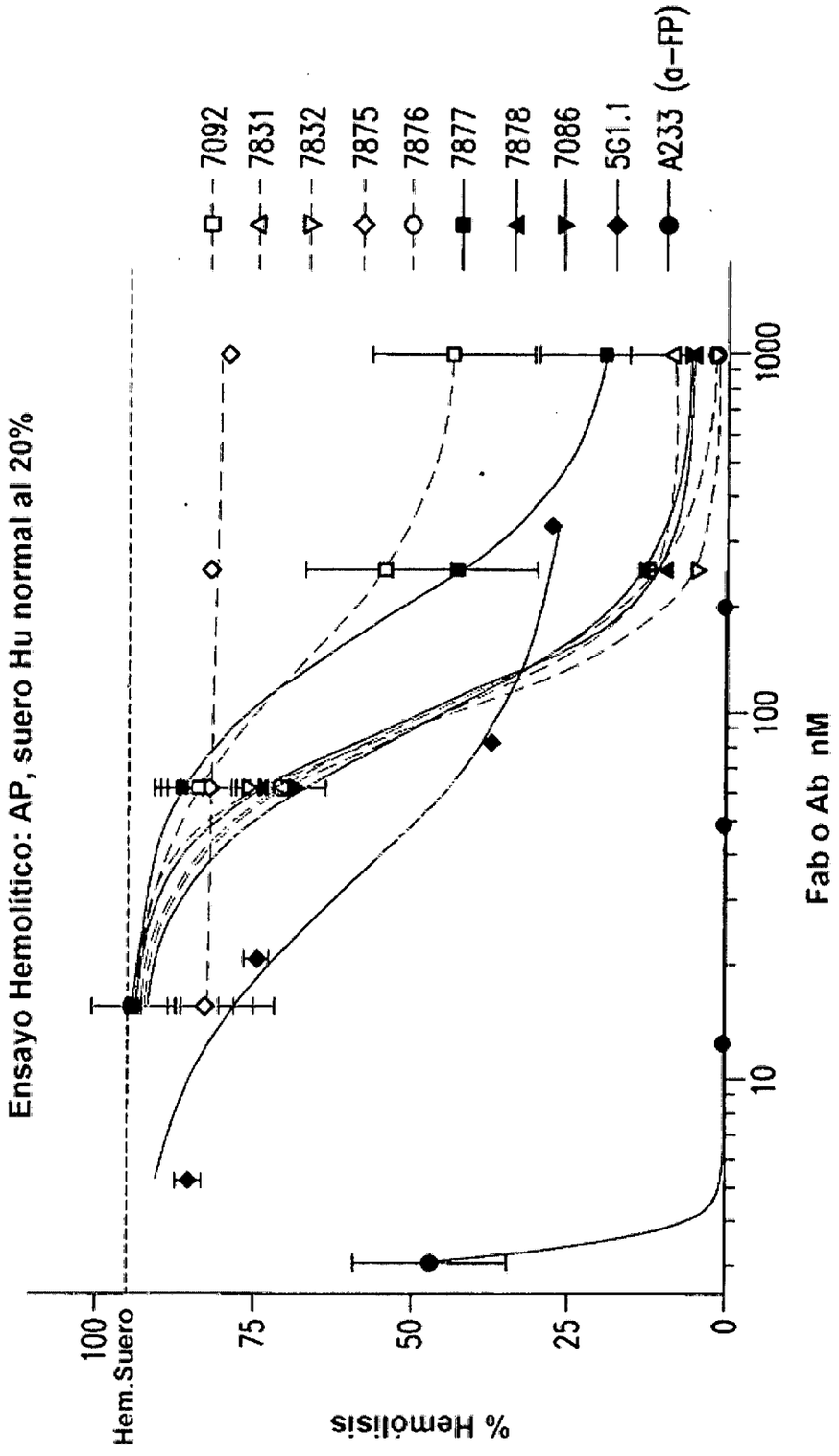

Ensayo Hemolítico: AP, suero Hu normal al 20%
% Hemolisis
Hem.Suero
100
75
50
25
0
10
100
1000
Fab o Ab nM
7092
7831
7832
7875
7876
7877
7878
7086
5C1.1
A233 (α-FP)

FIG. 10a

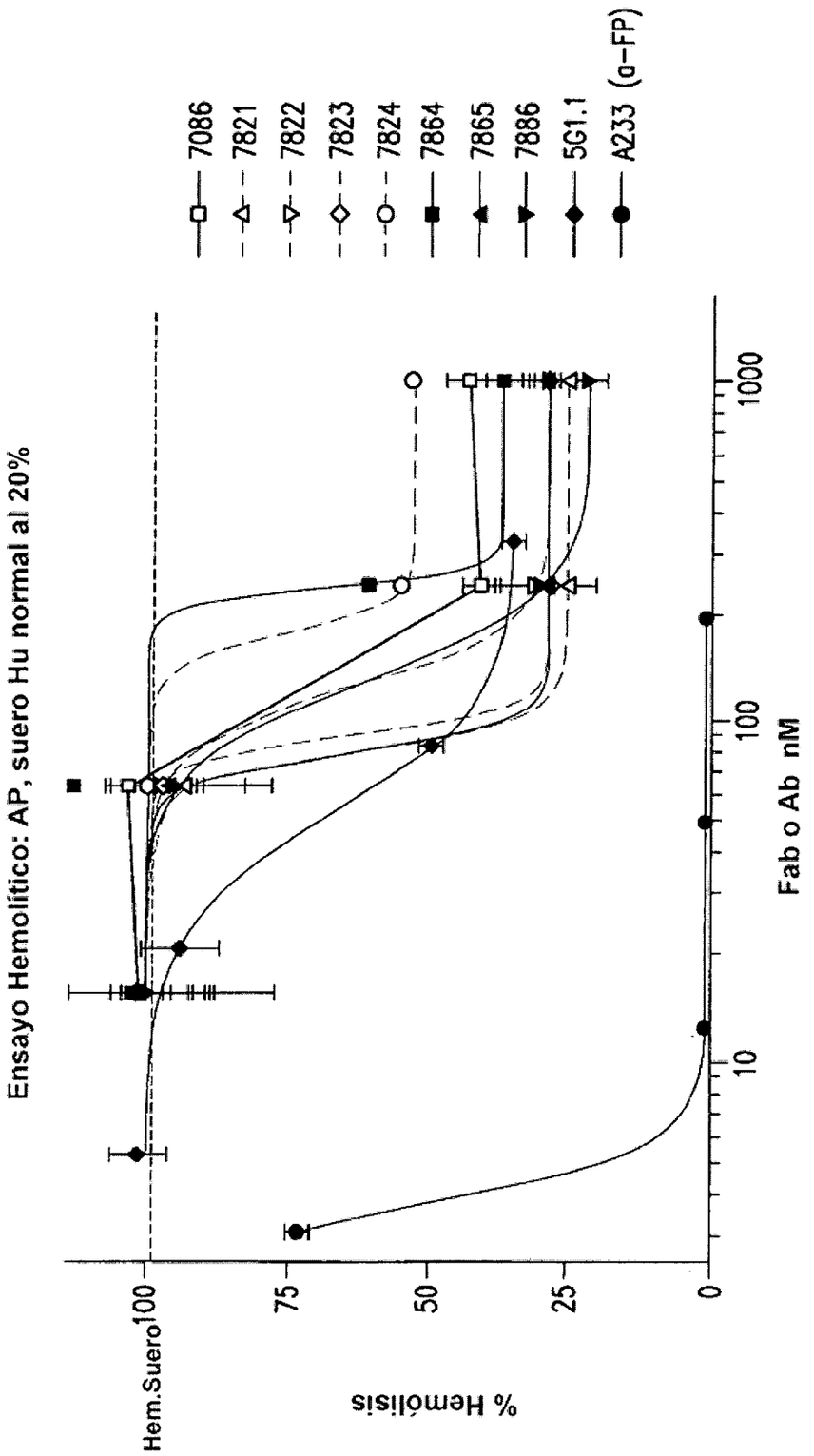

Ensayo Hemolítico: AP, suero Hu normal al 20%
Hem.Suero
100
75
50
25
0
% Hemólisis
10
100
1000
Fab o Ab nM
7086
7821
7822
7823
7824
7864
7865
7886
5G1.1
A233 (a-FP)

FIG. 10b

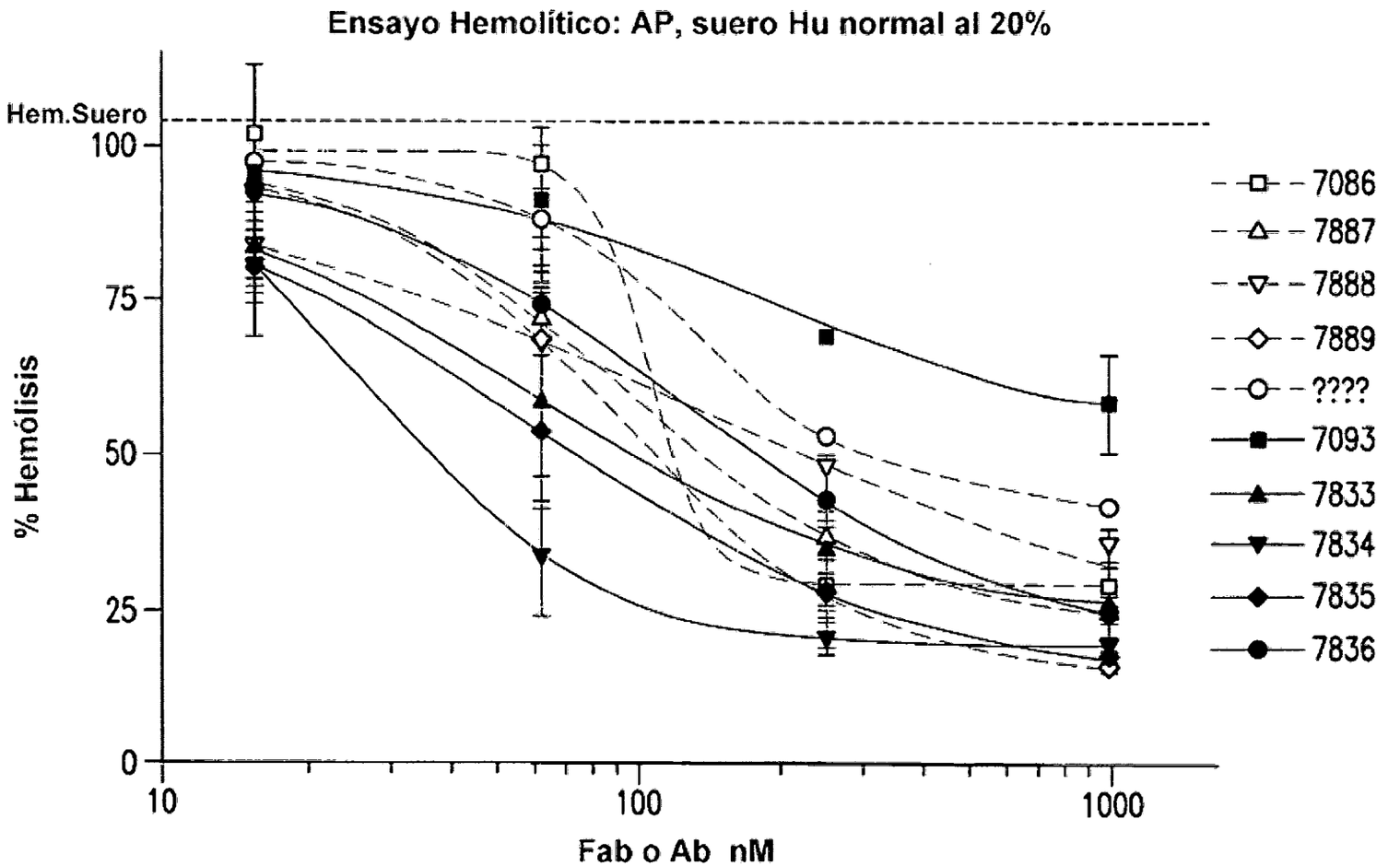

Ensayo Hemolítico: AP, suero Hu normal al 20%
Hem.Suero
100
75
50
25
0
% Hemólisis
10
100
1000
Fab o Ab nM
7086
7887
7888
7889
????
7093
7833
7834
7835
7836

FIG. 10c

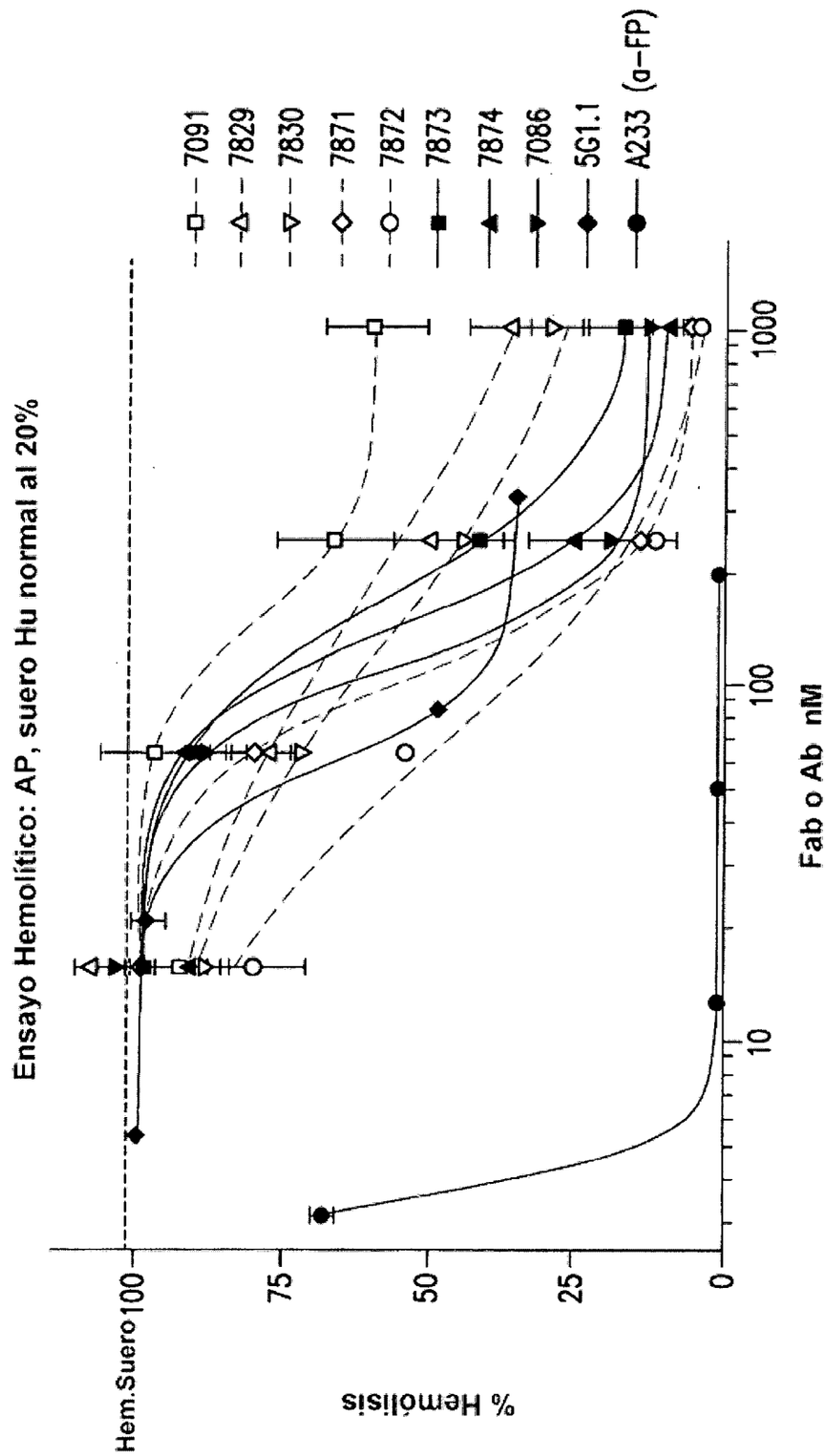

Ensayo Hemolítico: AP, suero Hu normal al 20%
Hem.Suero 100
% Hemólisis
0
25
50
75
10
100
1000
Fab o Ab nM
7091
7829
7830
7871
7872
7873
7874
7086
5G1.1
A233 (a-FP)

FIG. 10d

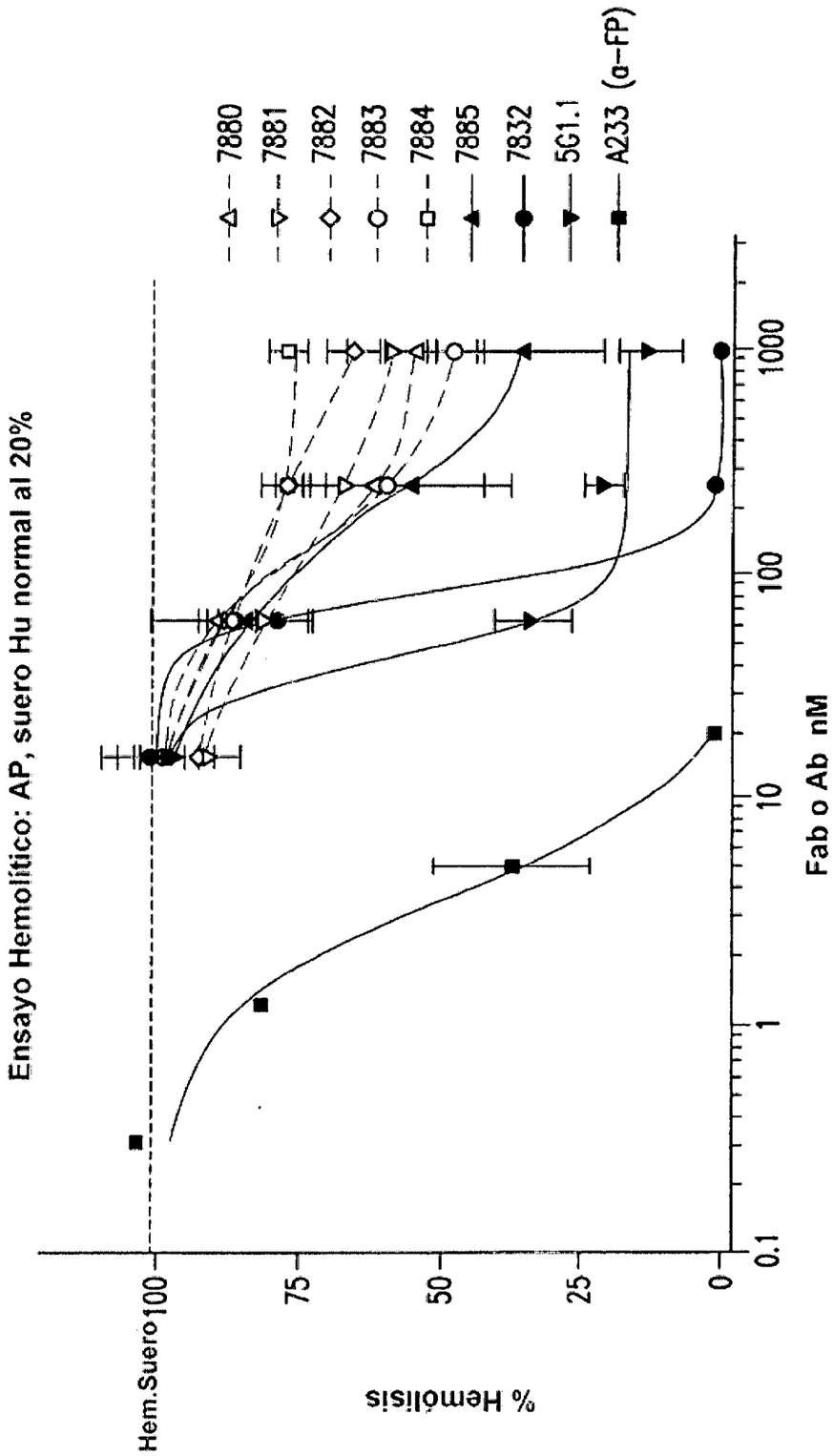

Ensayo Hemolítico: AP, suero Hu normal al 20%
Hem.Suero
100
75
50
25
0
% Hemólisis
0.1
1
10
100
1000
Fab o Ab nM
7880
7881
7882
7883
7884
7885
7832
5C1.1
A233 (α-FP)

FIG. 10e

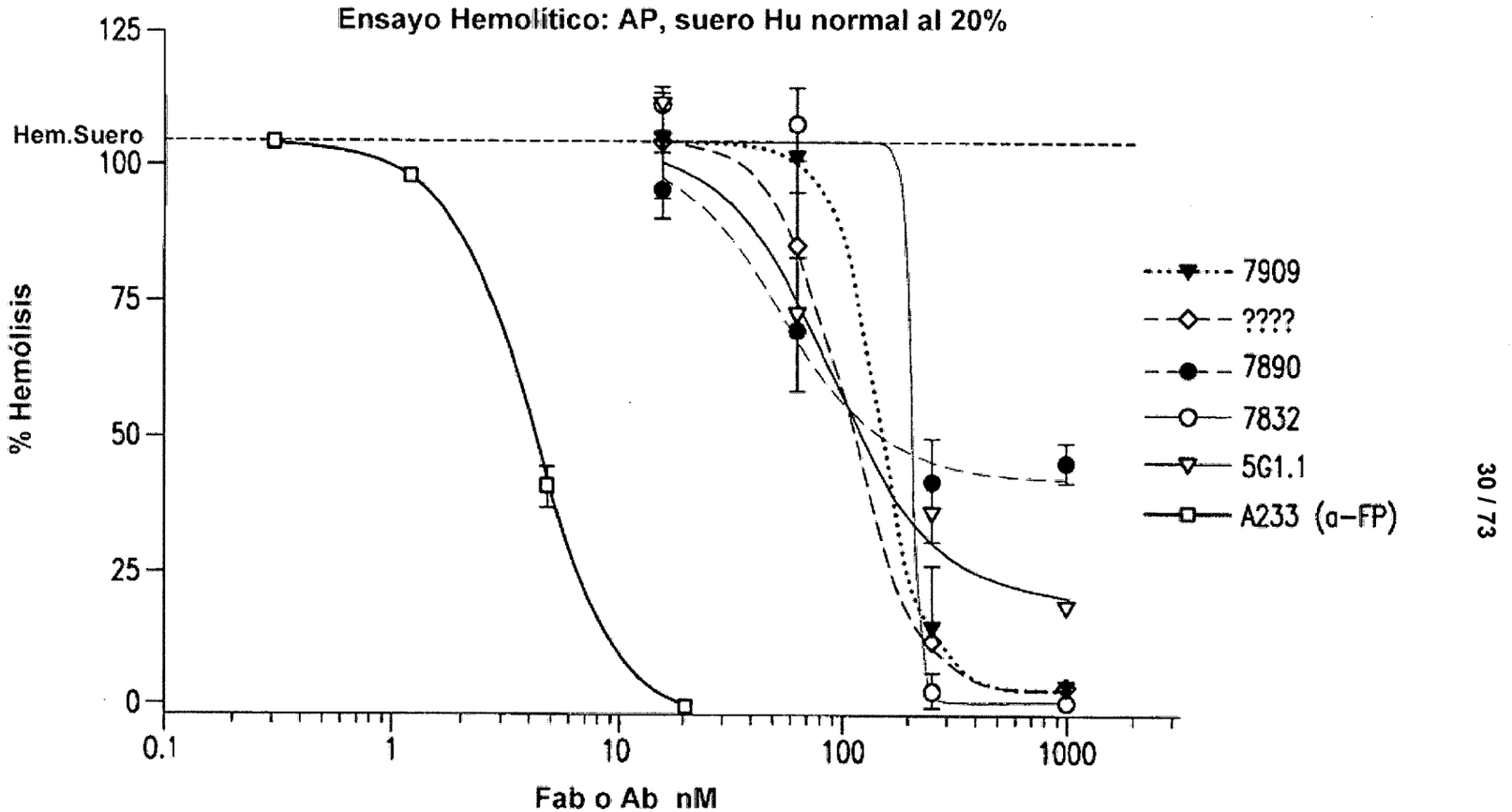

Ensayo Hemolítico: AP, suero Hu normal al 20%
125
Hem.Suero
100
75
50
25
0
% Hemólisis
0.1
1
10
100
1000
Fab o Ab nM
7909
????
7890
7832
5G1.1
A233 (α-FP)

FIG. 10f

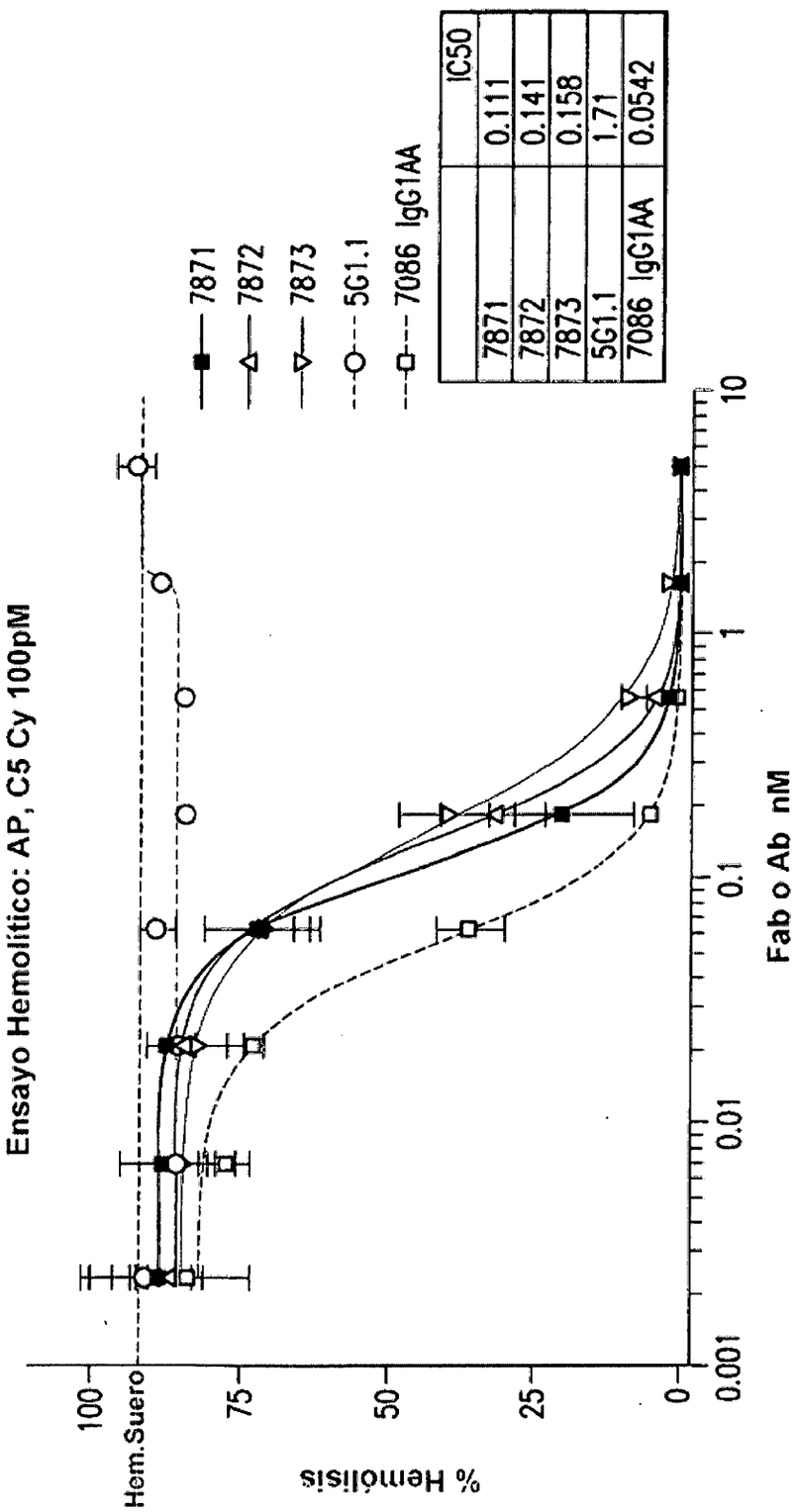

Ensayo Hemolítico: AP, C5 Cy 100pM
% Hemólisis
Hem.Suero
100
75
50
25
0
0.001
0.01
0.1
1
10
Fab o Ab nM
7871
7872
7873
5G1.1
7086 IgG1AA
IC50
7871 0.111
7872 0.141
7873 0.158
5G1.1 1.71
7086 IgG1AA 0.0542

FIG. 11a

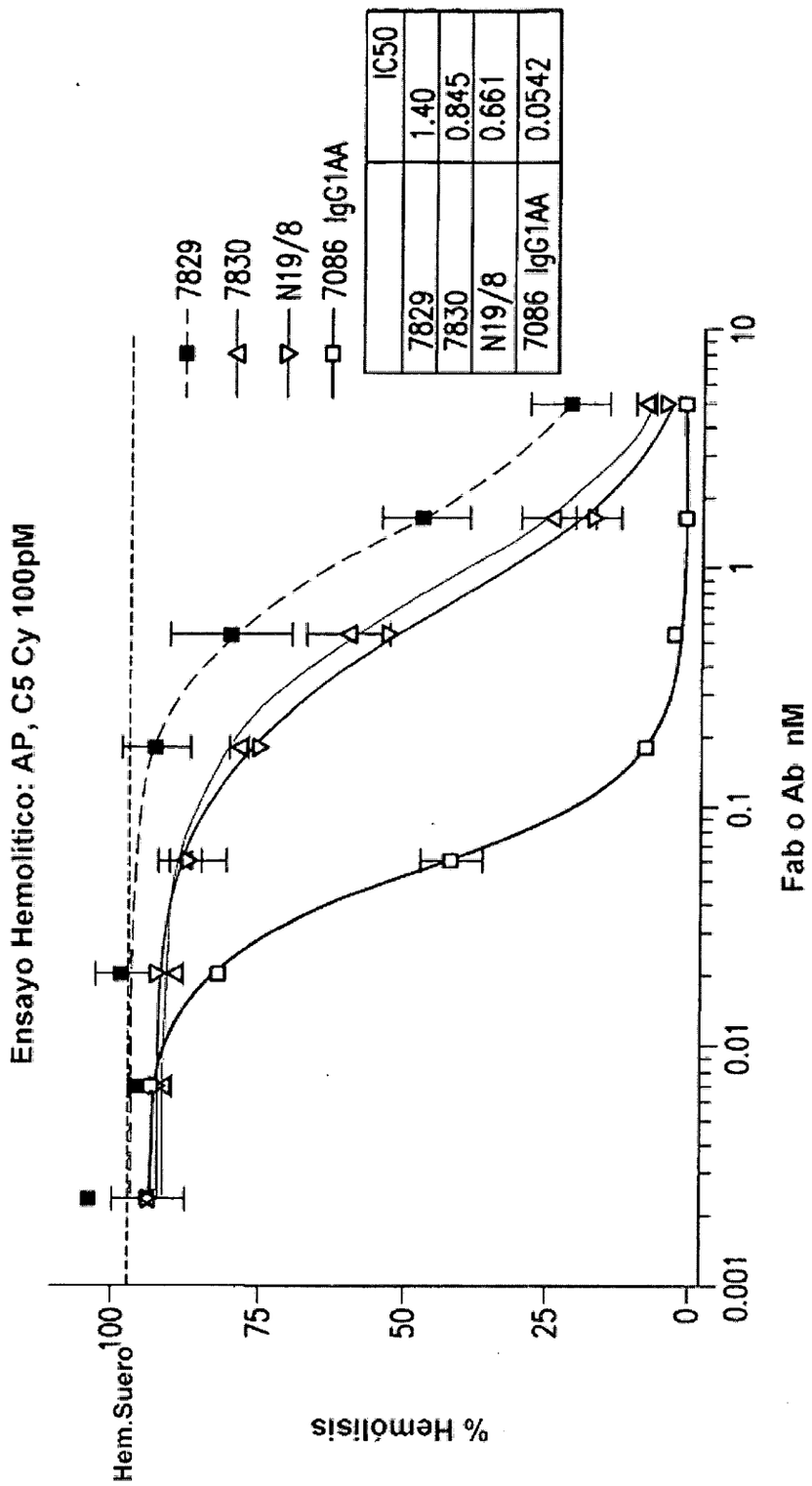

Ensayo Hemolitico: AP, C5 Cy 100pM
7829
7830
N19/8
7086 IgG1AA
IC50
7829 1.40
7830 0.845
N19/8 0.661
7086 IgG1AA 0.0542
Hem.Suero 100
% Hemolisis
100
75
50
25
0
0.001
0.01
0.1
1
10
Fab o Ab nM

FIG. 11b

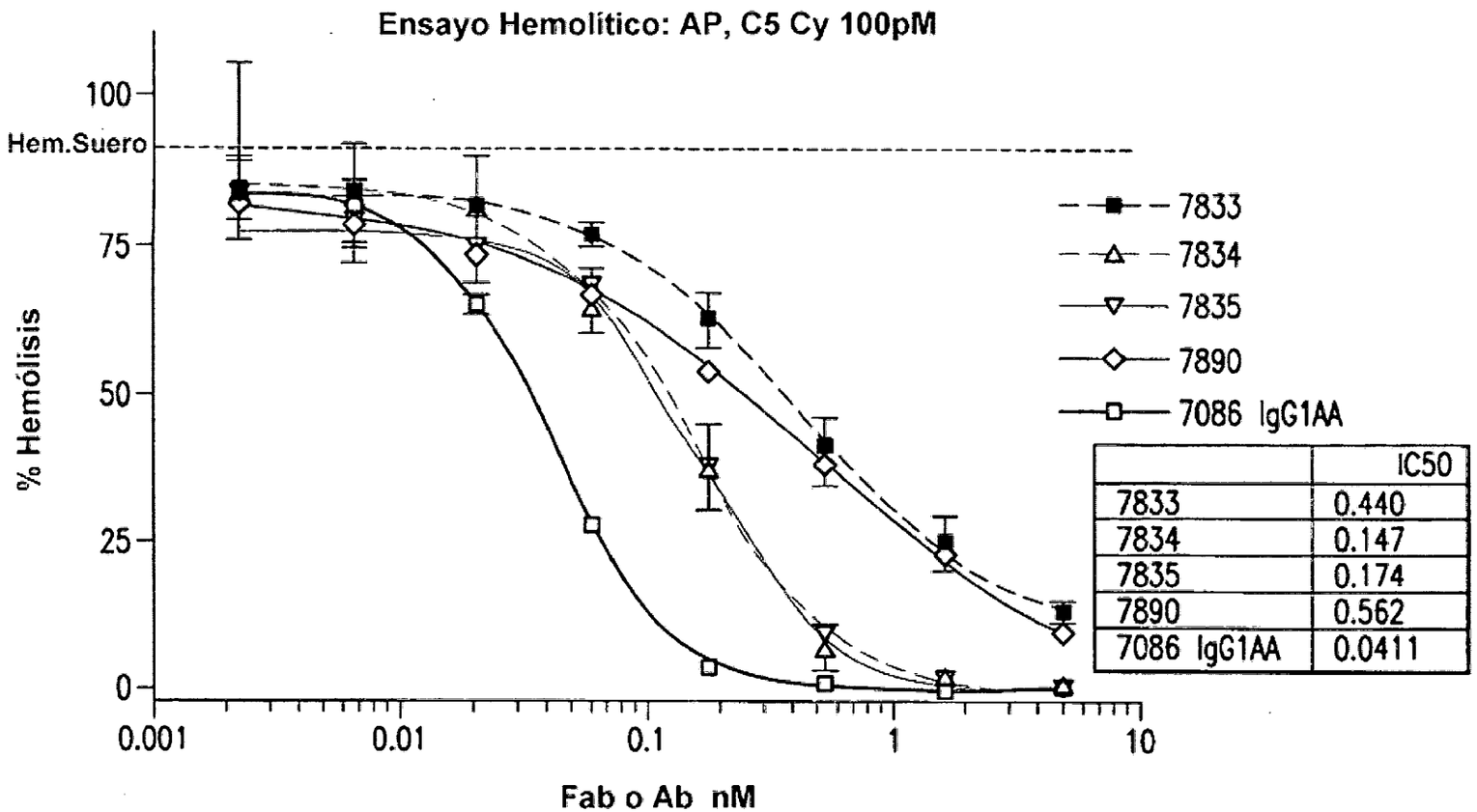

Ensayo Hemolítico: AP, C5 Cy 100pM
100
Hem.Suero
75
50
25
0
% Hemólisis
0.001
0.01
0.1
1
10
Fab o Ab nM
7833
7834
7835
7890
7086 IgG1AA
IC50
7833 0.440
7834 0.147
7835 0.174
7890 0.562
7086 IgG1AA 0.0411

FIG. 11c

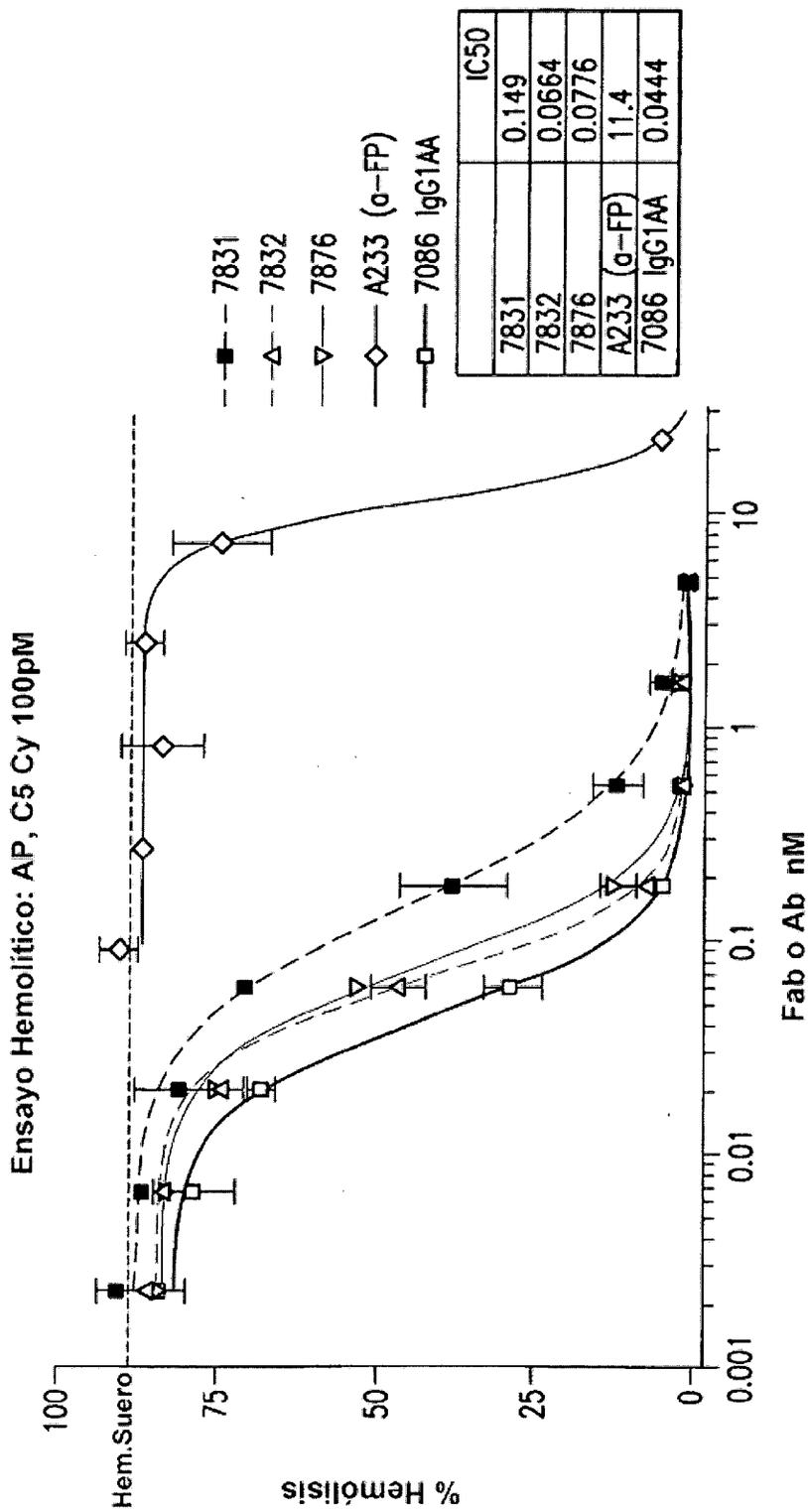

Ensayo Hemolítico: AP, C5 Cy 100pM
% Hemólisis
Fab o Ab nM
Hem.Suero
100
75
50
25
0
0.001
0.01
0.1
1
10
7831
7832
7876
A233 (α-FP)
7086 IgG1AA
IC50
7831 0.149
7832 0.0664
7876 0.0776
A233 (α-FP) 11.4
7086 IgG1AA 0.0444

FIG. 11d

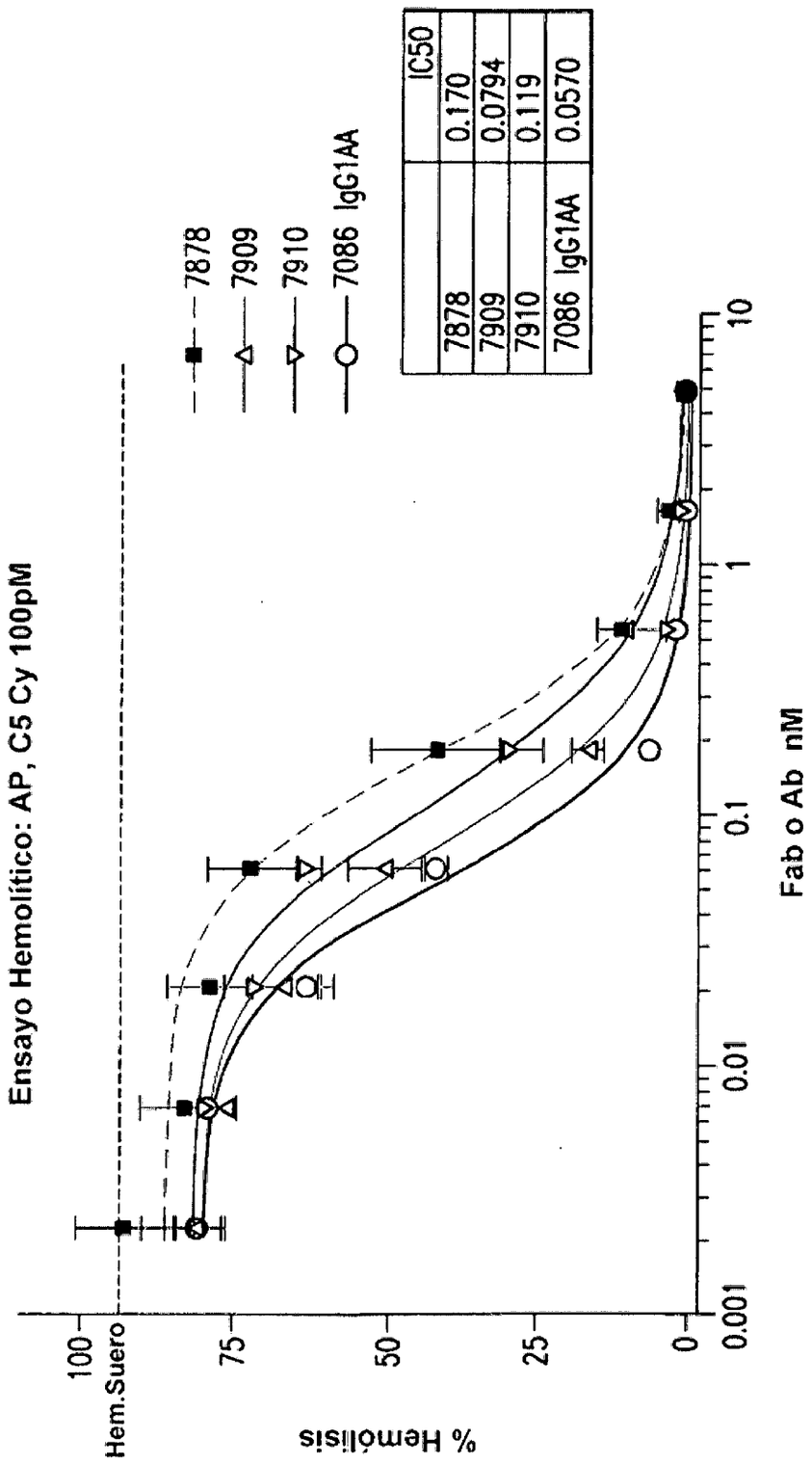

Ensayo Hemolítico: AP, C5 Cy 100pM
% Hemólisis
Fab o Ab nM
Hem.Suero
100
75
50
25
0
0.001
0.01
0.1
1
10
7878
7909
7910
7086 IgG1AA
IC50
7878 0.170
7909 0.0794
7910 0.119
7086 IgG1AA 0.0570

FIG. 11e

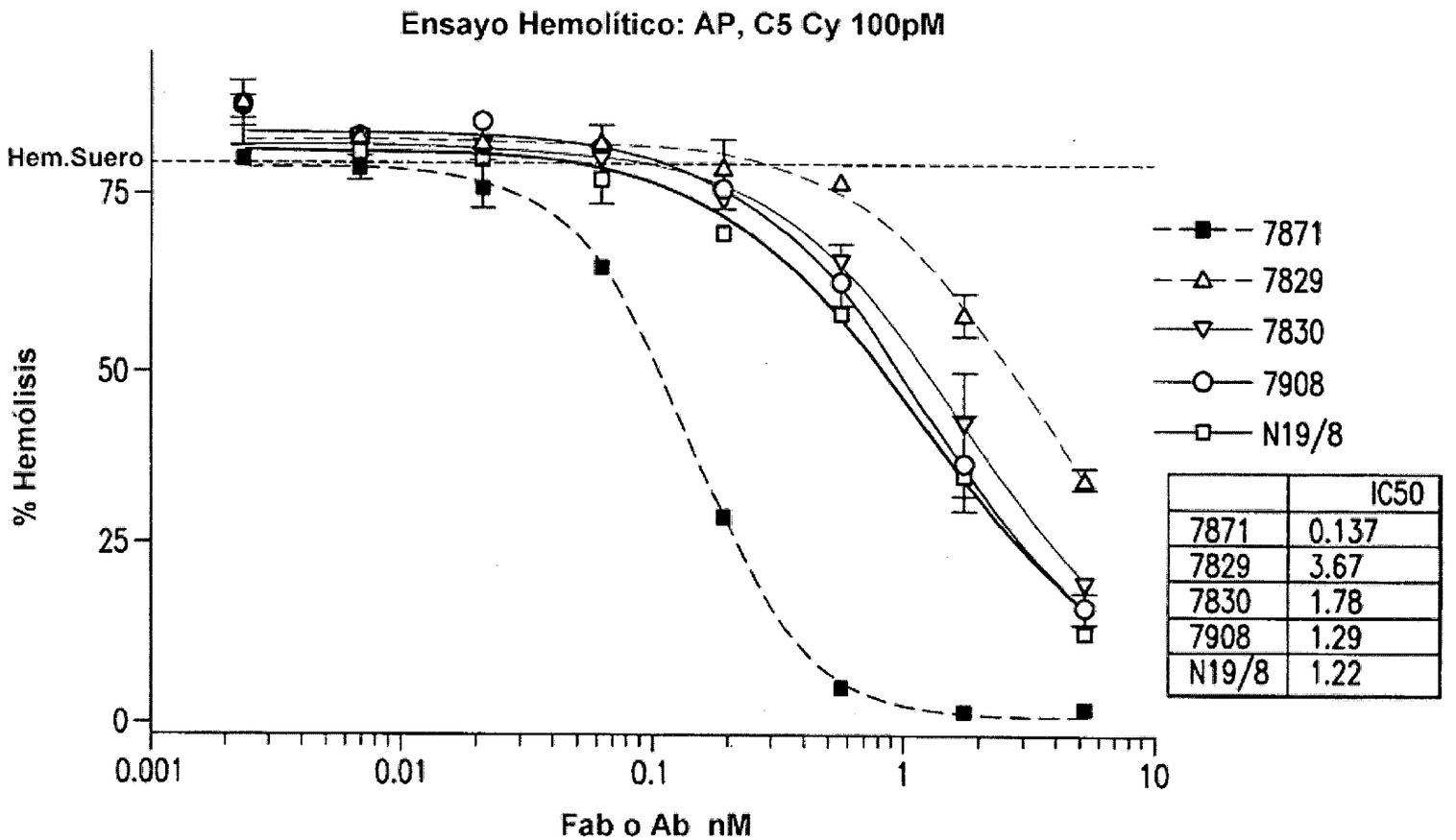
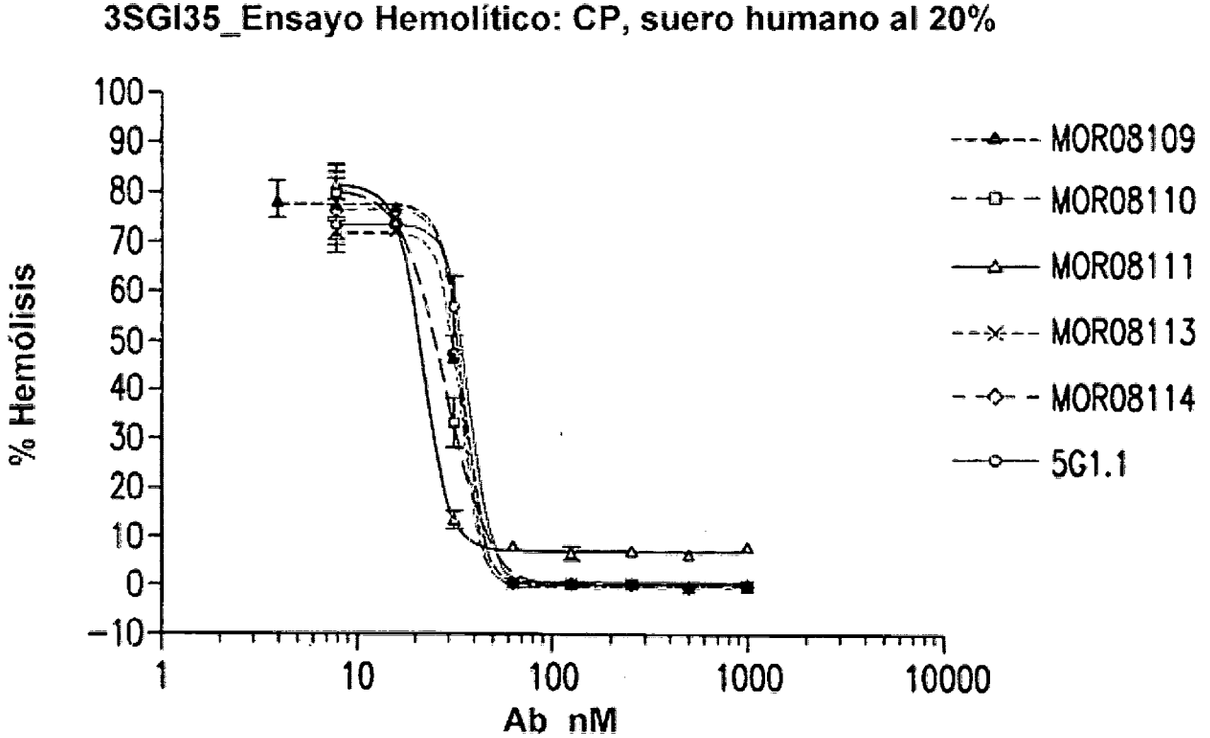

Ensayo Hemolítico: AP, C5 Cy 100pM
Hem.Suero
75
50
25
0
% Hemólisis
0.001
0.01
0.1
1
10
Fab o Ab nM
7871
7829
7830
7908
N19/8
IC50
7871 0.137
7829 3.67
7830 1.78
7908 1.29
N19/8 1.22

FIG. 11f



	MOR08109	MOR08110	MOR08111	MOR08113	MOR08114	5G1.1
IC50	34.83	28.38	21.51	33.61	34.15	37.81

FIG. 12

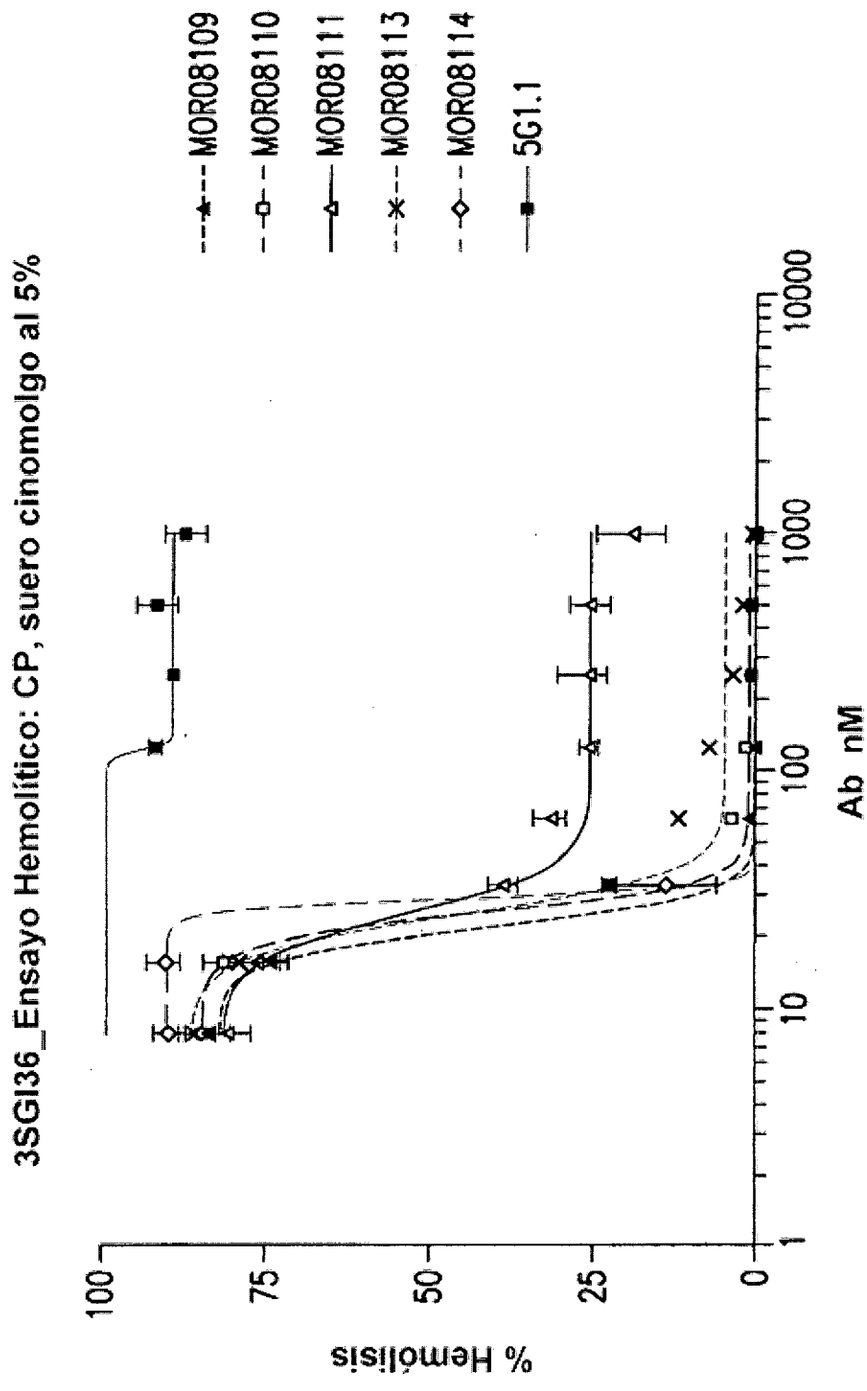

3SGI36_Ensayo Hemolítico: CP, suero cinomolgo al 5%
MOR08109
MOR08110
MOR08111
MOR08113
MOR08114
5G1.1
% Hemólisis
100
75
50
25
0
1
10
100
1000
10000
Ab nM

FIG. 13

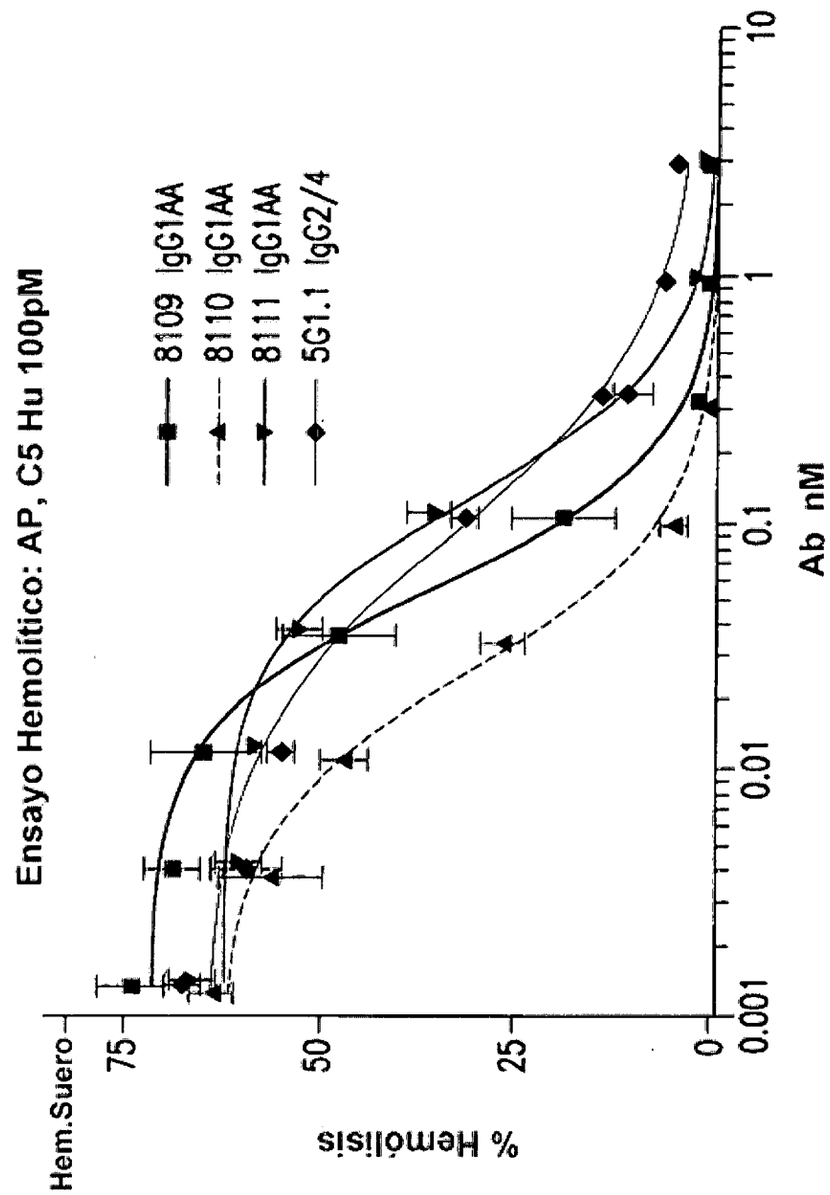

Ensayo Hemolítico: AP, C5 Hu 100pM
Hem.Suero
% Hemolisis
75
50
25
0
0.001
0.01
0.1
1
10
Ab nM
8109 IgG1AA
8110 IgG1AA
8111 IgG1AA
5G1.1 IgG2/4

FIG. 14a

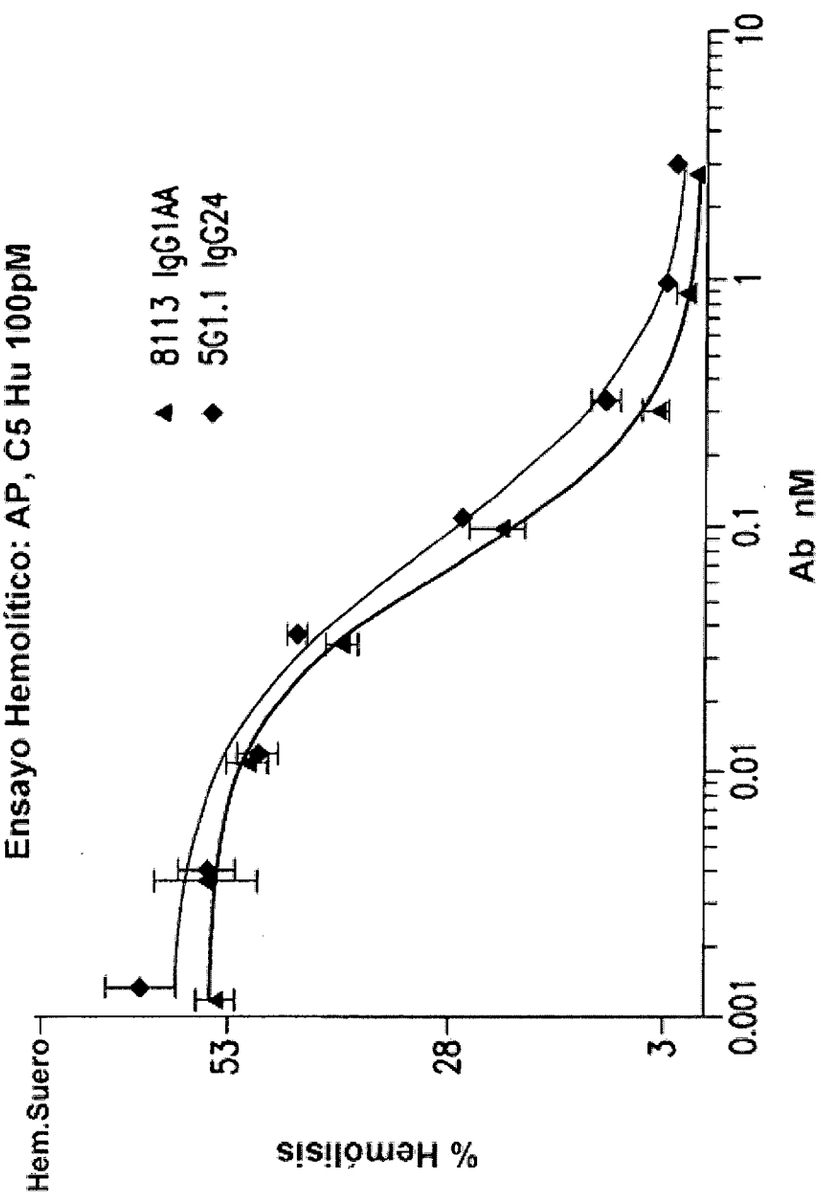

Ensayo Hemolítico: AP, C5 Hu 100pM
8113 IgG1AA
5G1.1 IgG24
% Hemolisis
Hem.Suero
53
28
3
0.001
0.01
0.1
1
10
Ab nM

FIG. 14b

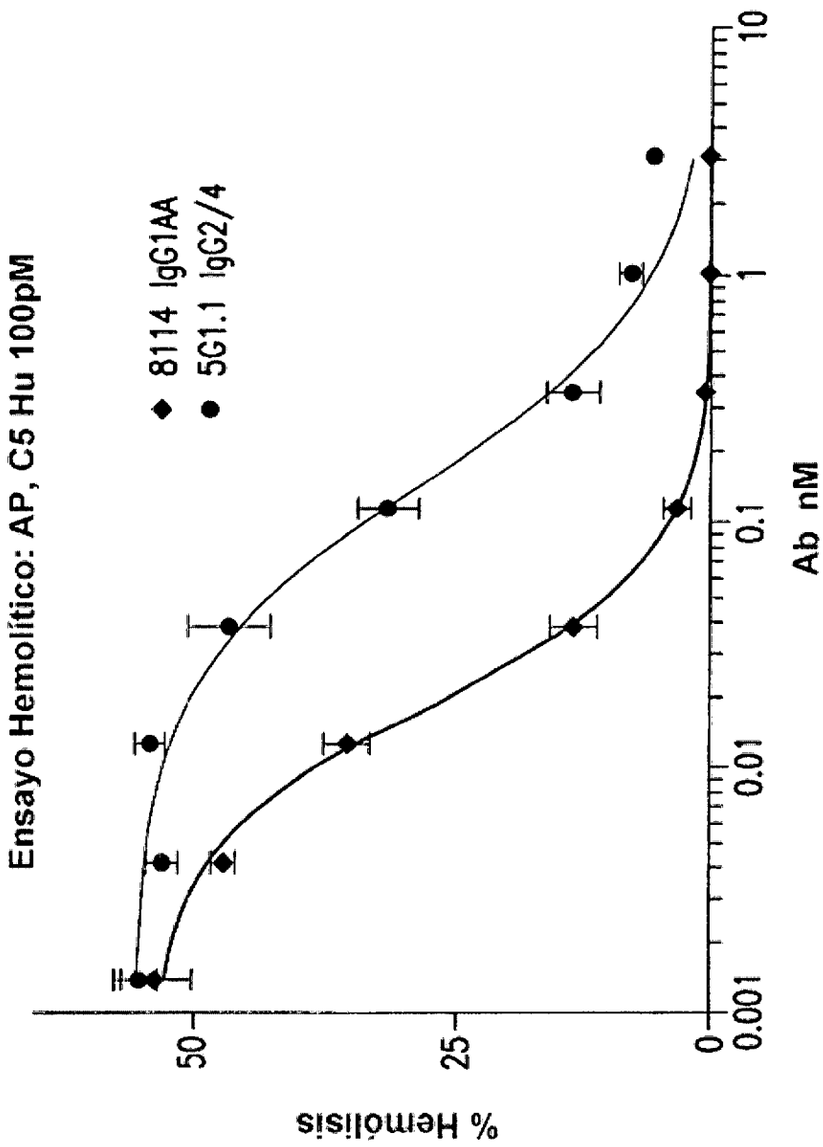

Ensayo Hemolítico: AP, C5 Hu 100pM
8114 IgG1AA
5G1.1 IgG2/4
% Hemólisis
50
25
0
0.001
0.01
0.1
1
10
Ab nM

FIG. 14c

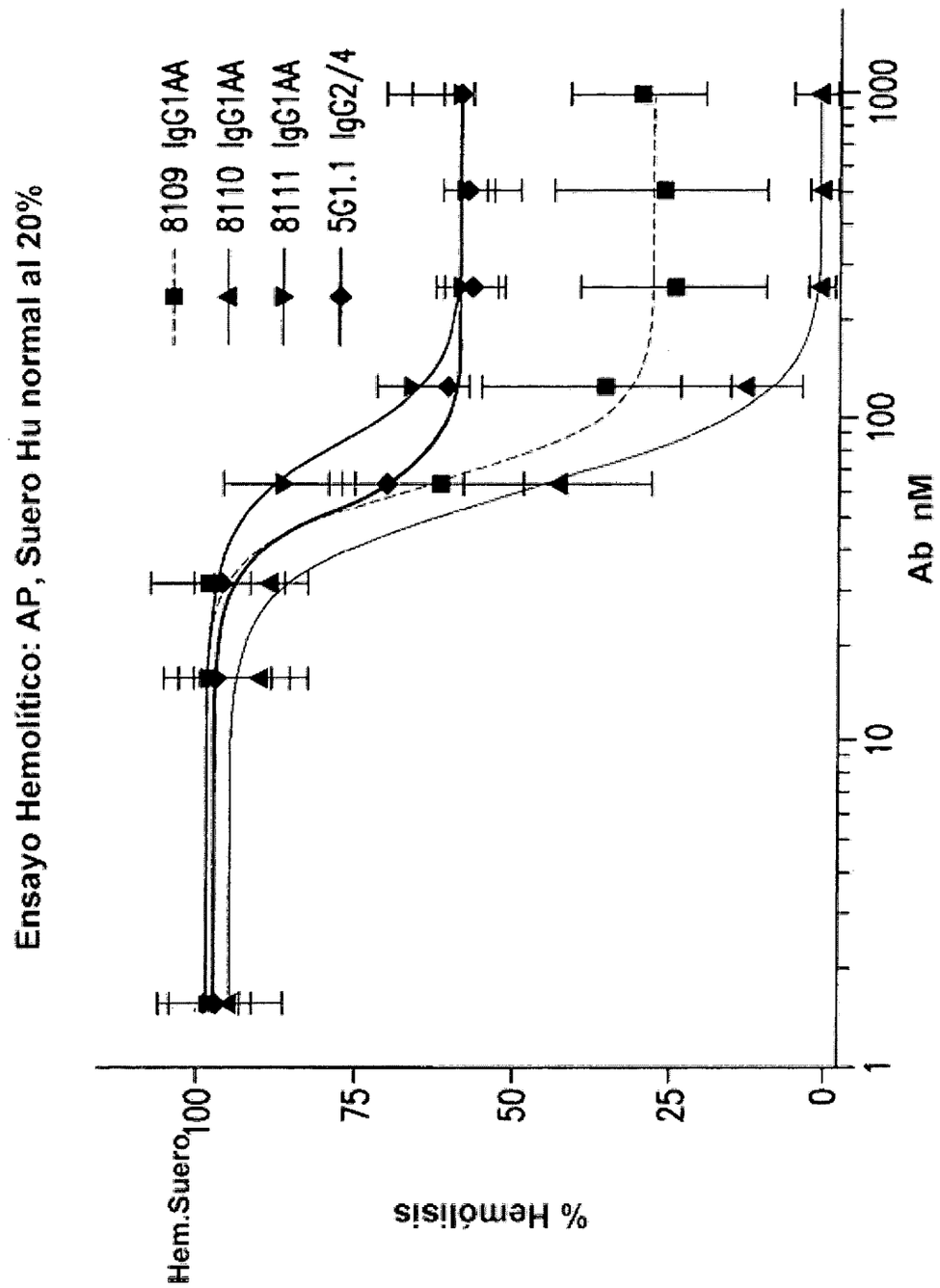

Ensayo Hemolítico: AP, Suero Hu normal al 20%
8109 IgG1AA
8110 IgG1AA
8111 IgG1AA
5G1.1 IgG2/4
Hem.Suero
100
75
50
25
0
% Hemólisis
1
10
100
1000
Ab nM

FIG. 15a

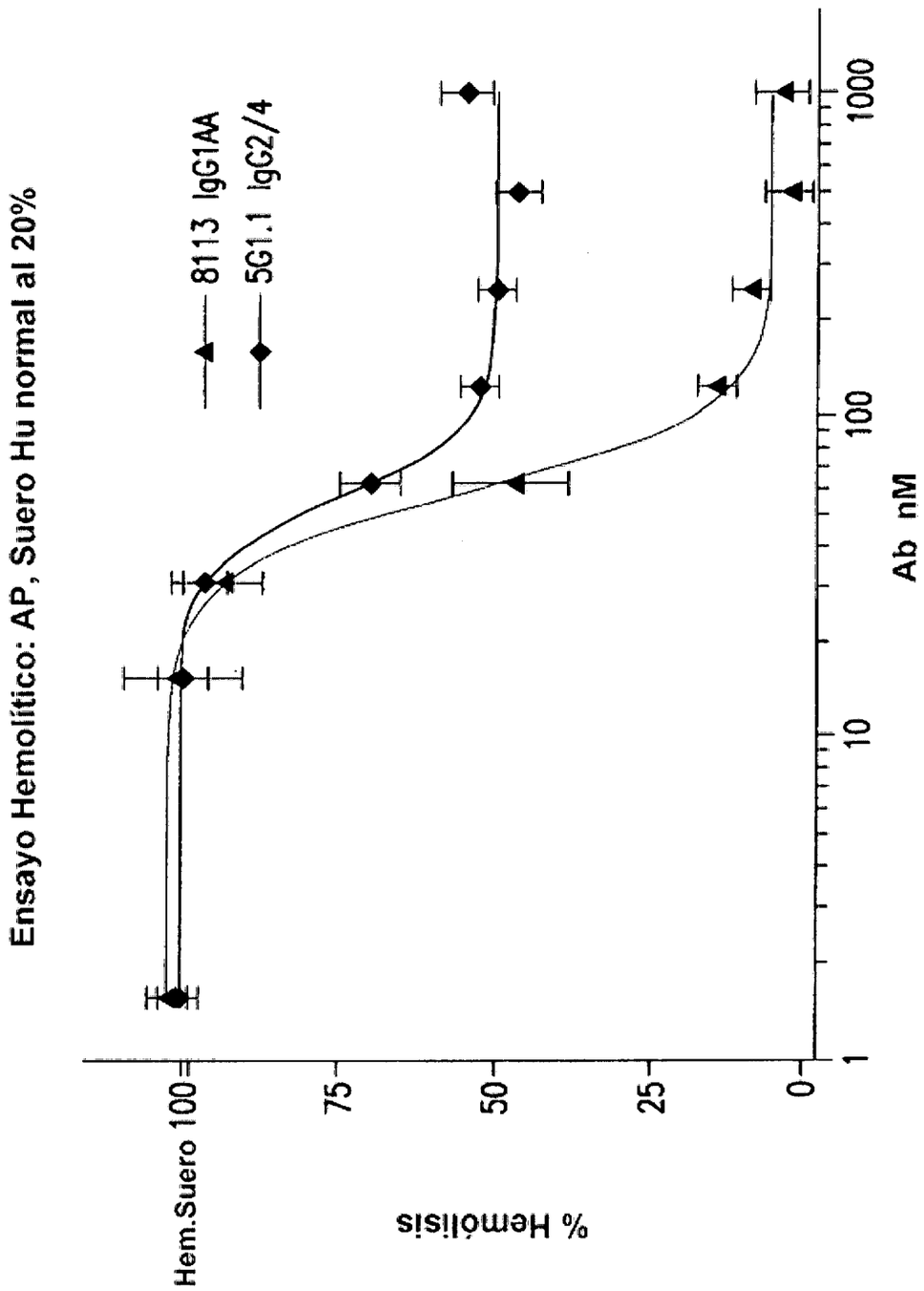

Ensayo Hemolítico: AP, Suero Hu normal al 20%
8113 IgG1AA
5G1.1 IgG2/4
Hem.Suero 100
% Hemólisis
0
25
50
75
1
10
100
1000
Ab nM

FIG. 15b

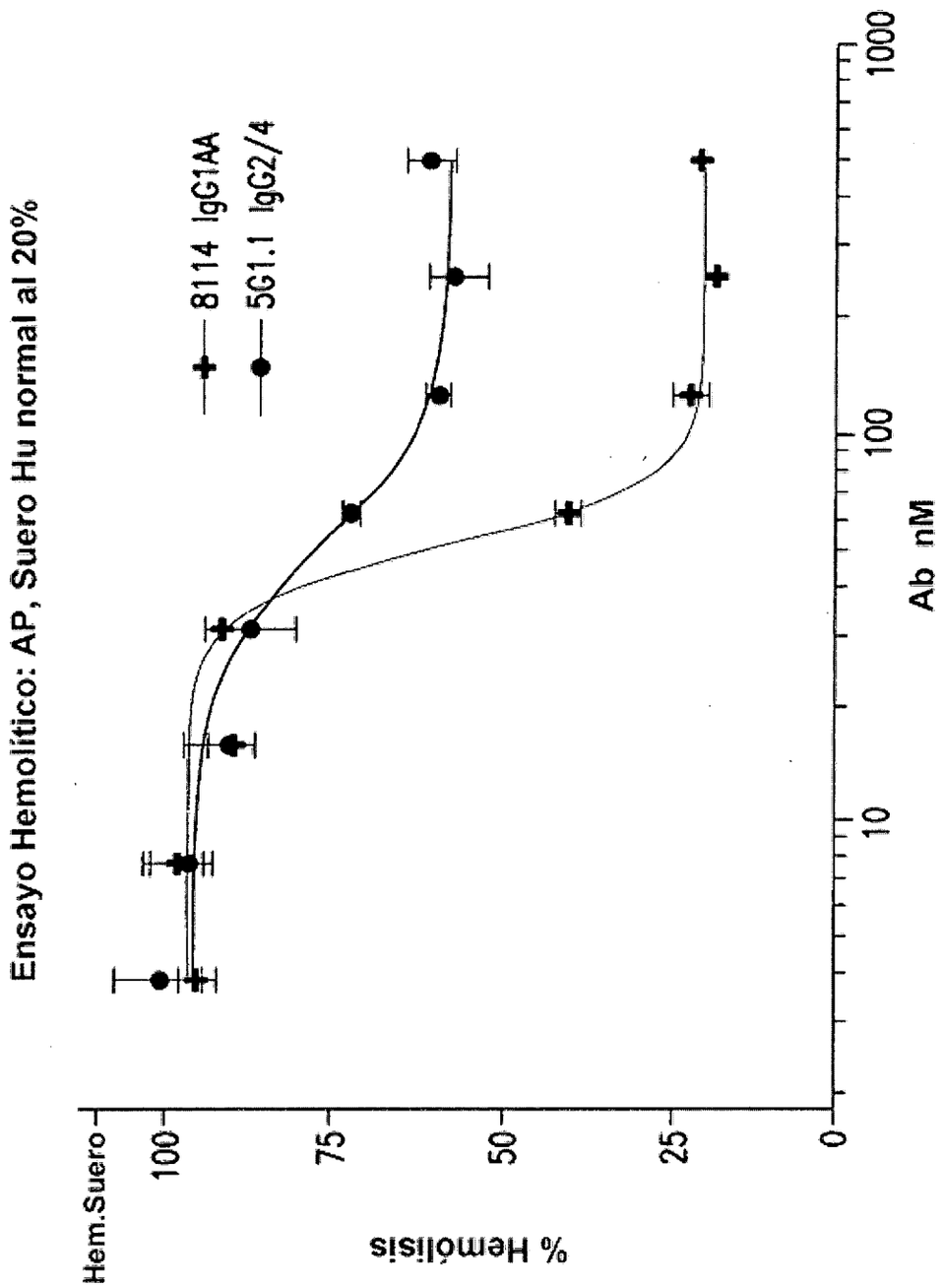

Ensayo Hemolítico: AP, Suero Hu normal al 20%
8114 IgG1AA
5G1.1 IgG2/4
Hem.Suero
100
75
50
25
0
% Hemólisis
10
100
1000
Ab nM

FIG. 15c

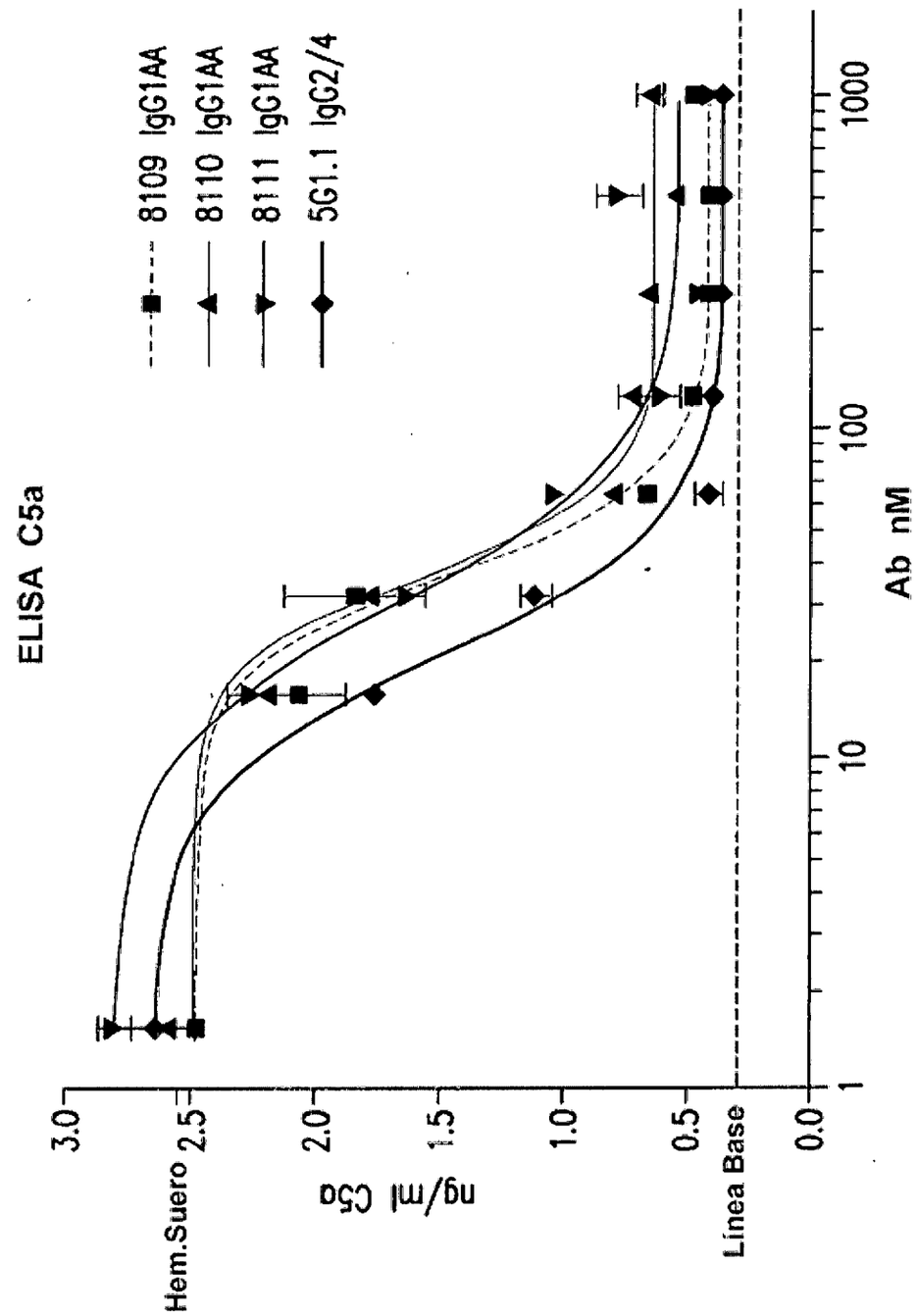

ELISA C5a
8109 IgG1AA
8110 IgG1AA
8111 IgG1AA
5G1.1 IgG2/4
ng/ml C5a
Hem.Suero
Línea Base
Ab nM
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1
10
100
1000

FIG. 15d

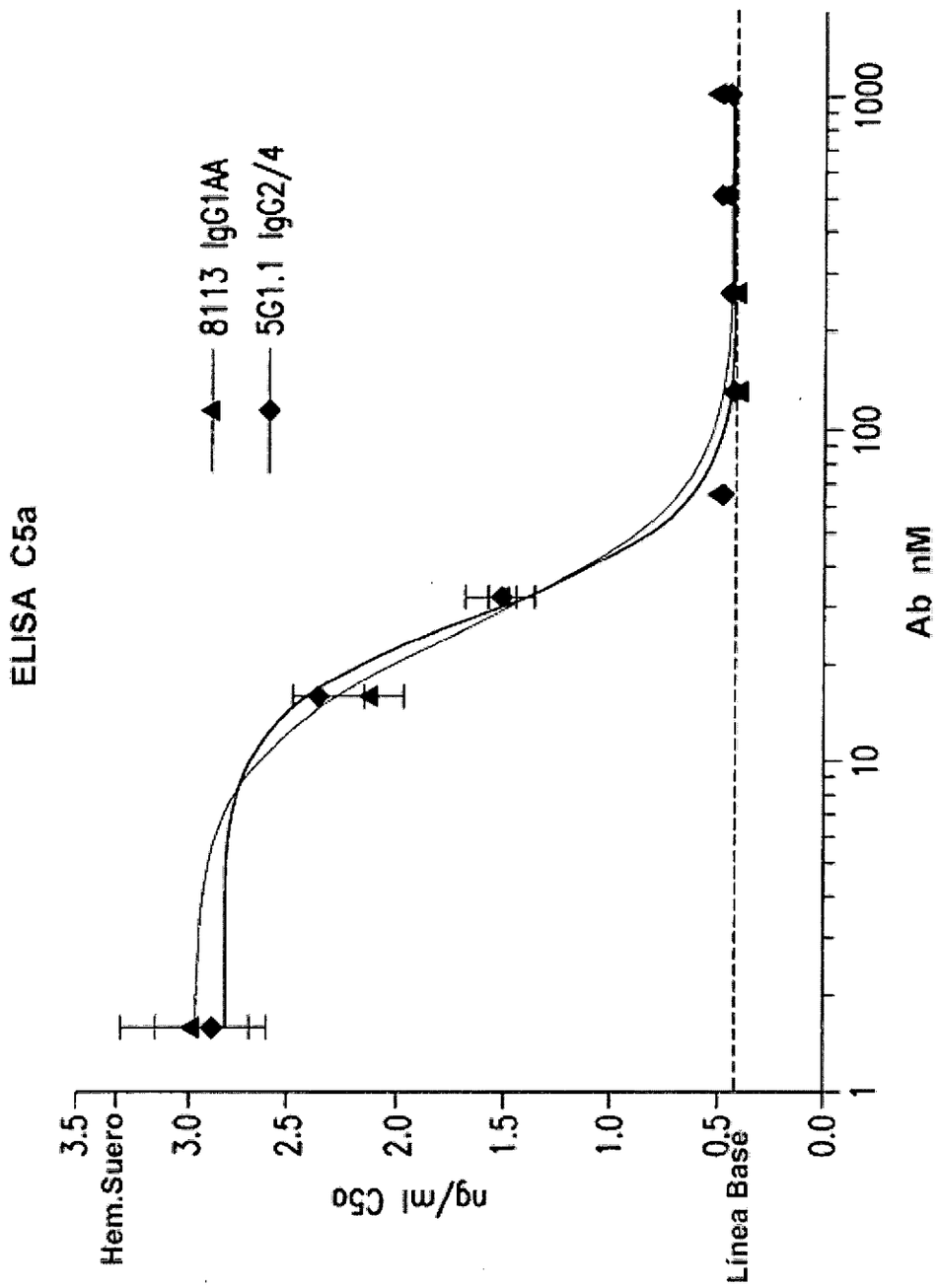

ELISA C5a
8113 IgG1AA
5G1.1 IgG2/4
ng/ml C5a
Hem.Suero
Línea Base
Ab nM
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1
10
100
1000

FIG. 15e

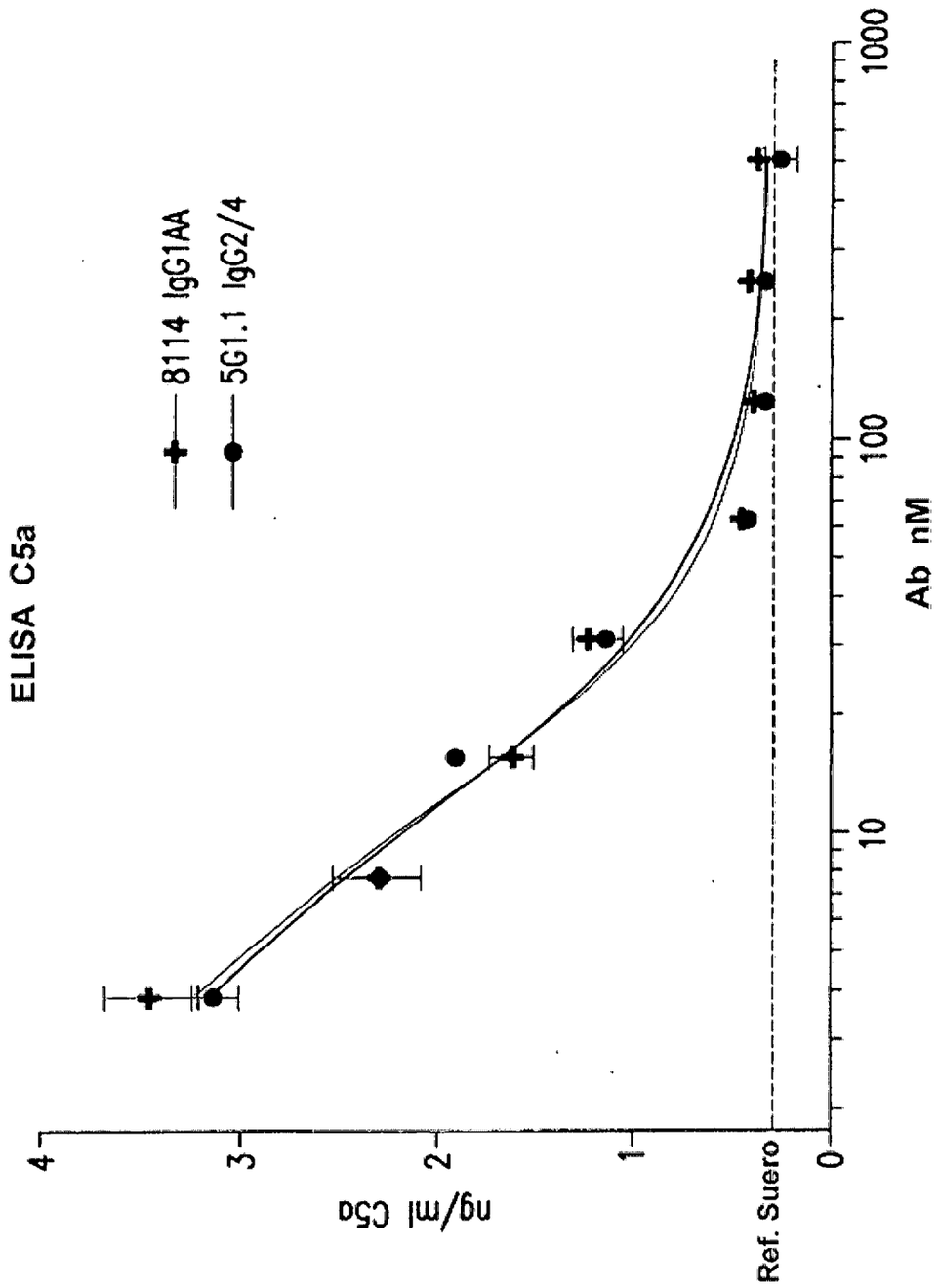

ELISA C5a
8114 IgG1AA
5G1.1 IgG2/4
ng/ml C5a
0
1
2
3
4
Ref. Suero
10
100
1000
Ab nM

FIG. 15f

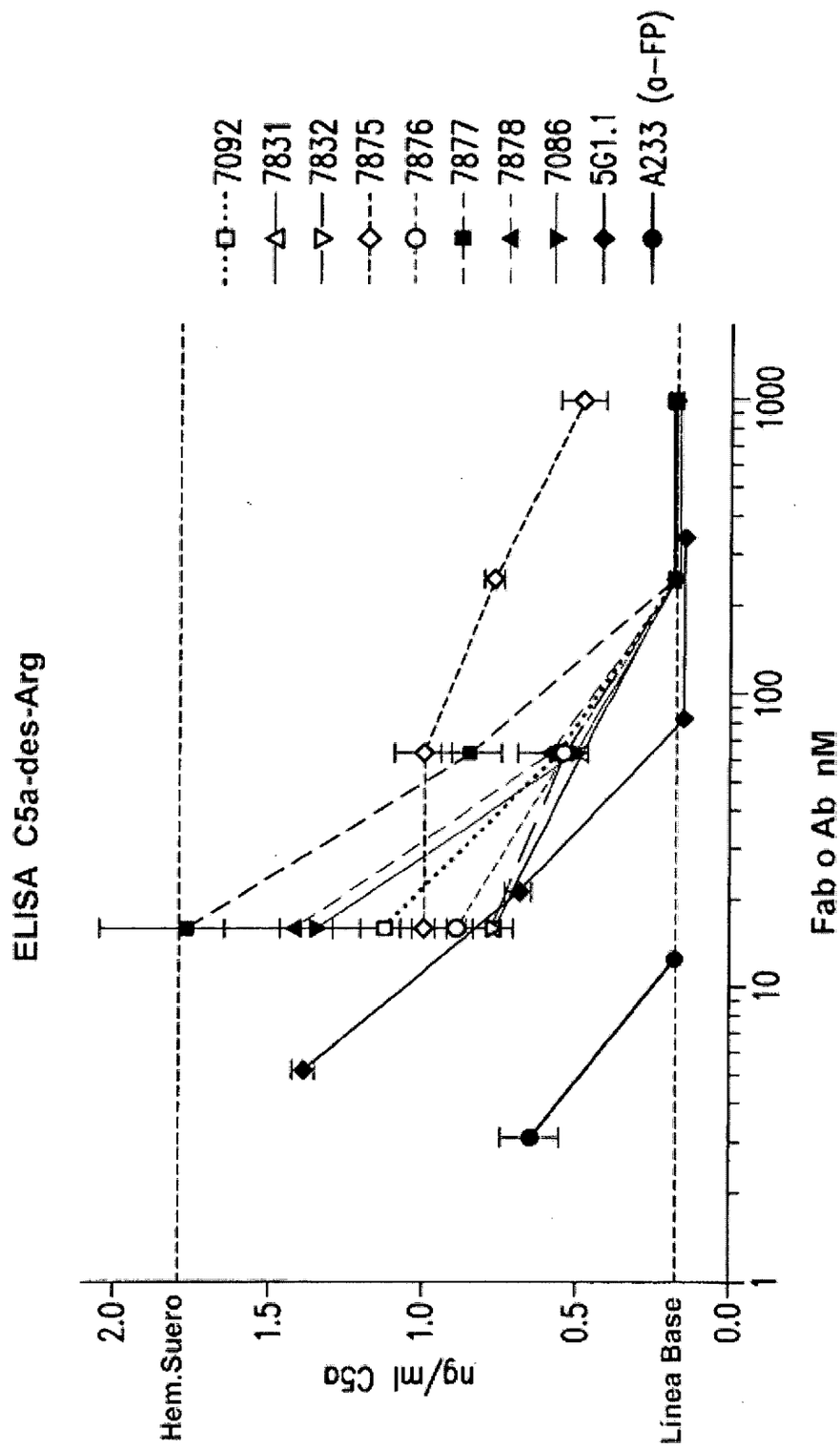

ELISA C5a-des-Arg
7092
7831
7832
7875
7876
7877
7878
7086
5G1.1
A233 (a-FP)
ng/ml C5a
2.0
1.5
1.0
0.5
0.0
Hem.Suero
Línea Base
1
10
100
1000
Fab o Ab nM

FIG. 16a

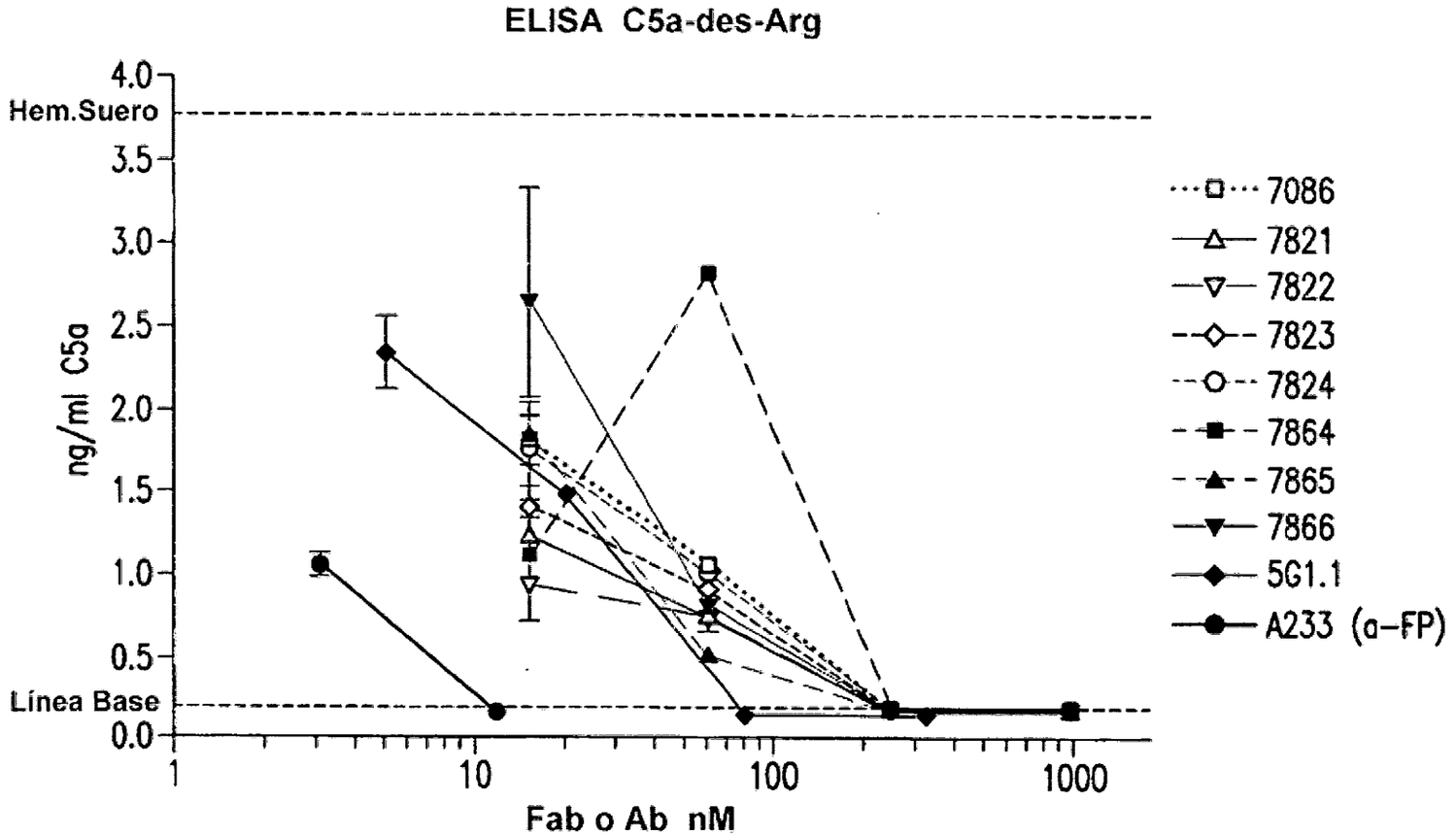

ELISA C5a-des-Arg
4.0
Hem.Suero
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Línea Base
0.0
ng/ml C5a
1
10
100
1000
Fab o Ab nM
7086
7821
7822
7823
7824
7864
7865
7866
5G1.1
A233 (α-FP)

FIG. 16b

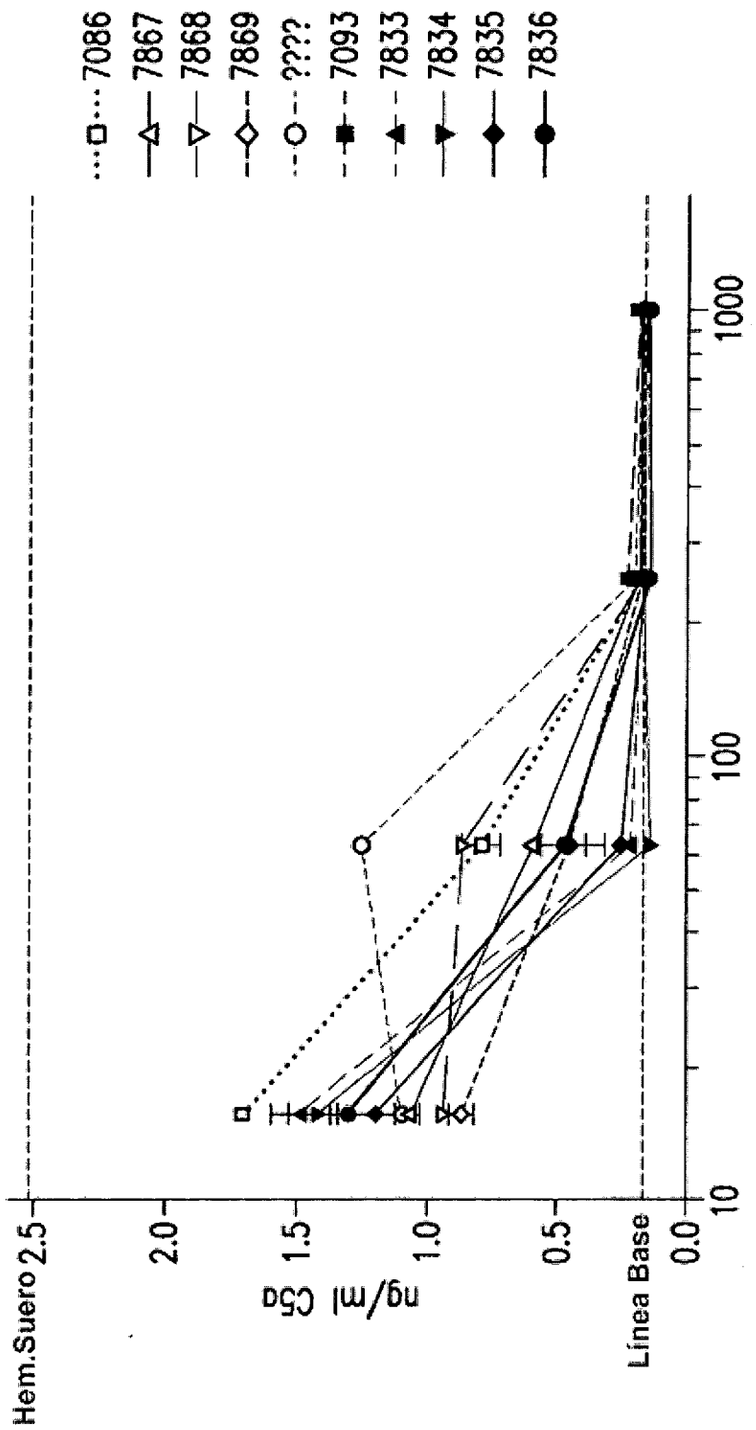

ELISA C5a-des-Arg
7086
7867
7868
7869
????
7093
7833
7834
7835
7836
Hem.Suero
Línea Base
ng/ml C5a
Fab o Ab nM
2.5
2.0
1.5
1.0
0.5
0.0
10
100
1000

FIG. 16c

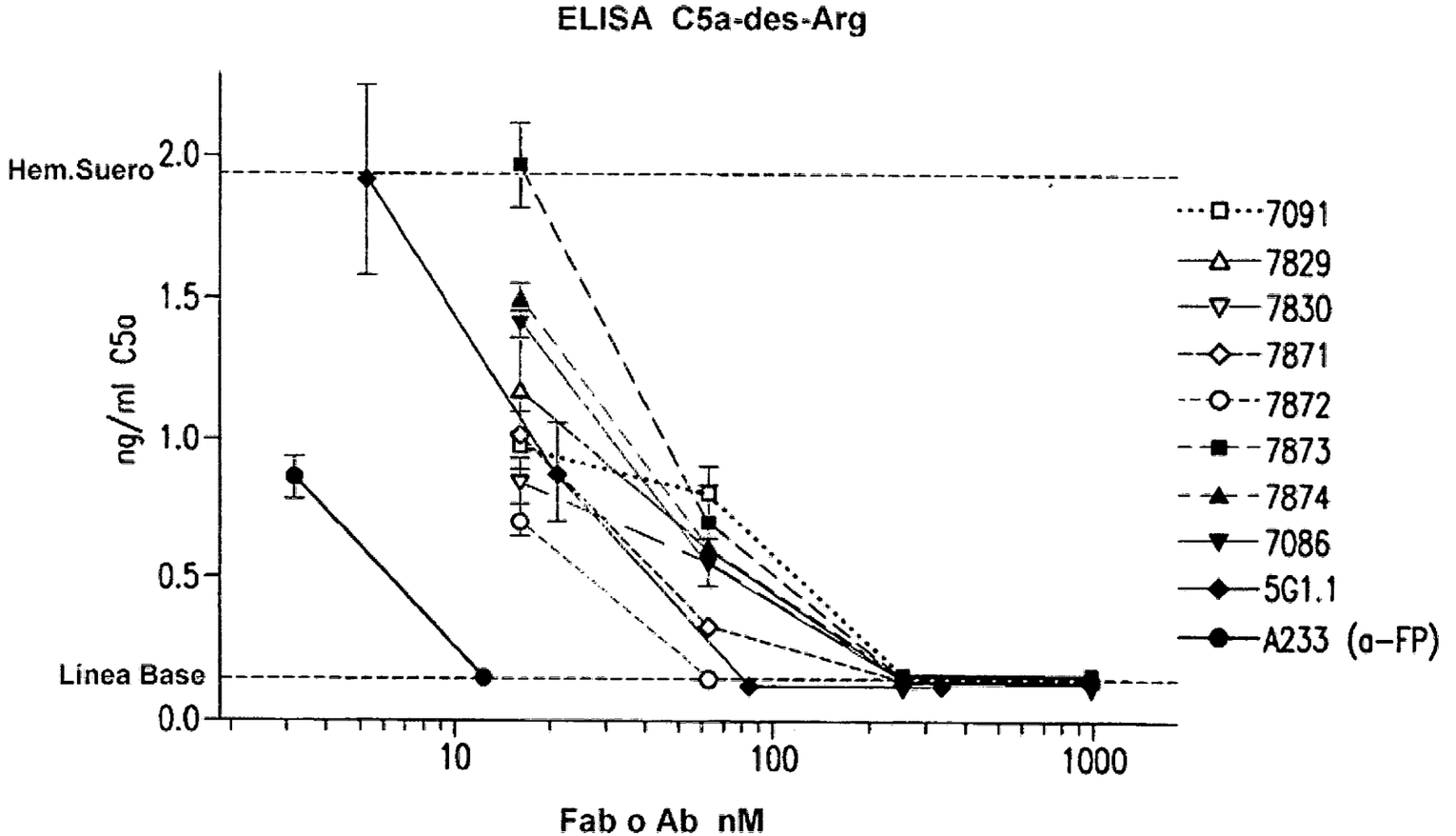
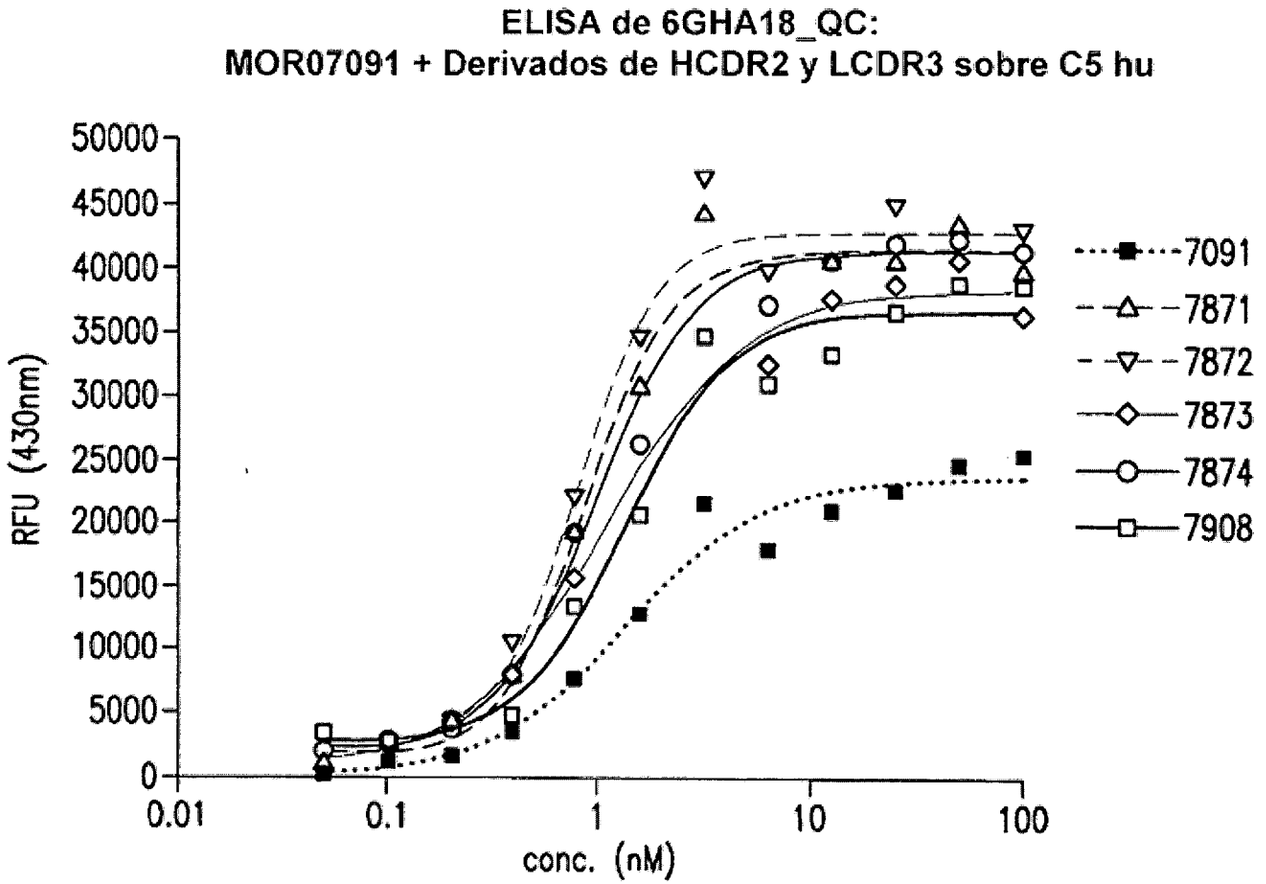

ELISA C5a-des-Arg
Hem.Suero
Linea Base
ng/ml C5a
2.0
1.5
1.0
0.5
0.0
10
100
1000
Fab o Ab nM
7091
7829
7830
7871
7872
7873
7874
7086
5G1.1
A233 (α-FP)

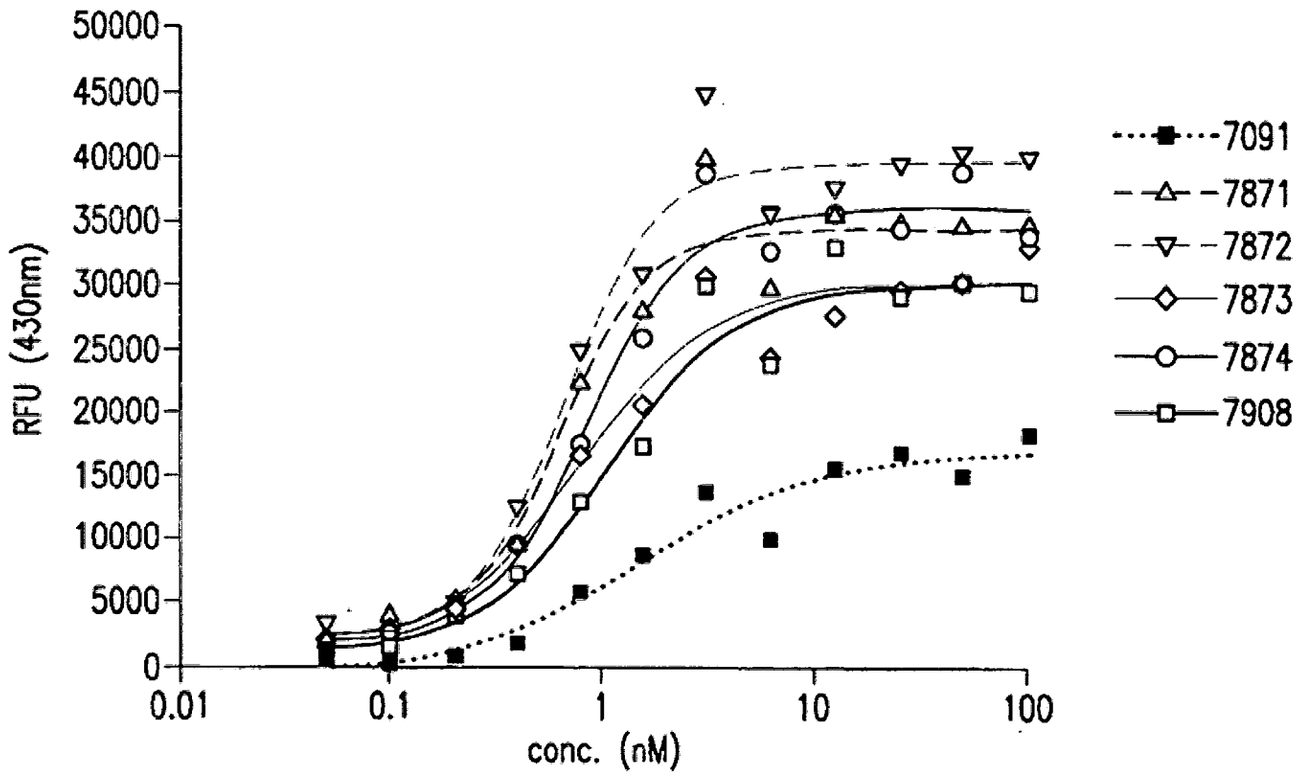
FIG. 16d



	7091	7871	7872	7873	7874	7908
EC50	1.316	0.8489	0.7889	1.051	0.9620	1.321

FIG. 17-1

ELISA de 6GHA18_QC:
MOR07091 + Derivados de HCDR2 y LCDR3 sobre C5 cinomolgo



	7091	7871	7872	7873	7874	7908
EC50	1.316	0.8489	0.7889	1.051	0.9620	1.321

FIG. 17-2

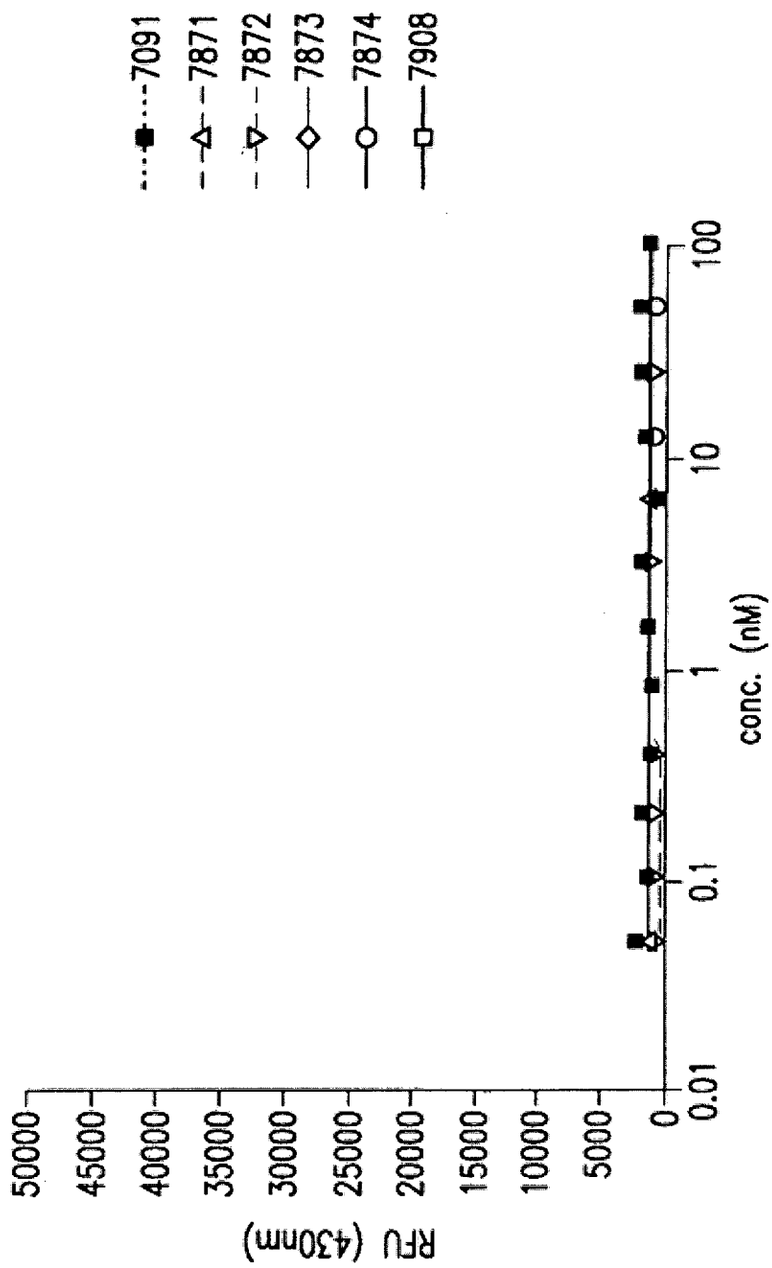

ELISA de 6GHA18_QC:
MOR07091 + Derivados de HCDR2 y LCDR3 sobre C3 hu
RFU (430nm)
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
0.01
0.1
1
10
100
conc. (nM)
7091
7871
7872
7873
7874
7908

FIG. 17-3

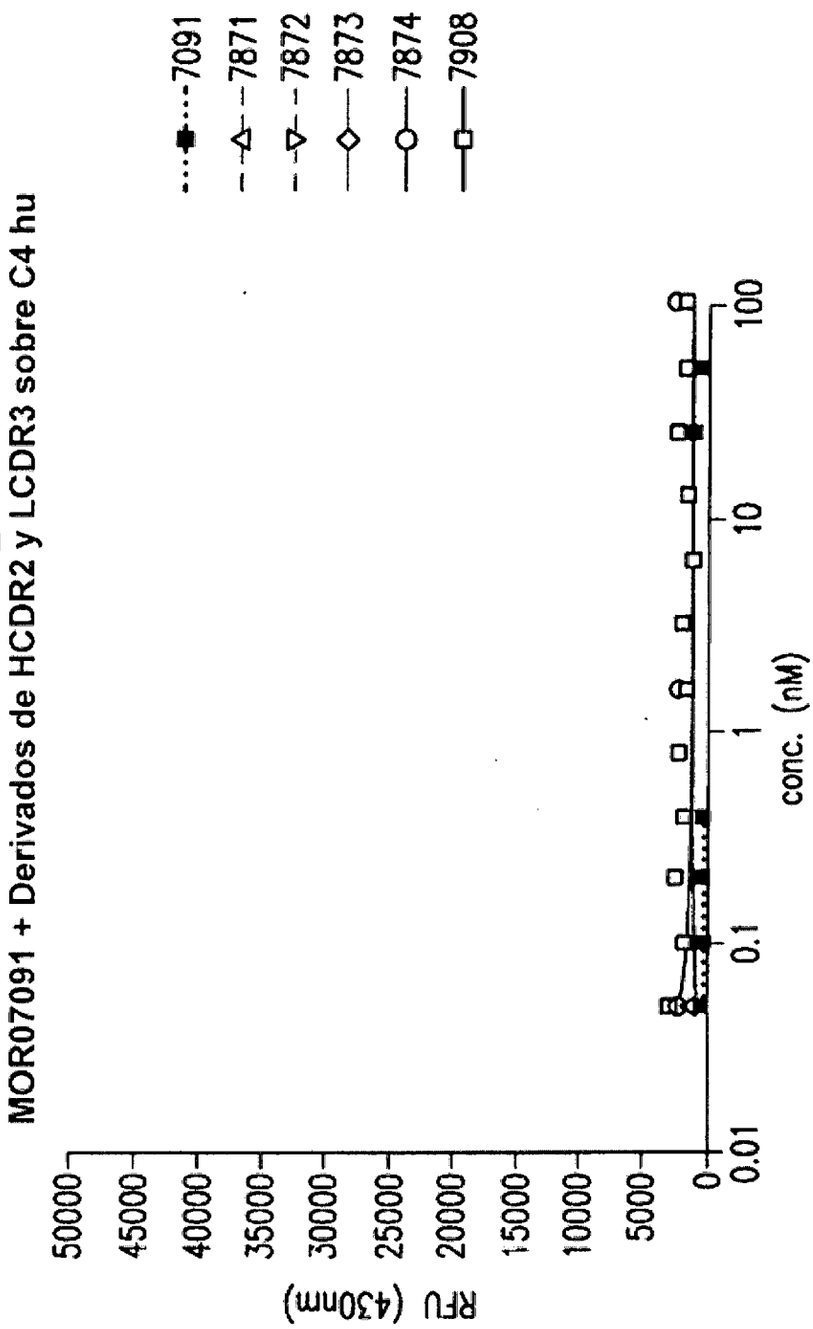
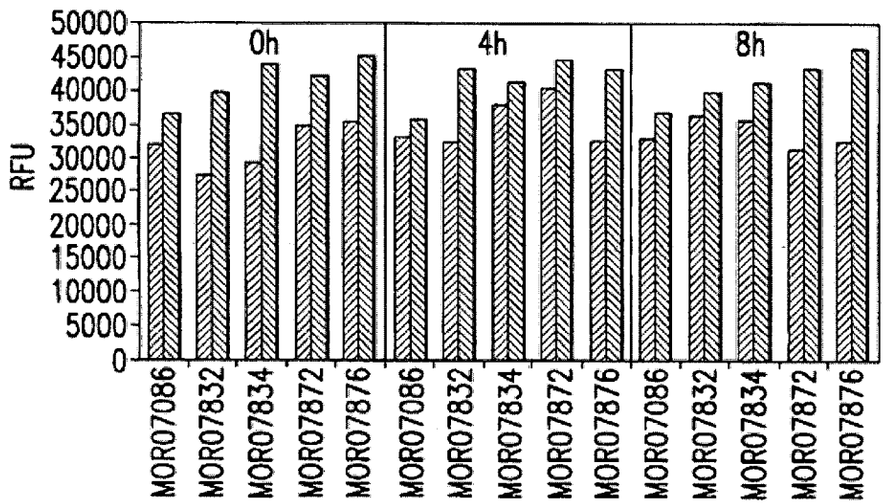

ELISA de 6GHA18_QC:
MOR07091 + Derivados de HCDR2 y LCDR3 sobre C4 hu
7091
7871
7872
7873
7874
7908
RFU (430nm)
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
0.01
0.1
1
10
100
conc. (nM)

FIG. 17-4



MOR0	Actividad de enlace retenida	
MOR07086	88.02%	0h
MOR07832	69.06%	
MOR07834	66.95%	
MOR07872	82.72%	
MOR07876	78.55%	
MOR07086	92.94%	4h
MOR07832	74.84%	
MOR07834	92.00%	
MOR07872	90.70%	
MOR07876	75.60%	
MOR07086	89.57%	8h
MOR07832	91.56%	
MOR07834	86.05%	
MOR07872	72.10%	
MOR07876	70.34%	

FIG. 18

Filas: Fab no marcado (exceso de 100 veces)	Columnas: Fab biotinilado							
MORO	7086	7832	7834	7871	7872	7873	7876	7878
7086	691	2597	853	1191	825	694	1002	495
7832	668	1186	404	586	3601	499	595	251
7834	618	1727	391	625	609	455	756	560
7871	426	1384	422	758	619	1009	392	451
7872	1553	3199	773	1486	944	882	842	781
7873	800	3342	965	1414	1491	922	1188	691
7876	892	2535	652	978	1366	1394	621	701
7878	850	2643	784	1228	2218	891	1180	643
100%	36816	37112	37340	43250	41651	33768	38078	37405
Competencia con Fab idéntico			Fab biotinilado sin competencia = 100% de señal					

FIG. 19

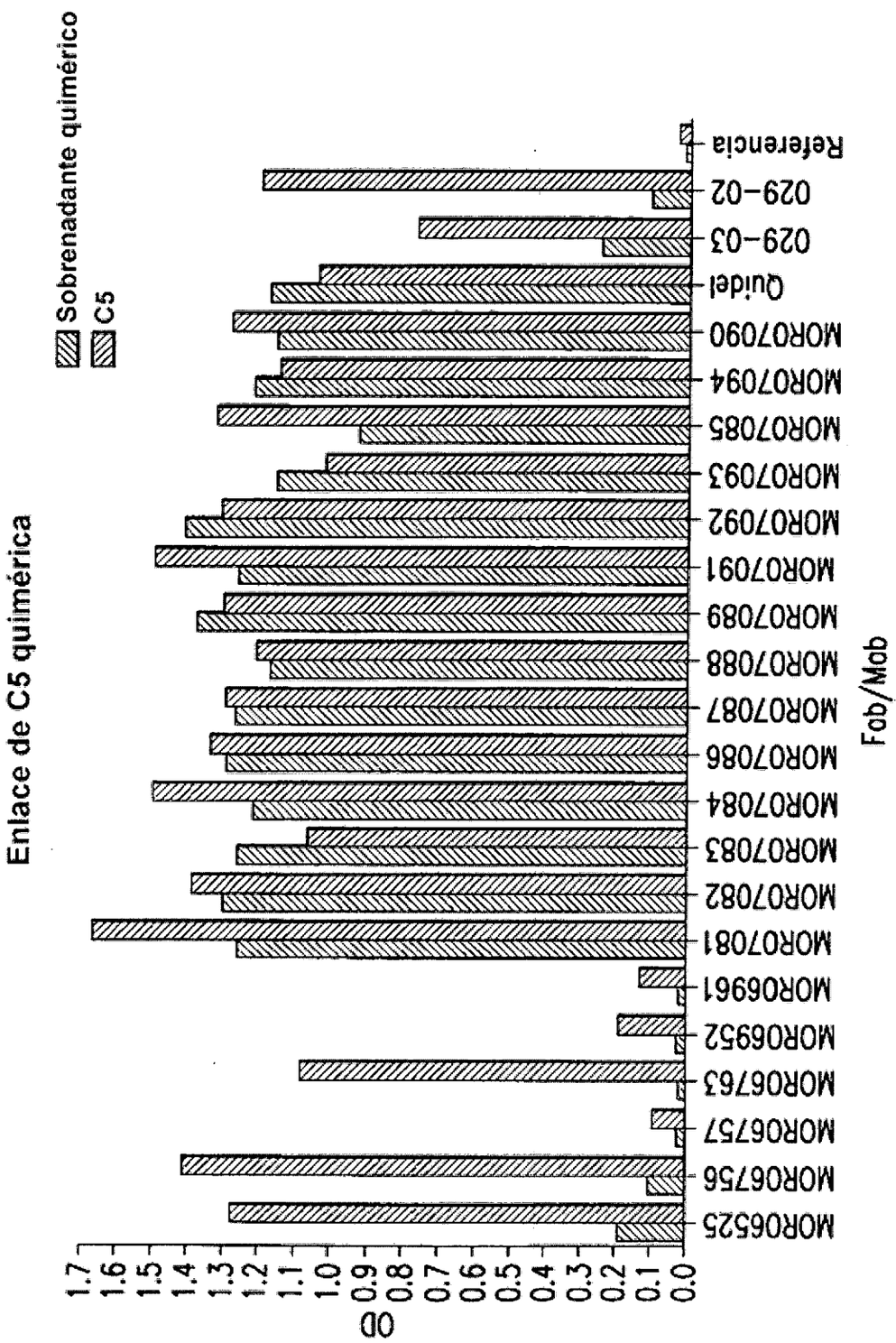

Enlace de C5 quimérica
Sobrenadante quimérico
C5
OD
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Referencia
029-02
029-03
Quidel
MOR07090
MOR07094
MOR07085
MOR07093
MOR07092
MOR07091
MOR07089
MOR07088
MOR07087
MOR07086
MOR07084
MOR07083
MOR07082
MOR07081
MOR06961
MOR06952
MOR06763
MOR06757
MOR06756
MOR06525
Fab/Mab

FIG. 20

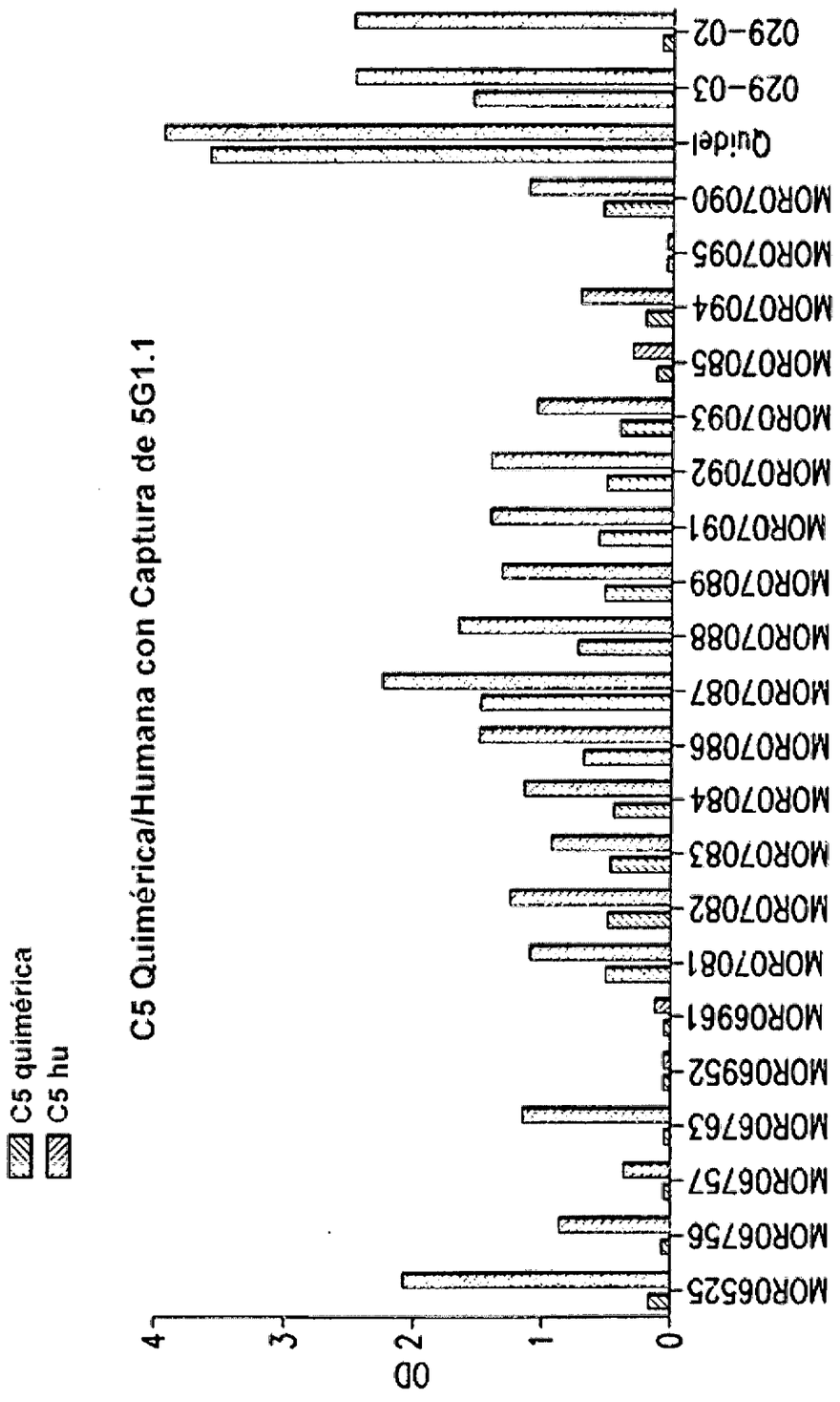

C5 quimérica
C5 hu
C5 Quimérica/Humana con Captura de 5G1.1
OD
0
1
2
3
4
MOR06525
MOR06756
MOR06757
MOR06763
MOR06952
MOR06961
MOR07081
MOR07082
MOR07083
MOR07084
MOR07086
MOR07087
MOR07088
MOR07089
MOR07091
MOR07092
MOR07093
MOR07085
MOR07094
MOR07095
MOR07090
Quidel
029-03
029-02

FIG. 21

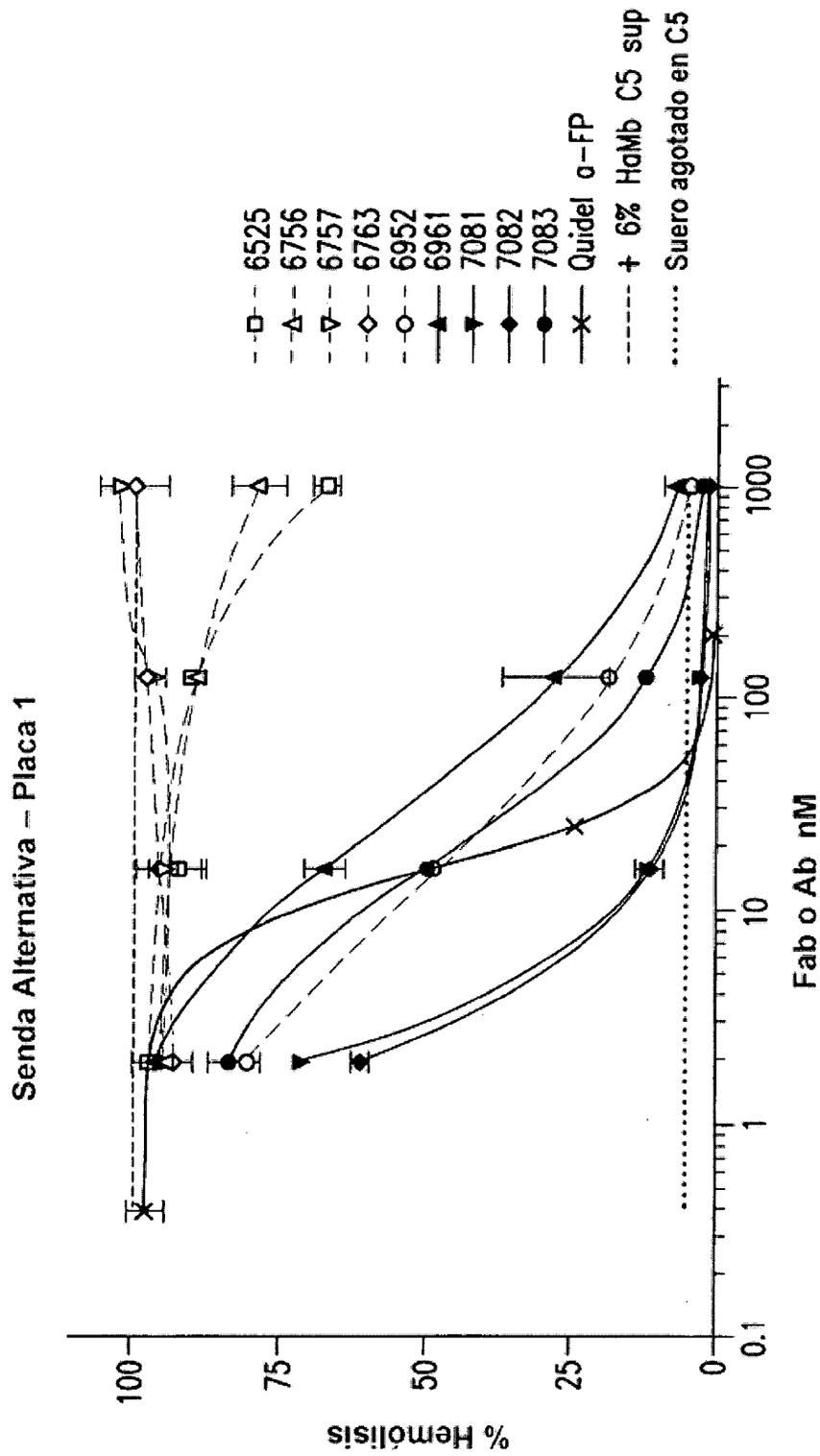

Senda Alternativa – Placa 1
% Hemólisis
Fab o Ab nM
0
25
50
75
100
0.1
1
10
100
1000
6525
6756
6757
6763
6952
6961
7081
7082
7083
Quidel α-FP
+ 6% HoMb C5 sup
Suero agotado en C5

FIG. 22-1

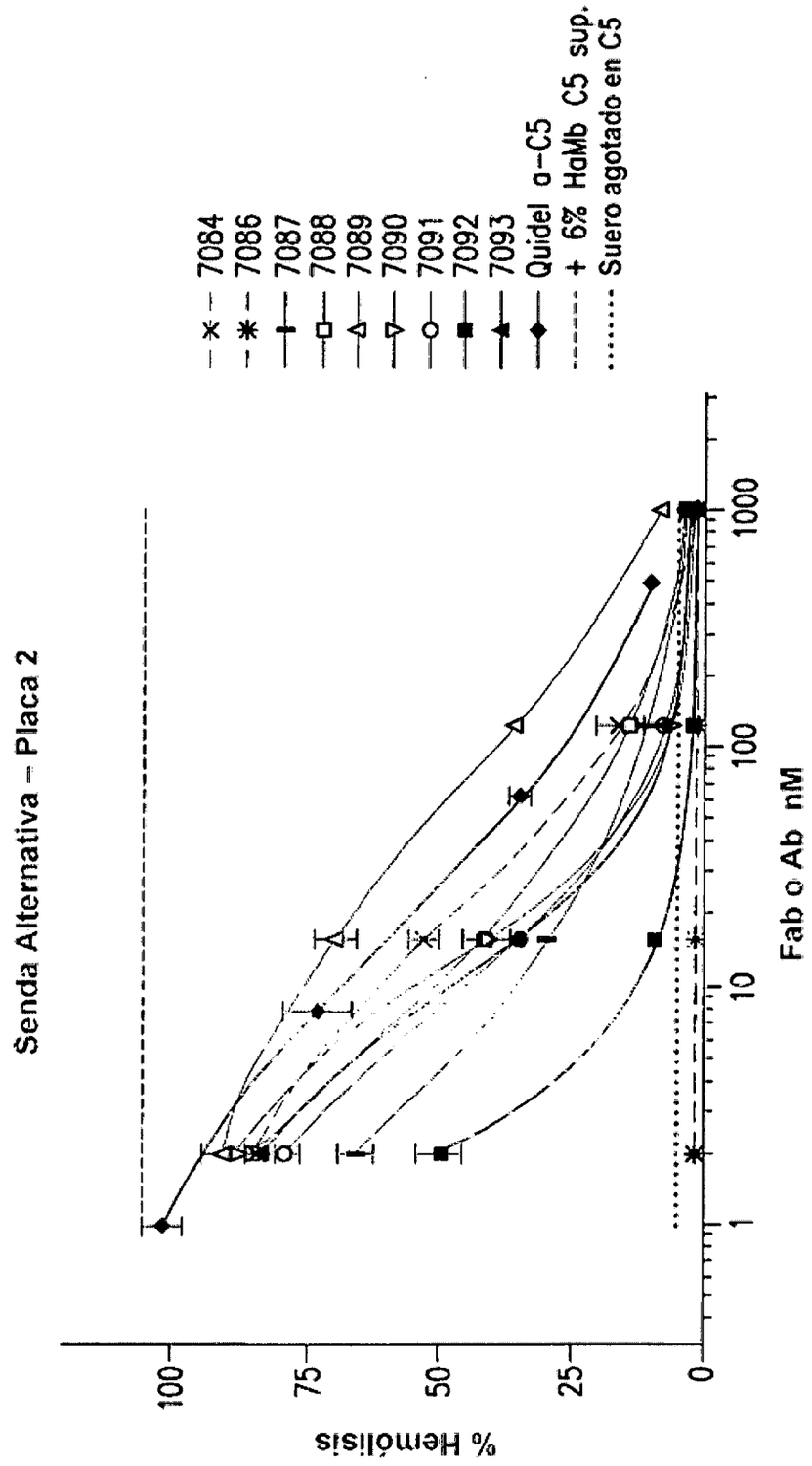

Senda Alternativa – Placa 2
% Hemólisis
Fab o Ab nM
0
25
50
75
100
1
10
100
1000
7084
7086
7087
7088
7089
7090
7091
7092
7093
Quidel α-C5
+ 6% HaMb C5 sup.
Suero agotado en C5

FIG. 22-2

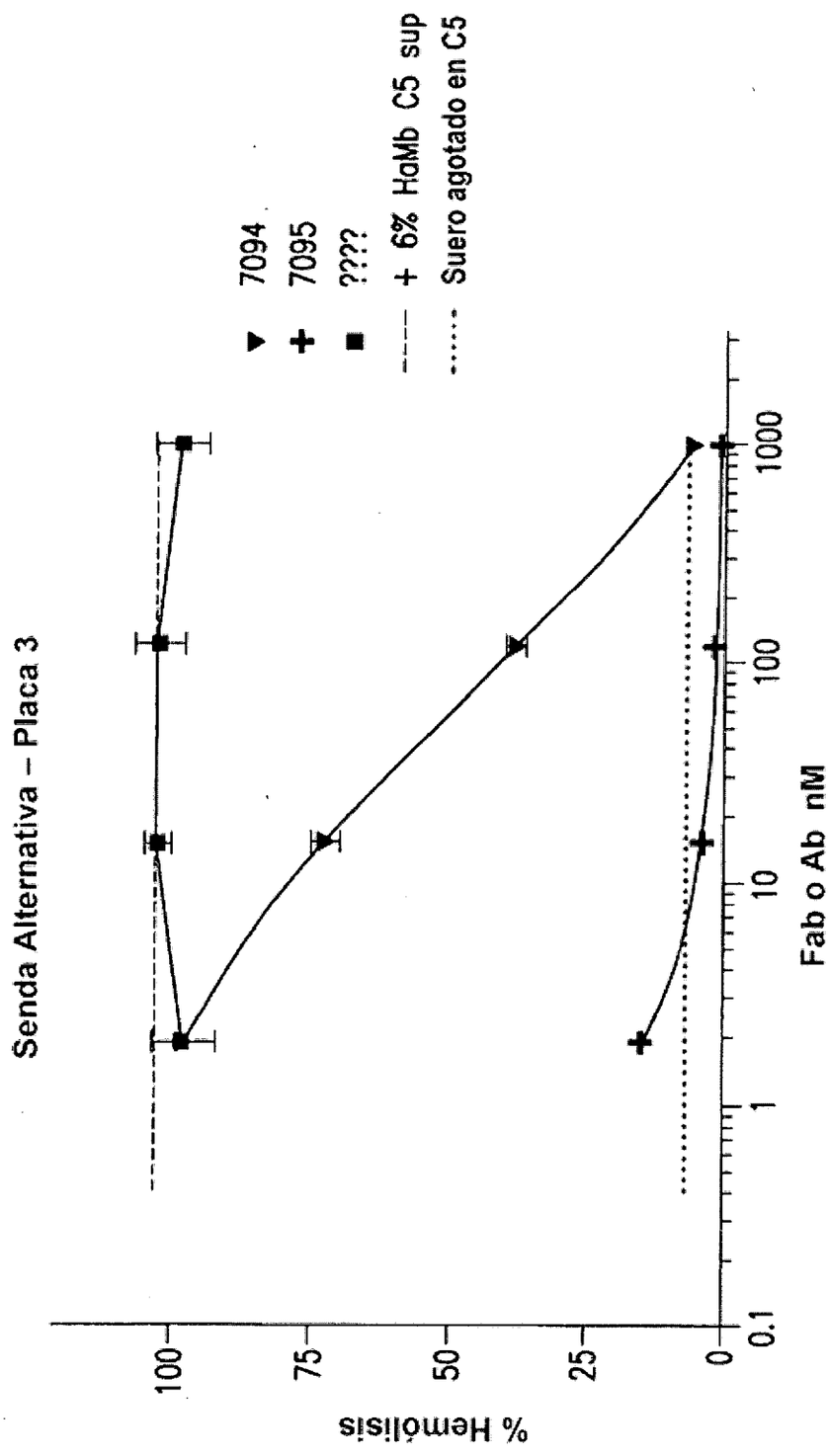

Senda Alternativa – Placa 3
% Hemólisis
100
75
50
25
0
0.1
1
10
100
1000
Fab o Ab nM
7094
7095
???
+ 6% HaMb C5 sup
Suero agotado en C5

FIG. 22-3

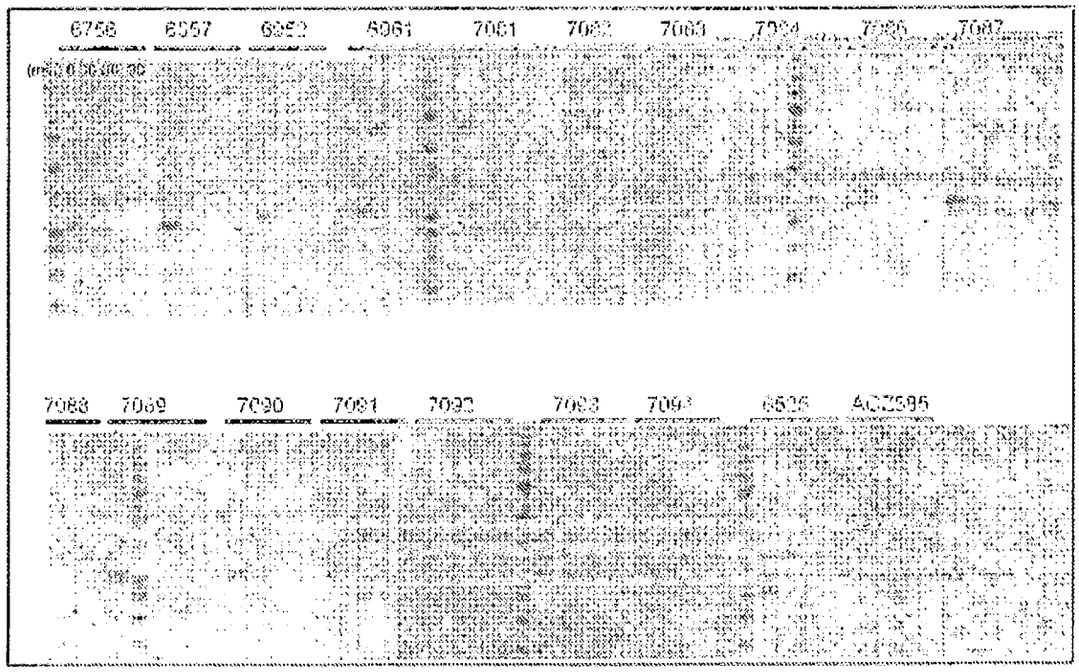


FIG. 23

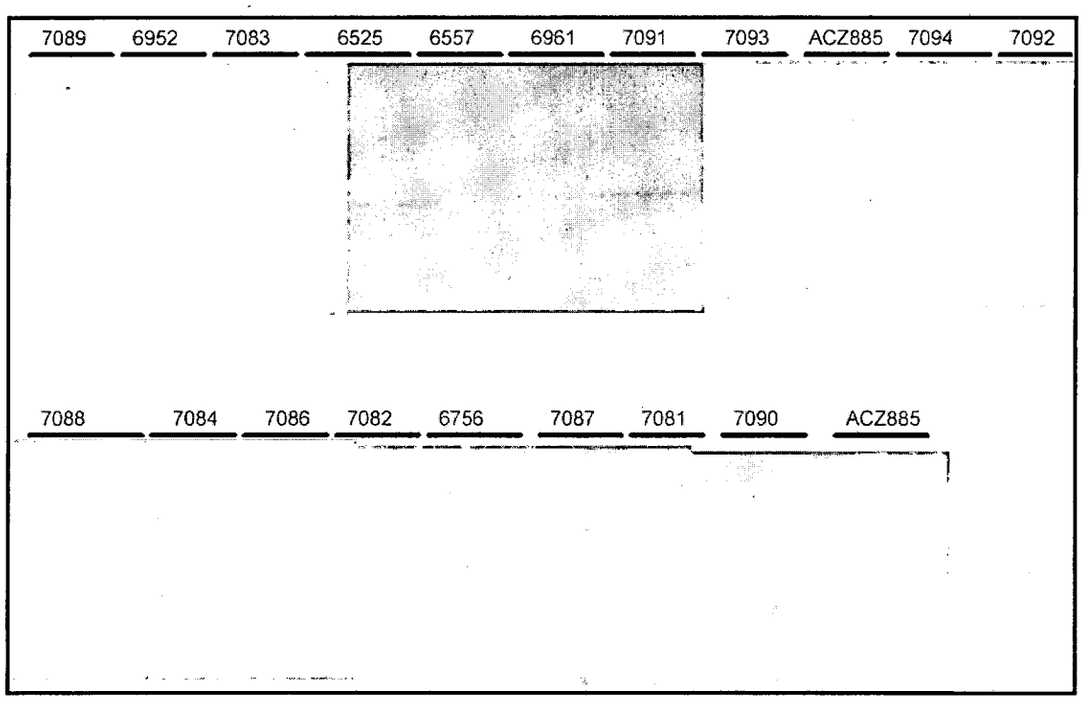

7089
6952
7083
6525
6557
6961
7091
7093
ACZ885
7094
7092
7088
7084
7086
7082
6756
7087
7081
7090
ACZ885

FIG. 24

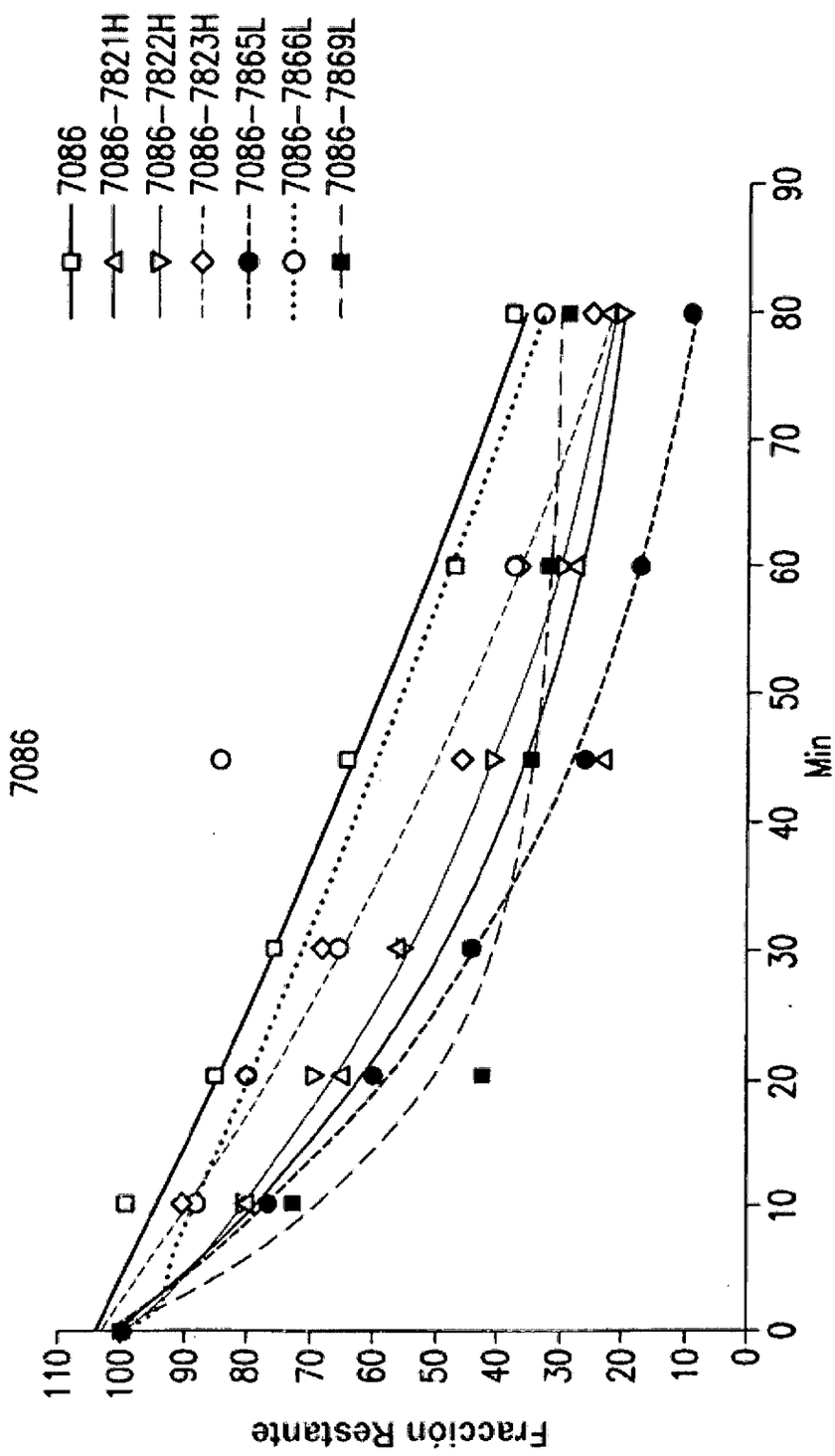

7086
7086
7086-7821H
7086-7822H
7086-7823H
7086-7865L
7086-7866L
7086-7869L
Fraccion Restante
Min
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90

FIG. 25-1

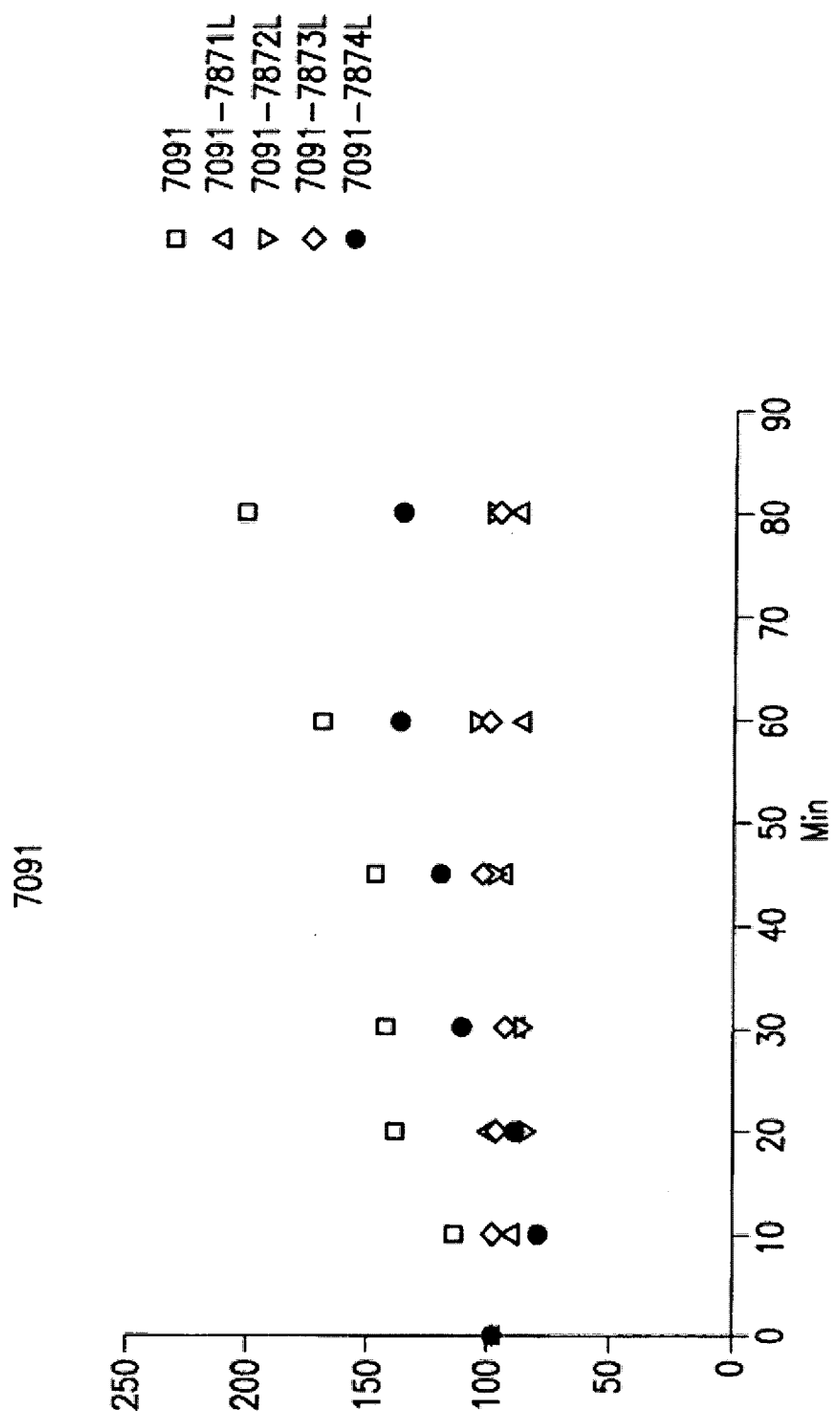

7091
7091
7091−7871L
7091−7872L
7091−7873L
7091−7874L
250
200
150
100
50
0
0
10
20
30
40
50
60
70
80
90
Min

FIG. 25-2

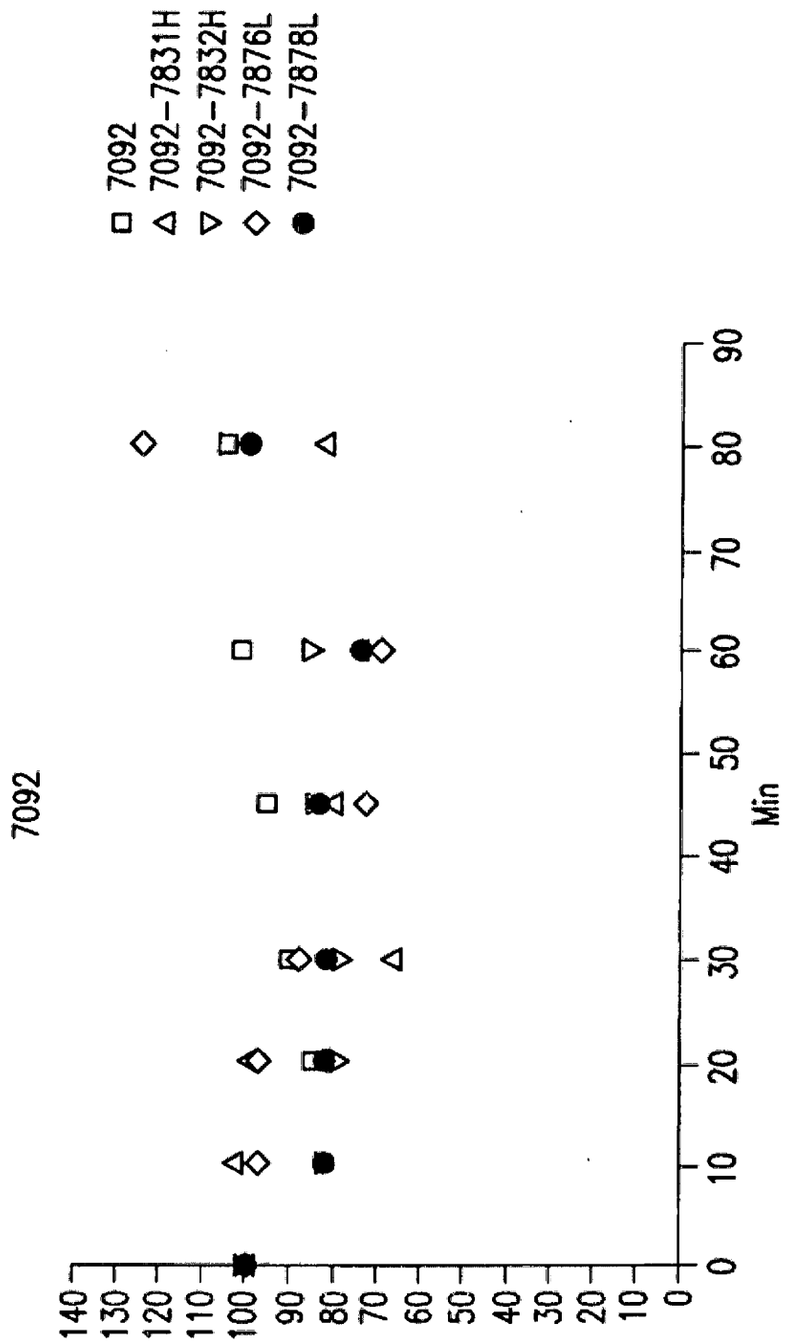

7092
7092
7092-7831H
7092-7832H
7092-7876L
7092-7878L
Min
0
10
20
30
40
50
60
70
80
90
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140

FIG. 25-3

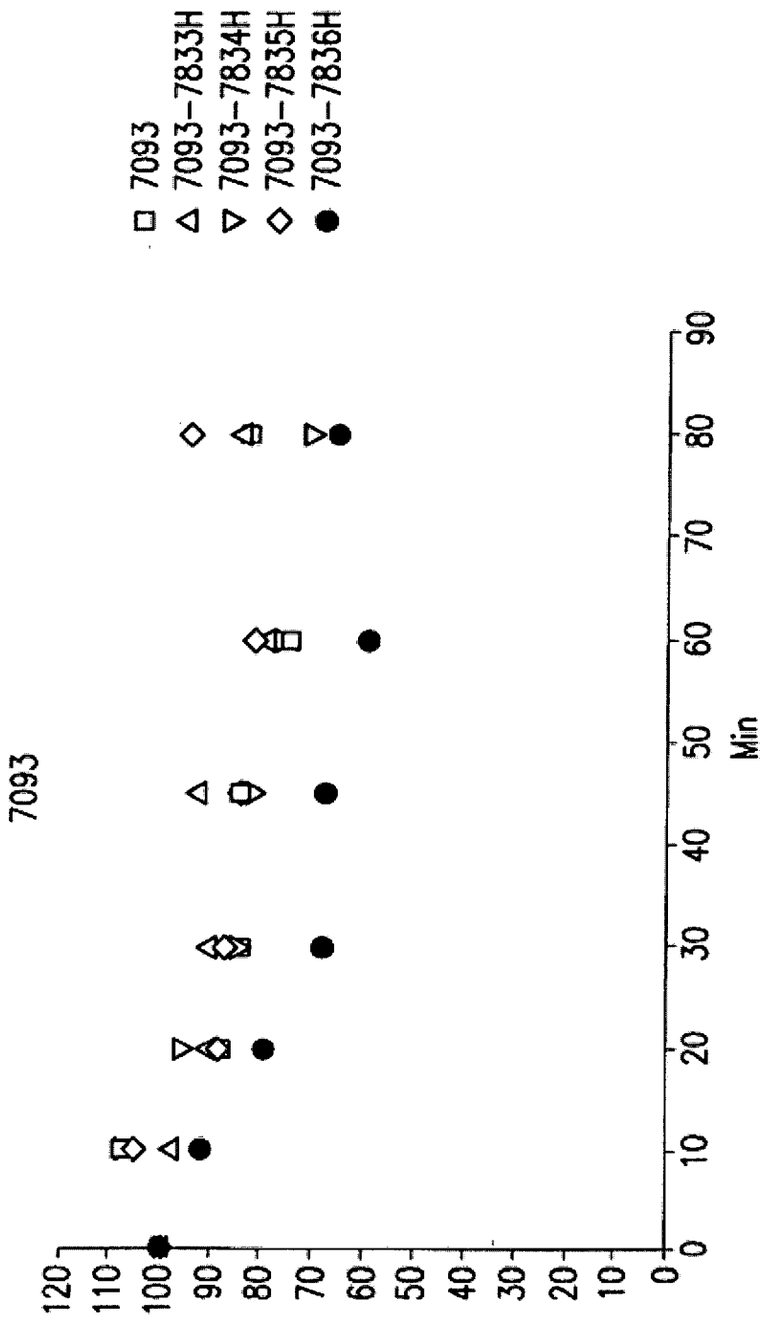

7093
7093
7093-7833H
7093-7834H
7093-7835H
7093-7836H
120
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
Min

FIG. 25-4

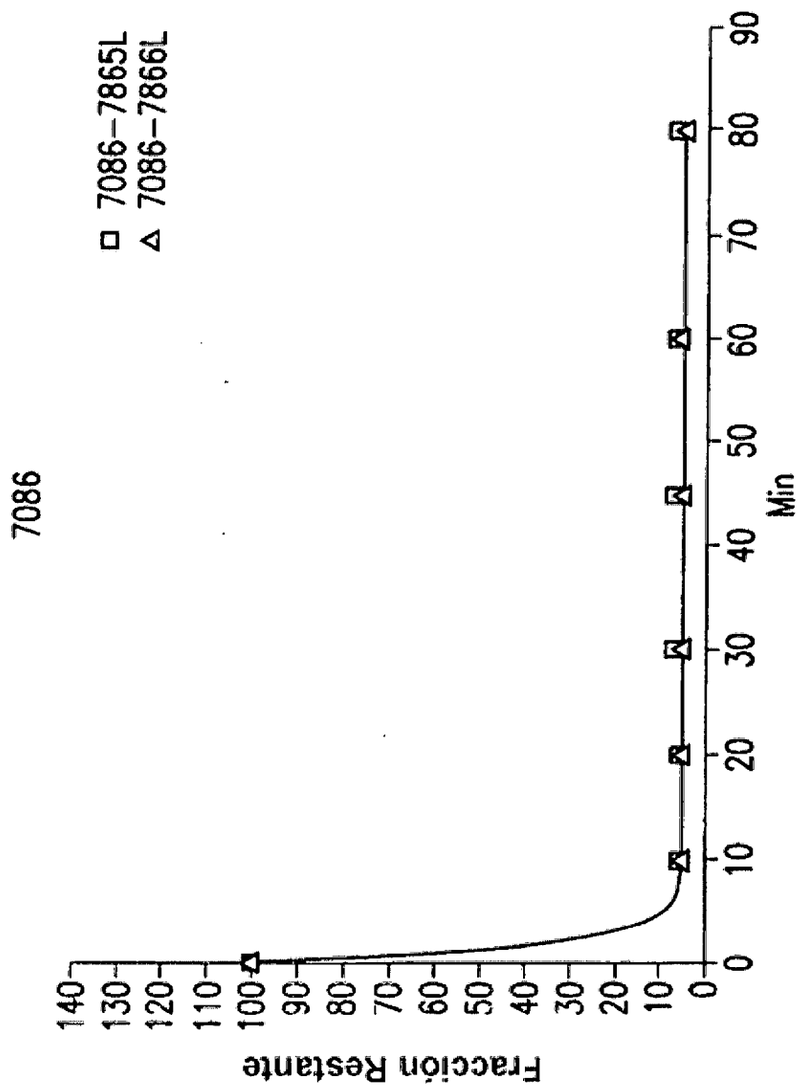

7086
□ 7086–7865L
△ 7086–7866L
Fracción Restante
Min
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140

FIG. 26-1

428

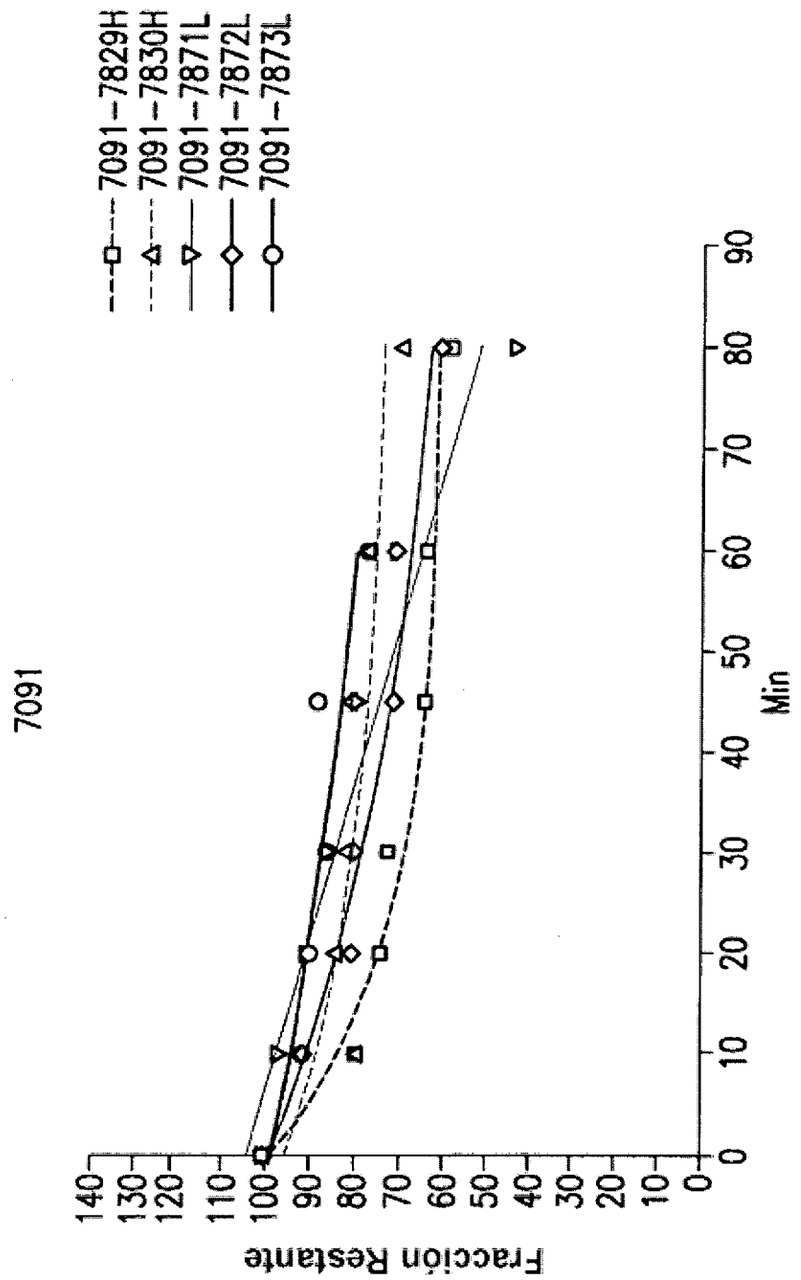

7091
7091-7829H
7091-7830H
7091-7871L
7091-7872L
7091-7873L
Fraccion Restante
Min
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140

FIG. 26-2

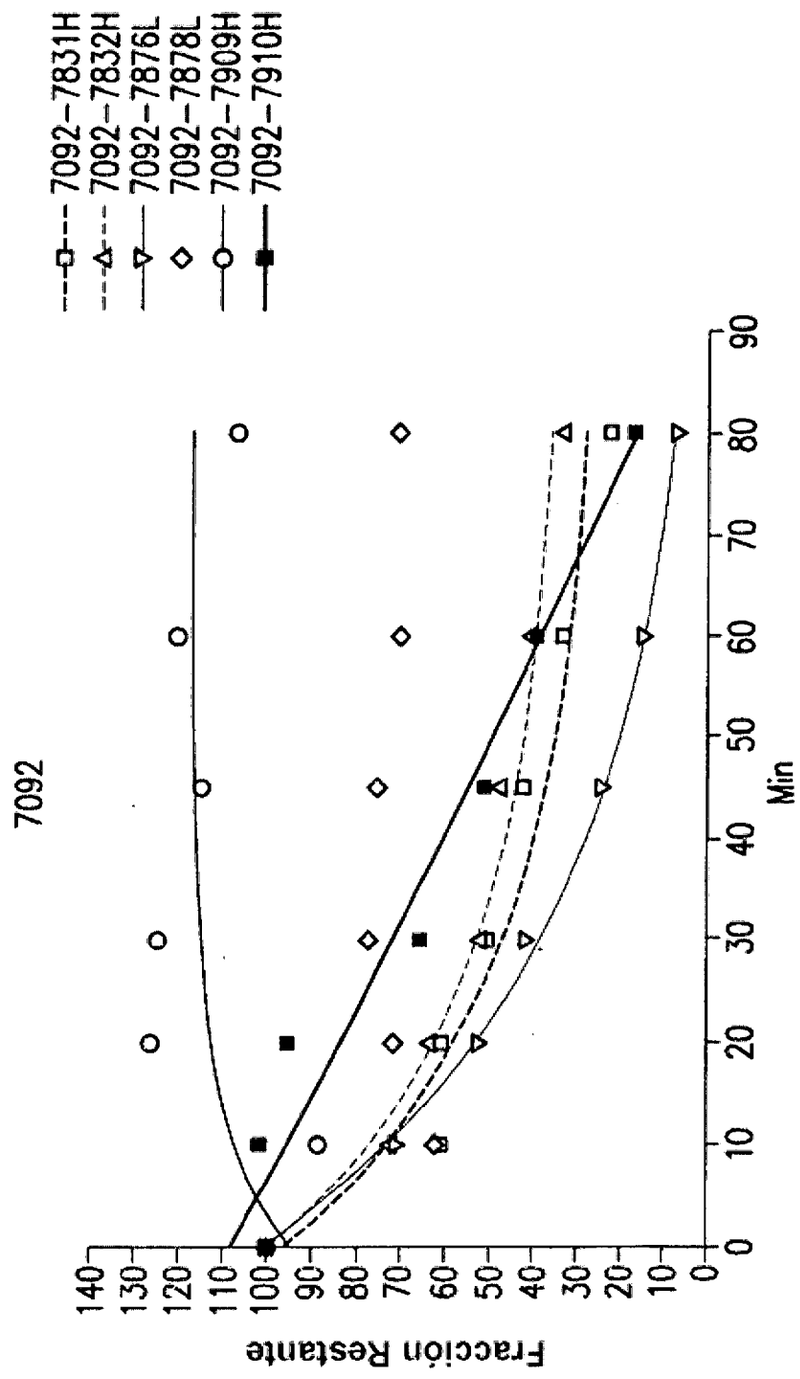

7092
Fraccion Restante
Min
7092-7831H
7092-7832H
7092-7876L
7092-7878L
7092-7909H
7092-7910H

FIG. 26-3

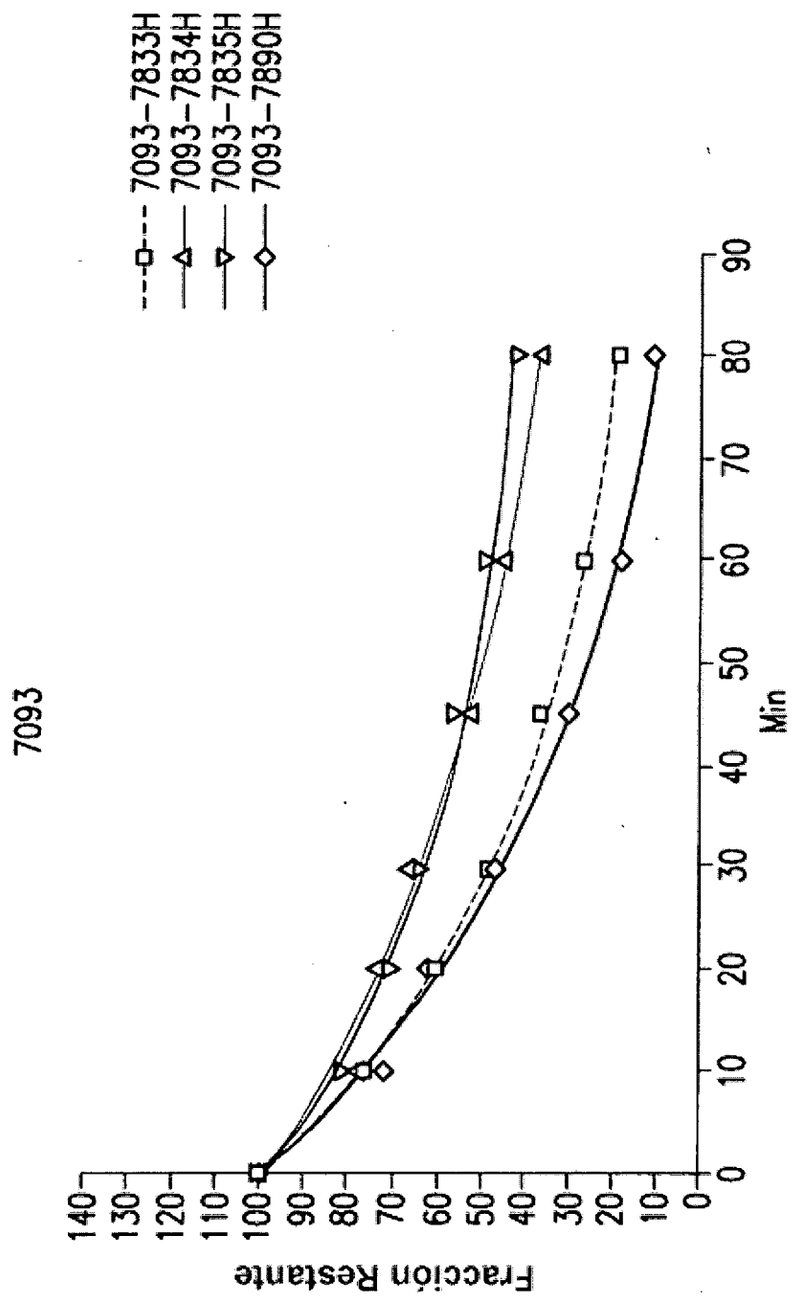

7093
7093-7833H
7093-7834H
7093-7835H
7093-7890H
Fraccion Restante
Min
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90

FIG. 26-4

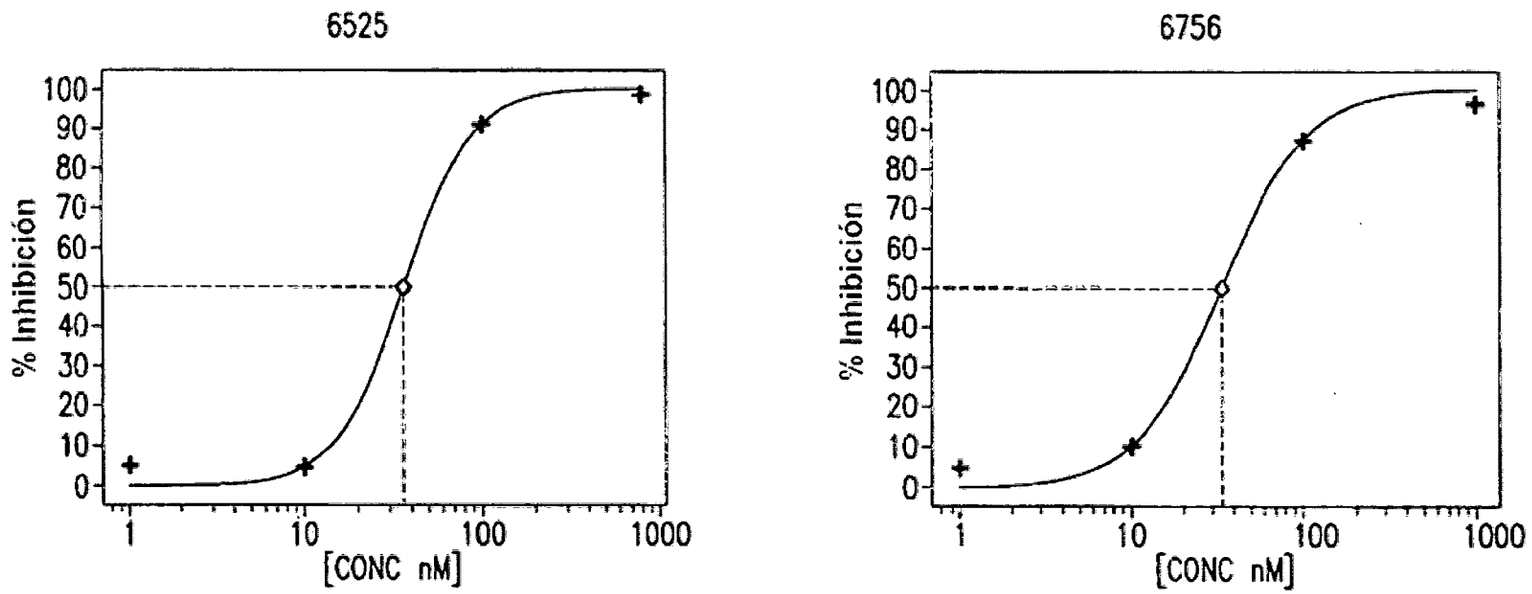

6525
% Inhibición
100
90
80
70
60
50
40
30
20
10
0
1
10
100
1000
[CONC nM]
6756
% Inhibición
100
90
80
70
60
50
40
30
20
10
0
1
10
100
1000
[CONC nM]

FIG. 27

LISTADO DE SECUENCIAS

<110> Novartis AG

<120> COMPOSICIONES Y MÉTODOS PARA ANTICUERPOS QUE SE DIRIGEN A LA PROTEÍNA DE COMPLEMENTO C5

<130> 52633-US-P

<140> 61/086,355

<141> 2008-08-05

<160> 297

<170> PatentIn versión 3.3

<210> 1

<211> 5

<212> PRT

<213> homo sapiens

<400> 1

Ser Tyr Ala Ile Ser
1 5

<210> 2

<211> 17

<212> PRT

<213> homo sapiens

<400> 2

Gly Ile Gly Pro Phe Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 3

<211> 7

<212> PRT

<213> homo sapiens

<400> 3

Asp Thr Pro Tyr Phe Asp Tyr

1 5

<210> 4

<211> 11

<212> PRT

<213> homo sapiens

<400> 4

Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val Tyr

1 5 10

<210> 5

<211> 7

<212> PRT

<213> homo sapiens

<400> 5

Asp Asp Ser Asn Arg Pro Ser

1 5

<210> 6

<211> 11

<212> PRT

<213> homo sapiens

<400> 6

Gln Ser Phe Asp Ser Ser Leu Asn Ala Glu Val

1 5 10

<210> 7

<211> 116

<212> PRT

<213> homo sapiens

<400> 7

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr

20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

Gly Gly Ile Gly Pro Phe Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe

50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr

65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Arg Asp Thr Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val

100 105 110

Thr Val Ser Ser

115

<210> 8

<211> 108

<212> PRT

<213> homo sapiens

<400> 8

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

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val
20 25 30

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

Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Ala Gln Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Ser Ser Leu Asn Ala
85 90 95

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 9

<211> 446

<212> PRT

<213> homo sapiens

<400> 9

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Gly Pro Phe Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Thr Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220
Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350
Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 10

<211> 214

<212> PRT

<213> homo sapiens

<400> 10

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

Thr Ala Arg Ile Thr Cys Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val
20 25 30

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

Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Ala Gln Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Ser Ser Leu Asn Ala
85 90 95

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 11

<211> 348

<212> ADN

<213> homo sapiens

<400> 11

gaggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60

agctgcaaag cctccggagg cacttttttct tcttatgcca tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcggt atcggtccgt tttttggcac tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300

ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 12

<211> 324

<212> ADN

<213> homo sapiens

<400> 12

tcctatgaac tcacacagcc cctgagcgtg agcgtggccc tgggccagac cgcccggatc 60

acctgctccg gcgacagcat ccccaactac tacgtgtact ggtaccagca gaagcccggc 120

caggcccccg tgctggtgat ctacgacgac agcaaccggc ccagcggcat ccccgagcgg 180

ttcagcggca gcaacagcgg caacaccgcc accctgacca tttccagagc acaggcaggc 240

gacgaggccg actactactg ccagagcttc gacagcagcc tgaacgccga ggtgttcggc 300

ggagggacca agttaaccgt ccta 324

<210> 13

<211> 1338

<212> ADN

<213> homo sapiens

<400> 13

gaggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60

agctgcaaag cctccggagg cacttttttct tcttatgcca tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcggt atcggtccgt tttttggcac tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300

ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctcagc ctccaccaag 360

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<400> 17

Asn Tyr Ile Ser

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Gly

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Tyr Glu Tyr Gly Gly Phe Asp Ile

1 5

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Lys Asp Asn Asp Arg Pro Ser

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Gly Thr Tyr Asp Ile Glu Ser Tyr Val

1 5

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

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

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350
Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
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Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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<400> 26

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20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Tyr Asp Ile Glu Ser Tyr Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125

Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140

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

Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175

Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
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Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro

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Thr Glu Cys Ser

210

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<211> 348

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<211> 1338

<212> ADN

<213> homo sapiens

<400> 29

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<210> 30

<211> 636

<212> ADN

<213> homo sapiens

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<210> 31

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<210> 33

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<213> homo sapiens

<400> 33

Thr Ser Gly Gly Gly Val Ser

1 5

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<211> 16

<212> PRT

<213> homo sapiens

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1 5 10 15

<210> 35

<211> 7

<212> PRT

<213> homo sapiens

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Gly Pro Tyr Gly Phe Asp Ser

1 5

<210> 36

<211> 14

<212> PRT

<213> homo sapiens

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1 5 10

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<211> 7

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Asp Asp Ser Asn Arg Pro Ser

1 5

<210> 38

<211> 9

<212> PRT

<213> homo sapiens

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Gln Ser Tyr Asp Ser Gln Ser Ile Val

1 5

<210> 39

<211> 117

<212> PRT

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<400> 39

Glu Val Thr Leu Lys Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln

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35 40 45

Trp Leu Ala Asn Ile Asp Asp Ala Asp Ile Lys Asp Tyr Ser Pro Ser

50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val

65 70 75 80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr

85 90 95

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

Met Ile Tyr Asp Asp Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
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Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Gln
85 90 95

Ser Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
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            20                  25                  30
Gly Gly Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
        35                  40                  45
Trp Leu Ala Asn Ile Asp Asp Ala Asp Ile Lys Asp Tyr Ser Pro Ser
    50                  55                  60
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80
Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95
Cys Ala Arg Gly Pro Tyr Gly Phe Asp Ser Trp Gly Gln Gly Thr Leu
            100                 105                 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175
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Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 42
<211> 215
<212> PRT
<213> homo sapiens
<400> 42

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Gln
85 90 95
Ser Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
100 105 110
Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
115 120 125
Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140
Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160
Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
165 170 175
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180 185 190
Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
195 200 205
Val Ala Pro Thr Glu Cys Ser
210 215

<210> 43
<211> 351
<212> ADN
<213> homo sapiens
<400> 43

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cagccgcctg ggaaagccct cgagtggctg gctaatattg atgatgctga tattaaggat 180

tattctcctt ctcttaagtc tcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240

gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgtggt 300

ccttatggtt ttgattcttg gggccaaggc accctggtga cggttagctc a 351

<210> 44

<211> 327

<212> ADN

<213> homo sapiens

<400> 44

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tcgtgtacgg gtactagcag cgatattggt acttataatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgatt ctaatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc cagtcttatg attctcagtc tattgtgttt 300

ggcggcggca cgaagttaac cgtccta 327

<210> 45

<211> 1341

<212> ADN

<213> homo sapiens

<400> 45

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cagccgcctg ggaaagccct cgagtggctg gctaatattg atgatgctga tattaaggat 180

tattctcctt ctcttaagtc tcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240

gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgtggt 300

ccttatggtt ttgattcttg gggccaaggc accctggtga cggttagctc agcctccacc 360

aagggtccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420

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cgggtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 960

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1020

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gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260

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ctctccctgt ctccgggtaa a 1341

<210> 46

<211> 645

<212> ADN

<213> homo sapiens

<400> 46

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tcgtgtacgg gtactagcag cgatattggt acttataatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgatt ctaatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc cagtctttatg attctcagtc tattgtgttt 300

ggcggcggca cgaagttaac cgtcctaggt cagcccaagg ctgccccctc ggtcactctg 360

ttcccgccct cctctgagga gcttcaagcc aacaaggcca cactggtgtg tctcataagt 420

gacttctacc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg 480

ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540

ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat 600

gaagggagca ccgtggagaa gacagtggcc cctacagaat gttca 645

<210> 47

<211> 1341

<212> ADN

<213> homo sapiens

<400> 47

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acttgcacct tcagcggctt cagcctgagc accagcggag ggggcgtgag ctggatcagg 120

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gtgctgacca tgaccaatat ggaccccgtg gacaccgcca cctactactg cgccagaggc 300

ccctacggct tcgacagctg gggccagggc accctggtga ccgtcagctc agctagcacc 360

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gacaagaccc acacctgccc cccctgccca gccccgaag ctgcaggcgg ccctccgtg 720

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aaccaggtgt ccctgacctg tctggtgaag ggcttctacc ccagcgacat cgccgtggag 1140

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gacggcagct tcttcctgta cagcaagctg accgtggaca agagcaggtg gcagcagggc 1260

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ctgagcctgt cacccggcaa g 1341

<210> 48

<211> 645

<212> ADN

<213> homo sapiens

<400> 48

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agctgcaccg gcacctccag cgatatcggc acctacaact acgtgagctg gtatcagcag 120

caccccggca aggccccaa gctgatgatc tacgacgaca gcaacaggcc cagcggcgtg 180

agcaacaggt tcagcggcag caagagcggc aacaccgcca gcctgacaat cagcggcctg 240

caggccgagg acgaggccga ctactactgc cagagctacg acagccagtc aatcgtgttc 300

ggcggaggga ccaagctgac cgtgctgggc cagcctaagg ctgccccag cgtgaccctg 360

ttccccccca gcagcgagga gctgcaggcc aacaaggcca ccctggtgtg cctgatcagc 420

gacttctacc caggcgccgt gaccgtggcc tggaaggccg acagcagccc cgtgaaggcc 480

ggcgtggaga ccaccacccc cagcaagcag agcaacaaca agtacgccgc cagcagctac 540

ctgagcctga cccccgagca gtggaagagc cacaggtcct acagctgcca ggtgacccac 600

gagggcagca ccgtggaaaa gaccgtggcc ccaaccgagt gcagc 645

<210> 49

<211> 17

<212> PRT

<213> homo sapiens

<400> 49

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln
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Gly

<210> 50

<211> 9

<212> PRT

<213> homo sapiens

<400> 50

Ala Thr Trp Gly Ser Glu Asp Gln Val
1 5

<210> 51

<211> 116

<212> PRT

<213> homo sapiens

<400> 51

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

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

<210> 52
<211> 106
<212> PRT
<213> homo sapiens
<400> 52

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30
His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

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

<210> 53
<211> 446
<212> PRT
<213> homo sapiens
<400> 53

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

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205
Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220
Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350
Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 54
<211> 212
<212> PRT
<213> homo sapiens

<400> 54

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Gly Ser Glu Asp Gln Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125

Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140

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

Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175

Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190

Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205

Thr Glu Cys Ser
210

<210> 55
<211> 348
<212> ADN
<213> homo sapiens
<400> 55

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gggaagggtc tcgagtggat gggcattatc gatccggatg atagctatac cgttattct 180
ccgagctttc agggacaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240
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<210> 56
<211> 318
<212> ADN
<213> homo sapiens
<400> 56

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tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120
caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
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acgaagttaa ccgtccta 318

<210> 57

<211> 1338

<212> ADN

<213> homo sapiens

<400> 57

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ccgagctttc agggacaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240

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gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320

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<212> ADN

<213> homo sapiens

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tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

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ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag 480

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accgtggaga agacagtggc ccctacagaa tgttca 636

<210> 59

<211> 1338

<212> ADN

<213> homo sapiens

<400> 59

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ggcaagggcc tggagtggat gggcatcatc gaccccgacg acagctacac caggtacagc 180

cccagcttcc agggccaggt gaccatcagc gccgacaaga gcatcagcac cgcctacctg 240

cagtggagca gcctgaaggc cagcgacacc gccatgtact actgcgccag atacgagtac 300

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aaggtctcca acaaggccct gcctgccccc atcgaaaaga ccatcagcaa ggccaagggc 1020

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caggtgtccc tgacctgtct ggtgaagggc ttctacccca gcgacatcgc cgtggagtgg 1140

gagagcaacg gccagcccga gaacaactac aagaccaccc ccccagtgct ggacagcgac 1200

ggcagcttct tcctgtacag caagctgacc gtggacaaga gcaggtggca gcagggcaac 1260

gtgttcagct gcagcgtgat gcacgaggcc ctgcacaacc actacaccca gaagagcctg 1320

agcctgtcac ccggcaag 1338

<210> 60

<211> 636

<212> ADN

<213> homo sapiens

<400> 60

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agctgcagcg gcgacaatat cggcaacagc tacgtgcact ggtatcagca gaagcccggc 120

caggcccccg tgctggtgat ctacaaggac aacgacaggc ccagcggcat ccccgagagg 180

ttcagcggca gcaactccgg caacaccgcc accctgacaa tcagcggcac ccaggccgag 240

gacgaggccg actactactg cgccacctgg ggctcagagg accaggtgtt cggcggaggg 300

accaagctga ccgtgctggg ccagcctaag gctgccccca gcgtgaccct gttccccccc 360

agcagcgagg agctgcaggc caacaaggcc accctggtgt gcctgatcag cgacttctac 420

ccaggcgccg tgaccgtggc ctggaaggcc gacagcagcc ccgtgaaggc cggcgtggag 480

accaccaccc ccagcaagca gagcaacaac aagtacgccg ccagcagcta cctgagcctg 540

acccccgagc agtggaagag ccacaggtcc tacagctgcc aggtgaccca cgagggcagc 600

accgtggaaa agaccgtggc cccaaccgag tgcagc 636

<210> 61

<211> 5

<212> PRT

<213> homo sapiens

<400> 61

Ser Tyr Tyr Ile Gly

1 5

<210> 62

<211> 17

<212> PRT

<213> homo sapiens

<400> 62

Ile Ile Asp Pro Thr Asp Ser Gln Thr Ala Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 63

<211> 8

<212> PRT

<213> homo sapiens

<400> 63

Tyr Met Met Arg Gly Phe Asp His
1 5

<210> 64

<211> 11

<212> PRT

<213> homo sapiens

<400> 64

Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala Tyr
1 5 10

<210> 65

<211> 7

<212> PRT

<213> homo sapiens

<400> 65

Lys Asp Asn Asn Arg Pro Ser
1 5

<210> 66

<211> 10

<212> PRT

<213> homo sapiens

<400> 66

Gln Thr Trp Asp Thr Gly Glu Ser Gly Val

1 5 10

<210> 67

<211> 117

<212> PRT

<213> homo sapiens

<400> 67

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr

20 25 30

Tyr Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

35 40 45

Gly Ile Ile Asp Pro Thr Asp Ser Gln Thr Ala Tyr Ser Pro Ser Phe

50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 68

<211> 107

<212> PRT

<213> homo sapiens

<400> 68

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Thr Gly Glu Ser Gly
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 69

<211> 447

<212> PRT

<213> homo sapiens

<400> 69

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Tyr Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Asp Pro Thr Asp Ser Gln Thr Ala Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 70
<211> 213
<212> PRT
<213> homo sapiens
<400> 70

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

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Thr Gly Glu Ser Gly
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110

Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125

Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140

Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160

Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
165 170 175

Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
180 185 190

Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
195 200 205

Pro Thr Glu Cys Ser
210

<210> 71

<211> 351

<212> ADN

<213> homo sapiens

<400> 71

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agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt attgatccta ctgattctca gactgcttat 180

tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc a 351

<210> 72

<211> 321

<212> ADN

<213> homo sapiens

<400> 72

agttacgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttgg gatactggtg agtctggtgt gtttggcggc 300

ggcacgaagt taaccgtcct a 321

<210> 73

<211> 1341

<212> ADN

<213> homo sapiens

<400> 73

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agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt attgatccta ctgattctca gactgcttat 180

tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc agcctccacc 360

aagggtccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 600

aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt 660

gacaaaactc acacatgccc accgtgccca gcacctgaag cagcgggggg accgtcagtc 720

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 780

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ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 900

cgggtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 960

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1020

gggcagcccc gagaaccaca ggtgtacacc ctgccccca cccgggagga gatgaccaag 1080

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1140

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1200

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320

ctctccctgt ctccgggtaa a 1341

<210> 74

<211> 639

<212> ADN

<213> homo sapiens

<400> 74

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tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttgg gatactggtg agtctggtgt gtttggcggc 300

ggcacgaagt taaccgtcct aggtcagccc aaggctgccc cctcggtcac tctgttcccg 360

cctcctctg aggagcttca agccaacaag gccacactgg tgtgtctcat aagtgacttc 420

tacccgggag ccgtgacagt ggcctggaag gcagatagca gccccgtcaa ggcgggagtg 480

gagaccacca caccctccaa acaaagcaac aacaagtacg cggccagcag ctatctgagc 540

ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgaaggg 600

agcaccgtgg agaagacagt ggcccctaca gaatgttca 639

<210> 75

<211> 1341

<212> ADN

<213> homo sapiens

<400> 75

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agctgcaagg gcagcggcta cagcttcacc agctactaca tcggctgggt gcggcagatg 120

cccggcaagg gcctggagtg gatgggcatc atcgacccca ccgacagcca gaccgcctac 180

agccccagct tccagggcca ggtgaccatc agcgccgaca agagcatcag caccgcctac 240

ctgcagtgga gcagcctgaa ggccagcgac accgccatgt actactgcgc cggtacatg 300

atgaggggct tcgaccactg gggtcagggc accctggtga ccgtcagctc agctagcacc 360

aagggcccca gcgtgttccc cctggccccc agcagcaaga gcacctccgg cggcacagcc 420

gccctgggct gcctggtgaa ggactacttc cccgagcccg tgaccgtgtc ctggaacagc 480

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aacgtgaacc acaagcccag caacaccaag gtggacaaga gagtggagcc caagagctgc 660

gacaagaccc acacctgccc ccctgccca gccccgaag ctgcaggcgg ccattccgtg 720

ttcctgttcc ccccaagcc caaggacacc ctgatgatca gcaggacccc cgaggtgacc 780

tgcgtggtgg tggacgtgag ccacgaggac ccagaggtga agttcaactg gtacgtggac 840

ggcgtggagg tgcacaacgc caagaccaag cccagagagg agcagtacaa cagcacctac 900

agggtggtgt ccgtgctgac cgtgctgcac caggactggc tgaacggcaa agaatacaag 960

tgcaaggtct ccaacaaggc cctgcctgcc cccatcgaaa agaccatcag caaggccaag 1020

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aaccaggtgt ccctgacctg tctggtgaag ggcttctacc ccagcgacat cgccgtggag 1140

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gacggcagct tcttcctgta cagcaagctg accgtggaca agagcaggtg gcagcagggc 1260

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ctgagcctgt cacccggcaa g 1341

<210> 76

<211> 639

<212> ADN

<213> homo sapiens

<400> 76

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agctgcagcg gcgacagcct gggcgactac tacgcctact ggtatcagca gaagcccggc 120

caggcccccg tgctggtgat ctacaaggac aacaacaggc ccagcggcat ccccgagagg 180

ttcagcggca gcaacagcgg caacaccgcc accctgacaa tcagcggcac ccaggccgag 240

gacgaggccg actactactg ccagacctgg gacaccggcg agtcaggcgt gttcggcgga 300

gggaccaagc tgaccgtgct gggtcagcct aaggctgccc ccagcgtgac cctgttcccc 360

cccagcagcg aggagctgca ggccaacaag gccaccctgg tgtgcctgat cagcgacttc 420

tacccaggcg ccgtgaccgt ggcctggaag gccgacagca gccccgtgaa ggcggcgtg 480

gagaccacca cccccagcaa gcagagcaac aacaagtacg ccgccagcag ctacctgagc 540

ctgacccccg agcagtggaa gagccacagg tcctacagct gccaggtgac ccacgagggc 600

agcaccgtgg aaaagaccgt ggccccaacc gagtgcagc 639

<210> 77

<211> 17

<212> PRT

<213> homo sapiens

<400> 77

Ile Ile Asp Pro Ser Asp Ser His Thr Thr Tyr Ser Pro Ser Phe Gln

1 5 10 15

Gly

<210> 78

<211> 11

<212> PRT

<213> homo sapiens

<400> 78

Gln Thr Trp Asp Ile Leu Pro His Gly Leu Val

1 5 10

<210> 79

<211> 117

<212> PRT

<213> homo sapiens

<400> 79

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

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

<210> 80
<211> 108
<212> PRT
<213> homo sapiens
<400> 80

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

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

<210> 81
<211> 447
<212> PRT
<213> homo sapiens
<400> 81

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

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220
Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240
Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255
Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270
Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300
Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320
Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335
Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350
Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 82
<211> 214
<212> PRT
<213> homo sapiens

<400> 82

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Ile Leu Pro His Gly
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val

195 200 205

Ala Pro Thr Glu Cys Ser

210

<210> 83

<211> 351

<212> ADN

<213> homo sapiens

<400> 83

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cctgggaagg gtctcgagtg gatgggcatt atcgatccgt ctgatagcca taccacttat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc a 351

<210> 84

<211> 324

<212> ADN

<213> homo sapiens

<400> 84

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tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttgg gatattcttc ctcatggtct tgtgtttggc 300

ggcggcacga agttaaccgt ccta 324

<210> 85

<211> 1341

<212> ADN

<213> homo sapiens

<400> 85

gaggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atcgatccgt ctgatagcca taccacttat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc agcctccacc 360

aagggtccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480

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<211> 642

<212> ADN

<213> homo sapiens

<400> 86

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<210> 87

<211> 1341

<212> ADN

<213> homo sapiens

<400> 87

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<211> 642

<212> ADN

<213> homo sapiens

<400> 88

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<210> 89

<211> 11

<212> PRT

<213> homo sapiens

<400> 89

Gln Ala Trp Thr Asp Ser Pro Thr Gly Leu Val

1 5 10

<210> 90

<211> 108

<212> PRT

<213> homo sapiens

<400> 90

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
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Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Thr Asp Ser Pro Thr Gly
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 91

<211> 214

<212> PRT

<213> homo sapiens

<400> 91

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Thr Asp Ser Pro Thr Gly
85 90 95
Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205
Ala Pro Thr Glu Cys Ser
210

<210> 92

<211> 324

<212> ADN

<213> homo sapiens

<400> 92

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ggcggcacga agttaaccgt ccta 324

<210> 93

<211> 642

<212> ADN

<213> homo sapiens

<400> 93

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gggagcaccg tggagaagac agtggccccc acagaatgtt ca 642

<210> 94

<211> 642

<212> ADN

<213> homo sapiens

<400> 94

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ggcagcaccg tggaaaagac cgtggccccca accgagtgca gc 642

<210> 95

<211> 17

<212> PRT

<213> homo sapiens

<400> 95

Ile Ile Asp Pro Thr Asp Ser Tyr Thr Val Tyr Ser Pro Ser Phe Gln

1 5 10 15

Gly

<210> 96

<211> 117

<212> PRT

<213> homo sapiens

<400> 96

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
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Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Thr Asp Ser Tyr Thr Val Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 97

<211> 447

<212> PRT

<213> homo sapiens

<400> 97

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Thr Asp Ser Tyr Thr Val Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
260 265 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
325 330 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
340 345 350

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 98
<211> 353
<212> ADN
<213> homo sapiens
<400> 98

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<210> 99
<211> 1343
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<400> 99

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<213> homo sapiens

<400> 100

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<210> 101

<211> 10

<212> PRT

<213> homo sapiens

<400> 101

Ser Thr Trp Asp Ile Glu Pro Thr Tyr Val

1 5 10

<210> 102

<211> 107

<212> PRT

<213> homo sapiens

<400> 102

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln

1 5 10 15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val

20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr

35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser

50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu

65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ser Thr Trp Asp Ile Glu Pro Thr Tyr
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 103

<211> 213

<212> PRT

<213> homo sapiens

<400> 103

Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
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Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ser Thr Trp Asp Ile Glu Pro Thr Tyr
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110

Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125

Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140
Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160
Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
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Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
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Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
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Pro Thr Glu Cys Ser
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<212> ADN

<213> homo sapiens

<400> 105

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ccctcctctg aggagcttca agccaacaag gccacactgg tgtgtctcat aagtgacttc 420

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gagaccacca caccctccaa acaaagcaac aacaagtacg cggccagcag ctatctgagc 540

ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgaaggg 600

agcaccgtgg agaagacagt ggcccctaca gaatgttca 639

<210> 106

<211> 639

<212> ADN

<213> homo sapiens

<400> 106

agctacgagc tgacccagcc ccccagcgtg agcgtggccc caggccagac cgccaggatc 60

agctgcagcg gcgacaatat cggcaacagc tacgtgcact ggtatcagca gaagcccggc 120

caggcccccg tgctggtgat ctacaaggac aacgacaggc ccagcggcat ccccgagagg 180

ttcagcggca gcaactccgg caacaccgcc accctgacaa tcagcggcac ccaggccgag 240

gacgaggccg actactactg ctctacttgg gatattgagc ctacttatgt gttcggcgga 300

gggaccaagc tgaccgtgct gggccagcct aaggctgccc ccagcgtgac cctgttcccc 360

cccagcagcg aggagctgca ggccaacaag gccaccctgg tgtgcctgat cagcgacttc 420

tacccaggcg ccgtgaccgt ggcctggaag gccgacagca gccccgtgaa ggccggcgtg 480

gagaccacca cccccagcaa gcagagcaac aacaagtacg ccgccagcag ctacctgagc 540

ctgacccccg agcagtggaa gagccacagg tcctacagct gccaggtgac ccacgagggc 600

agcaccgtgg aaaagaccgt ggccccaacc gagtgcagc 639

<210> 107

<211> 17

<212> PRT

<213> homo sapiens

<400> 107

Ile Ile Asp Pro Gln Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln

1 5 10 15

Gly

<210> 108

<211> 116

<212> PRT

<213> homo sapiens

<400> 108

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr

20 25 30

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

35 40 45

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

<210> 109
<211> 446
<212> PRT
<213> homo sapiens
<400> 109

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

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95
Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205
Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220
Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 110

<211> 348

<212> ADN

<213> homo sapiens

<400> 110

gaggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctcagg attcttatac tgagtattct 180

ccttctttte agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 111

<211> 1338

<212> ADN

<213> homo sapiens

<400> 111

gaggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctcagg attcttatac tgagtattct 180

ccttctttte agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc ctccaccaag 360

ggtccatcgg tcttcccccc ggcaccctcc tccaagagca cctctggggg cacagcggcc 420

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 480

gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc 540

ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac 600

gtgaatcaca agcccagcaa caccaaggtg gacaagagag ttgagcccaa atcttgtgac 660

aaaactcaca catgcccacc gtgcccagca cctgaagcag cgggggggacc gtcagtcttc 720

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggaccccctga ggtcacatgc 780

gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 840

gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgg 900

gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 960

aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggg 1020

cagccccgag aaccacaggt gtacaccctg ccccatcccc gggaggagat gaccaagaac 1080

caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg 1140

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac 1200

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320

tccctgtctc cgggtaaa 1338

<210> 112

<211> 1338

<212> ADN

<213> homo sapiens

<400> 112

gaggtgcagc tggtgcagag cggagccgag gtgaaaaagc ccggtgagag cctgaagatc 60

agctgcaagg gcagcggcta cagcttcacc aactacatca gctgggtgcg gcagatgccc 120

ggcaagggcc tggagtggat gggcatcatc gaccccccagg acagctacac cgagtacagc 180

cccagcttcc agggccaggt gaccatcagc gccgacaaga gcatcagcac cgcctacctg 240

cagtggagca gcctgaaggc cagcgacacc gccatgtact actgcgccag atacgagtac 300

ggcggcttcg acatctgggg ccagggcacc ctggtgaccg tcagctcagc tagcaccaag 360

ggccccagcg tgttccccct ggccccccagc agcaagagca cctccggcgg cacagccgcc 420

ctgggctgcc tggtgaagga ctacttcccc gagccgtga ccgtgtcctg gaacagcgga 480

gccctgacca gcggcgtgca caccttcccc gccgtgctgc agagcagcgg cctgtacagc 540

ctgtccagcg tggtgacagt gcccagcagc agcctgggca cccagaccta catctgcaac 600

gtgaaccaca agcccagcaa caccaaggtg gacaagagag tggagcccaa gagctgcgac 660

aagacccaca cctgcccccc ctgcccagcc cccgaagctg caggcggccc ttccgtgttc 720

ctgttccccc ccaagcccaa ggacaccctg atgatcagca ggacccccga ggtgacctgc 780

gtggtggtgg acgtgagcca cgaggaccca gaggtgaagt tcaactggta cgtggacggc 840

gtggaggtgc acaacgccaa gaccaagccc agagaggagc agtacaacag cacctacagg 900

gtggtgtccg tgctgaccgt gctgcaccag gactggctga acggcaaaga atacaagtgc 960

aaggtctcca acaaggccct gcctgccccc atcgaaaaga ccatcagcaa ggccaagggc 1020

cagccacggg agccccaggt gtacaccctg ccccctctc gggaggagat gaccaagaac 1080

caggtgtccc tgacctgtct ggtgaagggc ttctacccca gcgacatcgc cgtggagtgg 1140

gagagcaacg gccagcccga gaacaactac aagaccaccc ccccagtgct ggacagcgac 1200

ggcagcttct tcctgtacag caagctgacc gtggacaaga gcaggtggca gcagggcaac 1260

gtgttcagct gcagcgtgat gcacgaggcc ctgcacaacc actacaccca gaagagcctg 1320

agcctgtcac ccggcaag 1338

<210> 113

<211> 17

<212> PRT

<213> homo sapiens

<400> 113

Ile Ile Asp Pro Glu Asp Ser His Thr Glu Tyr Ser Pro Ser Phe Gln

1 5 10 15

Gly

<210> 114

<211> 116

<212> PRT

<213> homo sapiens

<400> 114

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Glu Asp Ser His Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 115

<211> 446

<212> PRT

<213> homo sapiens

<400> 115

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30
Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
35 40 45
Ile Ile Asp Pro Glu Asp Ser His Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95
Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220
Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350
Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 116

<211> 348

<212> ADN

<213> homo sapiens

<400> 116

gaggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctgagg attctcatac tgagtattct 180

ccttcttttc agggtcaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 117

<211> 1338

<212> ADN

<213> homo sapiens

<400> 117

gaggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctgagg attctcatac tgagtattct 180

ccttcttttc agggtcaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc ctccaccaag 360

ggtccatcgg tcttcccccc ggcaccctcc tccaagagca cctctggggg cacagcggcc 420

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 480

gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc 540

ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac 600

gtgaatcaca agcccagcaa caccaaggtg gacaagagag ttgagcccaa atcttgtgac 660

aaaactcaca catgcccacc gtgcccagca cctgaagcag cgggggggacc gtcagtcttc 720

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacatgc 780

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gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 960

aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggg 1020

cagccccgag aaccacaggt gtacaccctg ccccatcccc gggaggagat gaccaagaac 1080

caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg 1140

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac 1200

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320

tccctgtctc cgggtaaa 1338

<210> 118

<211> 1338

<212> ADN

<213> homo sapiens

<400> 118

gaggtgcagc tggtgcagag cggagccgag gtgaaaaagc ccggtgagag cctgaagatc 60

agctgcaagg gcagcggcta cagcttcacc aactacatca gctgggtgcg gcagatgccc 120

ggcaagggcc tggagtggat gggcatcatc gaccccgagg acagccatac cgagtacagc 180

cccagcttcc agggccaggt gaccatcagc gccgacaaga gcatcagcac cgcctacctg 240

cagtggagca gcctgaaggc cagcgacacc gccatgtact actgcgccag atacgagtac 300

ggcggcttcg acatctgggg ccagggcacc ctggtgaccg tcagctcagc tagcaccaag 360

ggccccagcg tgttccccct ggccccccagc agcaagagca cctccggcgg cacagccgcc 420

ctgggctgcc tggtgaagga ctacttcccc gagcccgtga ccgtgtcctg gaacagcgga 480

gccctgacca gcggcgtgca caccttcccc gccgtgctgc agagcagcgg cctgtacagc 540

ctgtccagcg tggtgacagt gcccagcagc agcctgggca cccagaccta catctgcaac 600

gtgaaccaca agcccagcaa caccaaggtg gacaagagag tggagcccaa gagctgcgac 660

aagacccaca cctgccccc ctgcccagcc cccgaagctg caggcggccc ttccgtgttc 720

ctgttccccc ccaagcccaa ggacaccctg atgatcagca ggacccccga ggtgacctgc 780

gtggtggtgg acgtgagcca cgaggaccca gaggtgaagt tcaactggta cgtggacggc 840

gtggaggtgc acaacgccaa gaccaagccc agagaggagc agtacaacag cacctacagg 900

gtggtgtccg tgctgaccgt gctgcaccag gactggctga acggcaaaga atacaagtgc 960

aaggtctcca acaaggccct gcctgccccc atcgaaaaga ccatcagcaa ggccaagggc 1020

cagccacggg agccccaggt gtacaccctg ccccctctc gggaggagat gaccaagaac 1080

caggtgtccc tgacctgtct ggtgaagggc ttctacccca gcgacatcgc cgtggagtgg 1140

gagagcaacg gccagccgga gaacaactac aagaccaccc ccccagtgct ggacagcgac 1200

ggcagcttct tcctgtacag caagctgacc gtggacaaga gcaggtggca gcagggcaac 1260

gtgttcagct gcagcgtgat gcacgaggcc ctgcacaacc actacaccca gaagagcctg 1320

agcctgtcac ccggcaag 1338

<210> 119

<211> 17

<212> PRT

<213> homo sapiens

<400> 119

Asn Ile Gly Pro Phe Phe Gly Ile Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 120

<211> 11

<212> PRT

<213> homo sapiens

<400> 120

Gln Thr Tyr Asp Asp Gly Ser Thr Ala Glu Val
1 5 10

<210> 121

<211> 116

<212> PRT

<213> homo sapiens

<400> 121

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

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

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

<210> 122
<211> 108
<212> PRT
<213> homo sapiens
<400> 122

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

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Asp Asp Gly Ser Thr Ala
85 90 95

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 123

<211> 442

<212> PRT

<213> homo sapiens

<400> 123

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

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

Gly Asn Ile Gly Pro Phe Phe Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
130 135 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe
180 185 190
Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr
195 200 205
Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro
210 215 220
Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
225 230 235 240
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
245 250 255
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
260 265 270
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
275 280 285
Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
290 295 300
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
305 310 315 320

Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
325 330 335

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
340 345 350

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
355 360 365

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
370 375 380

Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe
385 390 395 400

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
405 410 415

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
420 425 430

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 124

<211> 214

<212> PRT

<213> homo sapiens

<400> 124

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val
20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Asp Asp Gly Ser Thr Ala
85 90 95
Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205
Ala Pro Thr Glu Cys Ser
210

<210> 125

<211> 348

<212> ADN

<213> homo sapiens

<400> 125

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cctgggcagg gtctcgagtg gatgggcaat atcggtccgt tttttggcat tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300

ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 126

<211> 324

<212> ADN

<213> homo sapiens

<400> 126

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

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caggcgccag ttcttgtgat ttatgatgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttat gatgatggtt ctactgctga ggtgtttggc 300

ggcggcacga agttaaccgt tctt 324

<210> 127

<211> 1326

<212> ADN

<213> homo sapiens

<400> 127

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agctgcaaag cctccggagg cacttttttct tcttatgcca tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcaat atcggtccgt tttttggcat tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300

ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctcagc ttccaccaag 360

ggccccagcg tgttcccccct ggcccccctgc agcagaagca ccagcgagag cacagccgcc 420

ctgggctgcc tggtgaagga ctacttcccc gagcccgtga ccgtgagctg gaacagcgga 480

gccctgacca gcggcgtgca caccttcccc gccgtgctgc agagcagcgg cctgtacagc 540

ctgagcagcg tggtgaccgt gcccagcagc aacttcggca cccagaccta cacctgcaac 600

gtggaccaca agcccagcaa caccaaggtg gacaagaccg tggagcggaa gtgctgcgtg 660

gagtgcccccc cctgccctgc ccctcctgtg gccggaccct ccgtgttcct gttcccccccc 720

aagcccaagg acaccctgat gatcagccgg acccccgagg tgacctgcgt ggtggtggac 780

gtgagccacg aggaccccga ggtgcagttc aactggtacg tggacggcgt ggaggtgcac 840

aacgccaaga ccaagccccg ggaggaacag ttcaacagca ccttccgggt ggtgtccgtg 900

ctgaccgtgg tgcaccagga ctggctgaac ggcaaagaat acaagtgcaa ggtgtccaac 960

aagggcctgc ctgccccccat cgagaaaacc atcagcaaga caaagggcca gcccagggaa 1020

ccccaggtgt acaccctgcc ccccagccgg gaggaaatga ccaagaacca ggtgtccctg 1080

acctgtctgg tgaagggctt ctaccccagc gacatcgccg tggagtggga gagcaacggc 1140

cagcccgaga acaactacaa gaccacccccc cccatgctgg acagcgacgg cagcttcttc 1200

ctgtacagca agctgacagt ggacaagagc cggtggcagc agggcaacgt gttcagctgc 1260

agcgtgatgc acgaggccct gcacaaccac tacacccaga agagcctgag cctgtccccc 1320

ggcaaa 1326

<210> 128

<211> 642

<212> ADN

<213> homo sapiens

<400> 128

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tcgtgtagcg gcgattctat tcctaattat tatgtttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttat gatgatggtt ctactgctga ggtgtttggc 300

ggcggcacga agttaaccgt tcttggtcag cccaaggctg ccccctcggt cactctgttc 360

ccgccctcct ctgaggagct tcaagccaac aaggccacac tggtgtgtct cataagtgac 420

ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgaa 600

gggagcaccg tggagaagac agtggccccc acagaatgtt ca 642

<210> 129

<211> 1326

<212> ADN

<213> homo sapiens

<400> 129

caggtgcagc tggtgcagtc cggcgccgag gtgaagaagc ccggctcctc cgtgaaggtg 60

tcctgcaagg cctccggcgg caccttctcc tcctacgcca tctcctgggt gcggcaggcc 120

cccggccagg gcctggagtg gatgggcaac atcggccccc tcttcggcat cgccaactac 180

gcccagaagt tccagggccg ggtgaccatc accgccgacg agtccacctc cacccgctac 240

atggagctgt cctccctgcg gtccgaggac accgccgtgt actactgcgc ccgggacacc 300

ccctacttcg actactgggg ccagggcacc ctggtgaccg tgtcctccgc ctccaccaag 360

ggcccctccg tgttccccct ggccccctgc tcccggtcca cctccgagtc caccgccgcc 420

ctgggctgcc tggtgaagga ctacttcccc gagcccgtga ccgtgtcctg gaactccggc 480

gccctgacct ccggcgtgca caccttcccc gccgtgctgc agtcctccgg cctgtactcc 540

ctgtcctccg tggtgaccgt gccctcctcc aacttcggca cccagaccta cacctgcaac 600

gtggaccaca agccctccaa caccaaggtg gacaagaccg tggagcggaa gtgctgcgtg 660

gagtgcccct cctgccccgc ccccccgtg gccggccct ccgtgttcct gttccccccc 720

aagcccaagg acaccctgat gatctcccgg acccccgagg tgacctgcgt ggtggtggac 780

gtgtcccacg aggaccccga ggtgcagttc aactggtacg tggacggcgt ggaggtgcac 840

aacgccaaga ccaagccccg ggaggagcag ttcaactcca ccttccgggt ggtgtccgtg 900

ctgaccgtgg tgcaccagga ctggctgaac ggcaaggagt acaagtgcaa ggtgtccaac 960

aagggcctgc ccgccccat cgagaagacc atctccaaga ccaagggcca gccccgggag 1020

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acctgcctgg tgaagggctt ctaccctcc gacatcgccg tggagtggga gtccaacggc 1140

cagccgaga acaactacaa gaccacccc cccatgctgg actccgacgg ctccttcttc 1200

ctgtactcca agctgaccgt ggacaagtcc cggtggcagc agggcaacgt gttctcctgc 1260

tccgtgatgc acgaggccct gcacaaccac tacacccaga agtccctgtc cctgtccccc 1320

ggcaag 1326

<210> 130

<211> 642

<212> ADN

<213> homo sapiens

<400> 130

gacatcgagc tgacccagcc ccctccgtg tccgtggccc ccggccagac cgcccggatc 60

tcctgctccg gcgactccat ccccaactac tacgtgtact ggtaccagca gaagcccggc 120

caggcccccg tgctggtgat ctacgacgac tccaaccggc cctccggcat ccccgagcgg 180

ttctccggct ccaactccgg caacaccgcc accctgacca tctccggcac ccaggccgag 240

gacgaggccg actactactg ccagacctac gacgacggct ccaccgccga ggtgttcggc 300

ggcggcacca agctgaccgt gctgggccag cctaaggctg ccccctcggt gaccctgttc 360

ccccccagca gcgaggagct gcaggccaac aaggccaccc tggtgtgcct gatcagcgac 420

ttctacccag gcgccgtgac cgtggcctgg aaggccgaca gcagccccgt gaaggccggc 480

gtggagacca ccaccccccag caagcagagc aacaacaagt acgccgccag cagctacctg 540

agcctgaccc ccgagcagtg gaagagccac aggtcctaca gctgccaggt gacccacgag 600

ggcagcaccg tggaaaagac cgtggccccca accgagtgca gc 642

<210> 131

<211> 5

<212> PRT

<213> homo sapiens

<400> 131

Ser Tyr Trp Ile Ser

1 5

<210> 132

<211> 17

<212> PRT

<213> homo sapiens

<400> 132

Ile Ile Asp Pro Asp Asp Ser Lys Thr Asn Tyr Ser Pro Ser Phe Gln

1 5 10 15

Gly

<210> 133

<211> 8

<212> PRT

<213> homo sapiens

<400> 133

Arg Ser Tyr Tyr Pro Met Asp Tyr

1 5

<210> 134

<211> 15

<212> PRT

<213> homo sapiens

<400> 134

Thr Gly Thr Ser Ser Asp Val Val Gly Val Tyr Asn Phe Val Ser

1 5 10 15

<210> 135

<211> 7

<212> PRT

<213> homo sapiens

<400> 135

Tyr Val Asp Asn Arg Pro Ser

1 5

<210> 136

<211> 11

<212> PRT

<213> homo sapiens

<400> 136

Gln Ser Phe Asp Gly Phe Gly Ile Asp Met Val

1 5 10

<210> 137

<211> 117

<212> PRT

<213> homo sapiens

<400> 137

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr

20 25 30

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

35 40 45

Gly Ile Ile Asp Pro Asp Asp Ser Lys Thr Asn Tyr Ser Pro Ser Phe

50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

85 90 95

Ala Arg Arg Ser Tyr Tyr Pro Met Asp Tyr Trp Gly Gln Gly Thr Leu

100 105 110

Val Thr Val Ser Ser

115

<210> 138

<211> 112

<212> PRT

<213> homo sapiens

<400> 138

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Val Gly Val
20 25 30

Tyr Asn Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys
35 40 45

Leu Met Ile Tyr Tyr Val Asp Asn Arg Pro Ser Gly Val Ser Asn Arg
50 55 60

Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly
65 70 75 80

Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Gly
85 90 95

Phe Gly Ile Asp Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 139

<211> 220

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (220)..(220)

<223> X puede ser C, EF, ó CEF

<400> 139

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Asp Asp Ser Lys Thr Asn Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Arg Ser Tyr Tyr Pro Met Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215 220

<210> 140

<211> 217

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (217)..(217)

<223> X puede ser CS ó A

<400> 140

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Val Gly Val
20 25 30

Tyr Asn Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys
35 40 45

Leu Met Ile Tyr Tyr Val Asp Asn Arg Pro Ser Gly Val Ser Asn Arg
50 55 60

Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly
65 70 75 80

Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Gly
85 90 95

Phe Gly Ile Asp Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
115 120 125

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
130 135 140

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
145 150 155 160

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
165 170 175

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
180 185 190

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
195 200 205

Glu Lys Thr Val Ala Pro Thr Glu Xaa
210 215

<210> 141

<211> 351

<212> ADN

<213> homo sapiens

<400> 141

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattgga tttcttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atcgatccgg atgatagcaa gaccaattat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtcgttct 300

tattatccta tggattattg gggccaaggc accctggtga cggttagctc a 351

<210> 142

<211> 336

<212> ADN

<213> homo sapiens

<400> 142

gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttgtt ggtgtttata attttgtgtc ttggtaccag 120

cagcatcccg ggaaggcgcc gaaacttatg atttattatg ttgataatcg tccctcaggc 180

gtgagcaacc gttttagcgg atccaaaagc ggcaacaccg cgagcctgac cattagcggc 240

ctgcaagcgg aagacgaagc ggattattat tgccagtctt ttgatggttt tggtattgat 300

atggtgtttg gcggcggcac gaagttaacc gttctt 336

<210> 143

<211> 658

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (658)..(658)

<223> n puede ser TGC, GAATTC, ó TGCGAATTC

<400> 143

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattgga tttcttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atcgatccgg atgatagcaa gaccaattat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgtcgttct 300

tattatccta tggattattg gggccaaggc accctggtga cggttagctc agcgtcgacc 360

aaaggtccaa gcgtgtttcc gctggctccg agcagcaaaa gcaccagcgg cggcacggct 420

gccctgggct gcctggttaa agattatttc ccggaaccag tcaccgtgag ctggaacagc 480

ggggcgctga ccagcggcgt gcataccttt ccggcggtgc tgcaaagcag cggcctgtat 540

agcctgagca gcgttgtgac cgtgccgagc agcagcttag gcactcagac ctatatttgc 600

aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagtggaacc gaaaagcn 658

<210> 144

<211> 649

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (649)..(649)

<223> n puede ser TGCAGC ó GCC

<400> 144

gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttgtt ggtgtttata attttgtgtc ttggtaccag 120

cagcatcccg ggaaggcgcc gaaacttatg atttattatg ttgataatcg tccctcaggc 180

gtgagcaacc gttttagcgg atccaaaagc ggcaacaccg cgagcctgac cattagcggc 240

ctgcaagcgg aagacgaagc ggattattat tgccagtctt ttgatggttt tggtattgat 300

atggtgtttg gcggcggcac gaagttaacc gttcttggcc agccgaaagc cgcaccgagt 360

gtgacgctgt ttccgccgag cagcgaagaa ttgcaggcga acaaagcgac cctggtgtgc 420

ctgattagcg acttttatcc gggagccgtg acagtggcct ggaaggcaga tagcagcccc 480

gtcaaggcgg gagtggagac caccacaccc tccaaacaaa gcaacaacaa gtacgcggcc 540

agcagctatc tgagcctgac gcctgagcag tggaagtccc acagaagcta cagctgccag 600

gtcacgcatg aggggagcac cgtggaaaaa accgttgcgc cgactgagn 649

<210> 145

<211> 5

<212> PRT

<213> homo sapiens

<400> 145

Ser Tyr Trp Ile Ala

1 5

<210> 146

<211> 17

<212> PRT

<213> homo sapiens

<400> 146

Ile Ile Tyr Pro Gly Asp Ser Asp Thr Asn Tyr Ser Pro Ser Phe Gln

1 5 10 15

Gly

<210> 147

<211> 8

<212> PRT

<213> homo sapiens

<400> 147

Ser Lys Tyr Gly Ser Phe Asp Tyr

1 5

<210> 148

<211> 14

<212> PRT

<213> homo sapiens

<400> 148

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser

1 5 10

<210> 149

<211> 7

<212> PRT

<213> homo sapiens

<400> 149

Asn Val Asn Ser Arg Pro Ser

1 5

<210> 150

<211> 11

<212> PRT

<213> homo sapiens

<400> 150

Gln Ser Tyr Asp Asp Gly Gln Asp Asn Glu Val

1 5 10

<210> 151

<211> 117

<212> PRT

<213> homo sapiens

<400> 151

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

<210> 152

<211> 111

<212> PRT

<213> homo sapiens

<400> 152

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asn Val Asn Ser Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Asp Gly
85 90 95

Gln Asp Asn Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 153

<211> 220

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (220)..(220)

<223> X puede ser C, EF, ó CEF

<400> 153

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30
Trp Ile Ala Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
35 40 45
Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Asn Tyr Ser Pro Ser Phe
50 55 60
Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Ser Lys Tyr Gly Ser Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215 220

<210> 154

<211> 216

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (216)..(216)

<223> X puede ser CS ó A

<400> 154

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asn Val Asn Ser Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Asp Gly
85 90 95

Gln Asp Asn Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
115 120 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
130 135 140

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

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
165 170 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180 185 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205

Lys Thr Val Ala Pro Thr Glu Xaa
210 215

<210> 155

<211> 351

<212> ADN

<213> homo sapiens

<400> 155

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattgga ttgcttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atctatccgg gtgatagcga taccaattat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttctaag 300

tatggttctt ttgattattg gggccaaggc accctggtga cggttagctc a 351

<210> 156

<211> 333

<212> ADN

<213> homo sapiens

<400> 156

gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt ggttataatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tataatgtta attctcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc cagtcttatg atgatggtca ggataatgag 300

gtgttttggcg gcggcacgaa gttaaccgtt ctt 333

<210> 157

<211> 658

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (658)..(658)

<223> n puede ser TGC, GAATTC, ó TGCGAATTC

<400> 157

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattgga ttgcttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atctatccgg gtgatagcga taccaattat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttctaag 300

tatggttctt ttgattattg gggccaaggc accctggtga cggttagctc agcgtcgacc 360

aaaggtccaa gcgtgtttcc gctggctccg agcagcaaaa gcaccagcgg cggcacggct 420

gccctgggct gcctggttaa agattatttc ccggaaccag tcaccgtgag ctggaacagc 480

ggggcgctga ccagcggcgt gcatacctt ccggcggtgc tgcaaagcag cggcctgtat 540

agcctgagca gcgttgtgac cgtgccgagc agcagcttag gcactcagac ctatatttgc 600

aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagtggaacc gaaaagcn 658

<210> 158

<211> 646

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (646)..(646)

<223> n puede ser TGCAGC ó GCC

<400> 158

gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt ggttataatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tataatgtta attctcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc cagtcttatg atgatggtca ggataatgag 300

gtgtttggcg gcggcacgaa gttaaccgtt cttggccagc cgaaagccgc accgagtgtg 360

acgctgtttc cgccgagcag cgaagaattg caggcgaaca aagcgaccct ggtgtgcctg 420

attagcgact ttttatccggg agccgtgaca gtggcctgga aggcagatag cagccccgtc 480

aaggcgggag tggagaccac cacaccctcc aaacaaagca acaacaagta cgcggccagc 540

agctatctga gcctgacgcc tgagcagtgg aagtcccaca gaagctacag ctgccaggtc 600

acgcatgagg ggagcaccgt ggaaaaaacc gttgcgccga ctgagn 646

<210> 159

<211> 5

<212> PRT

<213> homo sapiens

<400> 159

Ser Tyr Ala Met His

1 5

<210> 160

<211> 17

<212> PRT

<213> homo sapiens

<400> 160

Ala Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val Lys

1 5 10 15

Gly

<210> 161

<211> 7

<212> PRT

<213> homo sapiens

<400> 161

Glu Ser Trp Phe Leu Asp Leu

1 5

<210> 162

<211> 11

<212> PRT

<213> homo sapiens

<400> 162

Arg Ala Ser Gln Ser Ile Ser Asn Trp Leu Ala

1 5 10

<210> 163

<211> 7

<212> PRT

<213> homo sapiens

<400> 163

Leu Ala Ser Ser Leu Gln Ser

1 5

<210> 164

<211> 9

<212> PRT

<213> homo sapiens

<400> 164

Gln Gln Tyr Tyr Asp Phe Ser Asp Thr

1 5

<210> 165

<211> 116

<212> PRT

<213> homo sapiens

<400> 165

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Ser Tyr
20 25 30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ala Ile Ser Ser Ser 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 Arg Glu Ser Trp Phe Leu Asp Leu Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

<210> 166
<211> 107
<212> PRT
<213> homo sapiens
<400> 166

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asn Trp
20 25 30

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

<210> 167
<211> 219
<212> PRT
<213> homo sapiens
<220>
<221> CARACTERÍSTICAS_VARIAS
<222> (219)..(219)
<223> X puede ser C, EF, ó CEF
<400> 167
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Ser Tyr
20 25 30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Ser Ser 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 Arg Glu Ser Trp Phe Leu Asp Leu Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215

<210> 168

<211> 214

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (214)..(214)

<223> X puede ser C ó A

<400> 168

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asn Trp
20 25 30

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

Tyr Leu Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asp Phe Ser Asp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Xaa
210

<210> 169
<211> 348
<212> ADN
<213> homo sapiens
<400> 169

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60
agctgcgcgg cctccggatt taccttttact tcttatgcta tgcattgggt gcgccaagcc 120
cctgggaagg gtctcgagtg ggtgagcgct atctcttctt ctggtagctc tacctattat 180
gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240
ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgagtct 300
tggtttcttg atcttttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 170
<211> 321
<212> ADN
<213> homo sapiens

<400> 170

gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gtctatttct aattggctgg cttggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatctt gcttcttctt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cggtttatta ttgccagcag tattatgatt tttctgatac ctttggccag 300

ggtacgaaag ttgaaattaa a 321

<210> 171

<211> 655

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (655)..(655)

<223> n puede ser TGC, TAATTC, ó TGCGAATTC

<400> 171

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttact tcttatgcta tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct atctcttctt ctggtagctc tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa cacgctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgagtct 300

tggtttcttg atctttgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360

ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420

ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg 480

gcgctgacca gcggcgtgca tacctttccg gcggtgctgc aaagcagcgg cctgtatagc 540

ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600

gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagcn 655

<210> 172

<211> 640

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (640)..(640)

<223> n puede ser TGC ó GCC

<400> 172

gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gtctatttct aattggctgg cttggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatctt gcttcttctt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cggtttatta ttgccagcag tattatgatt tttctgatac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacggtg gctgctccga gcgtgtttat ttttccgccg 360

agcgatgaac aactgaaaag cggcacggcg agcgtggtgt gcctgctgaa caacttttat 420

ccgcgtgaag cgaaagttca gtggaaagta gacaacgcgc tgcaaagcgg caacagccag 480

gaaagcgtga ccgaacagga tagcaaagat agcacctatt ctctgagcag caccctgacc 540

ctgagcaaag cggattatga aaaacataaa gtgtatgcgt gcgaagtgac ccatcaaggt 600

ctgagcagcc cggtgactaa atcttttaat cgtggcgagn 640

<210> 173

<211> 5

<212> PRT

463

<213> homo sapiens

<400> 173

Asn Tyr Gly Met His

1 5

<210> 174

<211> 16

<212> PRT

<213> homo sapiens

<400> 174

Val Ser Tyr Ala Gly Ser Phe Thr Asn Tyr Ala Asp Ser Val Lys Gly

1 5 10 15

<210> 175

<211> 12

<212> PRT

<213> homo sapiens

<400> 175

Ser Trp Leu Phe Gly Tyr Pro Asp Ile Phe Asp Tyr

1 5 10

<210> 176

<211> 14

<212> PRT

<213> homo sapiens

<400> 176

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser

1 5 10

<210> 177

<211> 7

<212> PRT

<213> homo sapiens

<400> 177

Asp Val Asn Asn Arg Pro Ser

1 5

<210> 178

<211> 9

<212> PRT

<213> homo sapiens

<400> 178

Ser Ser Tyr Asp Lys Phe Gln Thr Val

1 5

<210> 179

<211> 120

<212> PRT

<213> homo sapiens

<400> 179

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr

20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

35 40 45

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

<210> 180
<211> 109
<212> PRT
<213> homo sapiens
<400> 180

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

466

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Lys Phe
85 90 95

Gln Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 181

<211> 223

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (223)..(223)

<223> X puede ser C, EF, ó CEF

<400> 181

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ser Tyr Ala Gly Ser Phe Thr Asn Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Ser Trp Leu Phe Gly Tyr Pro Asp Ile Phe Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160
Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215 220

<210> 182
<211> 214
<212> PRT
<213> homo sapiens
<220>
<221> CARACTERÍSTICAS_VARIAS
<222> (214)..(214)
<223> X puede ser CS ó A

<400> 182

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Asn Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Lys Phe
85 90 95

Gln Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
100 105 110

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
115 120 125

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
165 170 175

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180 185 190

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr

195 200 205

Val Ala Pro Thr Glu Xaa

210

<210> 183

<211> 360

<212> ADN

<213> homo sapiens

<400> 183

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt taccttttct aattatggta tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgtt tcttatgctg gtagctttac caattatgcg 180

gatagcgtga aaggccgttt taccatttca cgtgataatt cgaaaaacac cctgtatctg 240

caaatgaaca gcctgcgtgc ggaagatacg gccgtgtatt attgcgcgcg ttcttggctt 300

tttggttatc ctgatatttt tgattattgg ggccaaggca ccctggtgac ggttagctca 360

<210> 184

<211> 327

<212> ADN

<213> homo sapiens

<400> 184

gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt ggttataatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tcttcttatg ataagtttca gactgtgttt 300

ggcggcggca cgaagttaac cgttctt 327

<210> 185

<211> 667

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (667)..(667)

<223> n puede ser TGC, TAATTC, ó TGCGAATTC

<400> 185

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt taccttttct aattatggta tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgtt tcttatgctg gtagctttac caattatgcg 180

gatagcgtga aaggccgttt taccatttca cgtgataatt cgaaaaacac cctgtatctg 240

caaatgaaca gcctgcgtgc ggaagatacg gccgtgtatt attgcgcgcg ttcttggctt 300

tttggttatc ctgatatttt tgattattgg ggccaaggca ccctggtgac ggttagctca 360

gcgtcgacca aaggtccaag cgtgtttccg ctggctccga gcagcaaaag caccagcggc 420

ggcacggctg ccctgggctg cctggttaaa gattatttcc cggaaccagt caccgtgagc 480

tggaacagcg gggcgctgac cagcggcgtg catacctttc cggcggtgct gcaaagcagc 540

ggcctgtata gcctgagcag cgttgtgacc gtgccgagca gcagcttagg cactcagacc 600

tatatttgca acgtgaacca taaaccgagc aacaccaaag tggataaaaa agtggaaccg 660

aaaagcn 667

<210> 186

<211> 640

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (640)..(640)

<223> n puede ser TGCAGC ó GCC

<400> 186

gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt ggttataatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgtta ataatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc tcttcttatg ataagtttca gactgtgttt 300

ggcggcggca cgaagttaac cgttcttggc cagccgaaag ccgcaccgag tgtgacgctg 360

tttccgccga gcagcgaaga attgcaggcg aacaaagcga ccctggtgtg cctgattagc 420

gacttttatc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg 480

ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540

ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat 600

gaggggagca ccgtggaaaa aaccgttgcg ccgactgagn 640

<210> 187

<211> 116

<212> PRT

<213> homo sapiens

<400> 187

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

1 5 10 15

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

<210> 188
<211> 108
<212> PRT
<213> homo sapiens
<400> 188

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

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

<210> 189
<211> 219
<212> PRT
<213> homo sapiens
<220>
<221> CARACTERÍSTICAS_VARIAS
<222> (219)..(219)
<223> X puede ser C, EF, ó CEF
<400> 189

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

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Thr Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215

<210> 190
<211> 213
<212> PRT
<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (213)..(213)

<223> X puede ser CS ó A

<400> 190

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val
20 25 30

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

Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Phe Asp Ser Ser Leu Asn Ala
85 90 95

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205
Ala Pro Thr Glu Xaa
210

<210> 191
<211> 348
<212> ADN
<213> homo sapiens
<400> 191

caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60
agctgcaaag cctccggagg cacttttttct tcttatgcca tttcttgggt gcgccaagcc 120
cctgggcagg gtctcgagtg gatgggcggt atcggtccgt tttttggcac tgcgaattac 180
gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240
atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300
ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 192
<211> 324
<212> ADN
<213> homo sapiens
<400> 192

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctat tcctaattat tatgtttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtctttt gattcttctc ttaatgctga ggtgtttggc 300

ggcggcacga agttaaccgt tctt 324

<210> 193

<211> 655

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (655)..(655)

<223> n puede ser TGC, GAATTC, ó TGCGAATTC

<400> 193

caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60

agctgcaaag cctccggagg cacttttttct tcttatgcca tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcggt atcggtccgt tttttggcac tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300

ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360

ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420

ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg 480

gcgctgacca gcggcgtgca taccttttccg gcggtgctgc aaagcagcgg cctgtatagc 540

ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600

gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagcn 655

<210> 194

<211> 637

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (637)..(637)

<223> n puede ser TGCAGC ó GCC

<400> 194

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctat tcctaattat tatgtttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtctttt gattcttctc ttaatgctga ggtgtttggc 300

ggcggcacga agttaaccgt tcttggccag ccgaaagccg cacccgagtgt gacgctgttt 360

ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac 420

ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600

gggagcaccg tggaaaaaac cgttgcgccg actgagn 637

<210> 195

<211> 5

<212> PRT

<213> homo sapiens

<400> 195

Ser Tyr Tyr Ile Ser

1 5

<210> 196

<211> 17

<212> PRT

<213> homo sapiens

<400> 196

Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln

1 5 10 15

Gly

<210> 197

<211> 19

<212> PRT

<213> homo sapiens

<400> 197

Gly Glu Ile Trp His Val His Gln Pro Tyr Lys Ser Gly Val Tyr Gly

1 5 10 15

Ala Ala Tyr

<210> 198

<211> 11

<212> PRT

<213> homo sapiens

<400> 198

Arg Ala Ser Gln Gly Ile Ser Asn Trp Leu Asn

1 5 10

<210> 199

<211> 7

<212> PRT

<213> homo sapiens

<400> 199

Gly Thr Ser Ser Leu Gln Ser

1 5

<210> 200

<211> 9

<212> PRT

<213> homo sapiens

<400> 200

Gln Gln Leu Asp Ser Phe Pro Ala Thr

1 5

<210> 201

<211> 128

<212> PRT

<213> homo sapiens

<400> 201

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr

20 25 30

Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Glu Ile Trp His Val His Gln Pro Tyr Lys Ser Gly Val
100 105 110
Tyr Gly Ala Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 202
<211> 107
<212> PRT
<213> homo sapiens
<400> 202

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

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

<210> 203
<211> 231
<212> PRT
<213> homo sapiens
<220>
<221> CARACTERÍSTICAS_VARIAS
<222> (231)..(231)
<223> X puede ser C, EF, ó CEF

<400> 203
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30
Tyr Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Gly Glu Ile Trp His Val His Gln Pro Tyr Lys Ser Gly Val
100 105 110
Tyr Gly Ala Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
130 135 140
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
145 150 155 160
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
165 170 175
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
180 185 190
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
195 200 205
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
210 215 220
Lys Val Glu Pro Lys Ser Xaa
225 230

<210> 204
<211> 214
<212> PRT
<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (214)..(214)

<223> X puede ser C ó A

<400> 204

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 Gly Ile Ser Asn Trp
20 25 30

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

Tyr Gly Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asp Ser Phe Pro Ala
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Xaa
210

<210> 205

<211> 384

<212> ADN

<213> homo sapiens

<400> 205

caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60

agctgcaaag cctccggagg cacttttttct tcttattata tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcggt atcattccga tttttggcac tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag cacgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtggtgag 300

atttggcatg ttcatcagcc ttataagtct ggtgtttatg gtgctgctta ttggggccaa 360

ggcaccctgg tgacggttag ctca 384

<210> 206

<211> 321

<212> ADN

<213> homo sapiens

<400> 206

gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gggtatttct aattggctga attggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatggt acttcttctt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cgacttatta ttgccagcag cttgattctt ttcctgctac ctttggccag 300

ggtacgaaag ttgaaattaa a 321

<210> 207

<211> 691

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (691)..(691)

<223> n puede ser TGC, GAATTC, ó TGCGAATTC

<400> 207

caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60

agctgcaaag cctccggagg cacttttttct tcttattata tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcggt atcattccga tttttggcac tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtggtgag 300

atttggcatg ttcatcagcc ttataagtct ggtgtttatg gtgctgctta ttggggccaa 360

ggcaccctgg tgacggttag ctcagcgtcg accaaaggtc caagcgtgtt tccgctggct 420

ccgagcagca aaagcaccag cggcggcacg gctgccctgg gctgcctggt taaagattat 480

ttccccggaac cagtcaccgt gagctggaac agcggggcgc tgaccagcgg cgtgcatacc 540

tttccggcgg tgctgcaaag cagcggcctg tatagcctga gcagcgttgt gaccgtgccg 600

agcagcagct taggcactca gacctatatt tgcaacgtga accataaacc gagcaacacc 660

aaagtggata aaaaagtgga accgaaaagc n 691

<210> 208

<211> 640

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (640)..(640)

<223> n puede ser TGC ó GCC

<400> 208

gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gggtatttct aattggctga attggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatggt acttcttctt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cgacttatta ttgccagcag cttgattctt ttcctgctac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacggtg gctgctccga gcgtgtttat ttttccgccg 360

agcgatgaac aactgaaaag cggcacggcg agcgtggtgt gcctgctgaa caacttttat 420

ccgcgtgaag cgaaagttca gtggaaagta gacaacgcgc tgcaaagcgg caacagccag 480

gaaagcgtga ccgaacagga tagcaaagat agcacctatt ctctgagcag caccctgacc 540

ctgagcaaag cggattatga aaaacataaa gtgtatgcgt gcgaagtgac ccatcaaggt 600

ctgagcagcc cggtgactaa atcttttaat cgtggcgagn 640

<210> 209

<211> 11

<212> PRT

<213> homo sapiens

<400> 209

Gln Ser Trp Thr Asp Ser Pro Asn Thr Leu Val
1 5 10

<210> 210

<211> 117

<212> PRT

<213> homo sapiens

<400> 210

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Ser Asp Ser His Thr Thr Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser

115

<210> 211

<211> 108

<212> PRT

<213> homo sapiens

<400> 211

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln

1 5 10 15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala

20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr

35 40 45

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser

50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu

65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Thr Asp Ser Pro Asn Thr

85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu

100 105

<210> 212

<211> 220

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (220)..(220)

<223> X puede ser C, EF, ó CEF

<400> 212

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Ser Asp Ser His Thr Thr Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215 220

<210> 213
<211> 213
<212> PRT
<213> homo sapiens
<220>
<221> CARACTERÍSTICAS_VARIAS
<222> (213)..(213)
<223> X puede ser CS ó A

<400> 213
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30
Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45
Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Thr Asp Ser Pro Asn Thr
85 90 95
Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205
Ala Pro Thr Glu Xaa
210

<210> 214

<211> 351

<212> ADN

<213> homo sapiens

<400> 214

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atcgatccgt ctgatagcca taccacttat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc a 351

<210> 215

<211> 324

<212> ADN

<213> homo sapiens

<400> 215

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttgg actgattctc ctaatactct tgtgtttggc 300

ggcggcacga agttaaccgt tctt 324

<210> 216

<211> 658

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (658)..(658)

<223> n puede ser TGC, GAATTC, ó TGCGAATTC

<400> 216

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atcgatccgt ctgatagcca taccacttat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc agcgtcgacc 360

aaaggtccaa gcgtgtttcc gctggctccg agcagcaaaa gcaccagcgg cggcacggct 420

gccctgggct gcctggttaa agattatttc ccggaaccag tcaccgtgag ctggaacagc 480

ggggcgctga ccagcggcgt gcatacctit ccggcggtgc tgcaaagcag cggcctgtat 540

agcctgagca gcgttgtgac cgtgccgagc agcagcttag gcactcagac ctatatttgc 600

aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagtggaacc gaaaagcn 658

<210> 217

<211> 637

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (637)..(637)

<223> n puede ser TGCAGC ó GCC

<400> 217

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttgg actgattctc ctaatactct tgtgtttggc 300

ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt 360

ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac 420

ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600

gggagcaccg tggaaaaaac cgttgcgccg actgagn 637

<210> 218

<211> 116

<212> PRT

<213> homo sapiens

<400> 218

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr

20 25 30

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

35 40 45

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln

50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu

65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala

85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 219

<211> 106

<212> PRT

<213> homo sapiens

<400> 219

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Tyr Asp Ile Glu Ser Tyr Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 220

<211> 219

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (219)..(219)

<223> X puede ser C, EF, ó CEF

<400> 220

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215

<210> 221
<211> 211
<212> PRT
<213> homo sapiens
<220>
<221> CARACTERÍSTICAS_VARIAS
<222> (211)..(211)
<223> X puede ser CS ó A
<400> 221

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15
Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30
His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Tyr Asp Ile Glu Ser Tyr Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Xaa
210

<210> 222

<211> 348

<212> ADN

<213> homo sapiens

<400> 222

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatc gatccggatg atagctatac ccgttattct 180

ccgagctttc agggacaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 223

<211> 318

<212> ADN

<213> homo sapiens

<400> 223

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cggtacttat gatattgagt cttatgtgtt tggcggcggc 300

acgaagttaa ccgttctt 318

<210> 224

<211> 655

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (655)..(655)

<223> n puede ser TGC, GAATTC, ó TGCGAATTC

<400> 224

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatc gatccggatg atagctatac cgttattct 180

ccgagctttc agggacaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360

ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420

ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg 480

gcgctgacca gcggcgtgca taccttttcg gcggtgctgc aaagcagcgg cctgtatagc 540

ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagacctа tatttgcaac 600

gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagcn 655

<210> 225

<211> 631

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (631)..(631)

<223> n puede ser TGCAGC ó GCC

<400> 225

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cggtacttat gatattgagt cttatgtgtt tggcggcggc 300

acgaagttaa ccgttcttgg ccagccgaaa gccgcaccga gtgtgacgct gtttccgccg 360

agcagcgaag aattgcaggc gaacaaagcg accctggtgt gcctgattag cgacttttat 420

ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag 480

accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg 540

acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgagggagc 600

accgtggaaa aaaccgttgc gccgactgag n 631

<210> 226

<211> 16

<212> PRT

<213> homo sapiens

<400> 226

His Ile Phe Ser Asp Asp Asp Lys Tyr Tyr Ser Thr Ser Leu Lys Thr

1 5 10 15

<210> 227

<211> 117

<212> PRT

<213> homo sapiens

<400> 227

Gln Val Gln Leu Lys Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln

1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser

20 25 30

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

<210> 228
<211> 109
<212> PRT
<213> homo sapiens
<400> 228

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

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

<210> 229
<211> 220
<212> PRT
<213> homo sapiens
<220>
<221> CARACTERÍSTICAS_VARIAS
<222> (220)..(220)
<223> X puede ser C, EF, ó CEF
<400> 229

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

1005

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95
Cys Ala Arg Gly Pro Tyr Gly Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110
Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215 220

<210> 230
<211> 214
<212> PRT
<213> homo sapiens
<220>
<221> CARACTERÍSTICAS_VARIAS

<222> (214)..(214)

<223> X puede ser CS ó A

<400> 230

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Thr Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Asp Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Gln
85 90 95

Ser Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
100 105 110

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
115 120 125

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
165 170 175

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180 185 190

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
195 200 205

Val Ala Pro Thr Glu Xaa
210

<210> 231
<211> 351
<212> ADN
<213> homo sapiens
<400> 231

caggtgcaat tgaaagaaag cggcccggcc ctggtgaaac cgacccaaac cctgaccctg 60
acctgtacct tttccggatt tagcctgtct acttctggtg gtggtgtgtc ttggattcgc 120
cagccgcctg ggaaagccct cgagtggctg gctcatatct tttctgatga tgataagtat 180
tatagcacca gcctgaaaac gcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240
gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgtggt 300
ccttatggtt ttgattcttg gggccaaggc accctggtga cggttagctc a 351

<210> 232
<211> 327
<212> ADN
<213> homo sapiens
<400> 232

gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60
tcgtgtacgg gtactagcag cgatattggt acttataatt atgtgtcttg gtaccagcag 120
catcccggga aggcgccgaa acttatgatt tatgatgatt ctaatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc cagtcttatg attctcagtc tattgtgttt 300

ggcggcggca cgaagttaac cgttctt 327

<210> 233

<211> 658

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (658)..(658)

<223> n puede ser TGC, GAATTC, ó TGCGAATTC

<400> 233

caggtgcaat tgaaagaaag cggcccggcc ctggtgaaac cgacccaaac cctgaccctg 60

acctgtacct tttccggatt tagcctgtct acttctggtg gtggtgtgtc ttggattcgc 120

cagccgcctg ggaaagccct cgagtggctg gctcatatct tttctgatga tgataagtat 180

tatagcacca gcctgaaaac gcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240

gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgtggt 300

ccttatggtt ttgattcttg gggccaaggc accctggtga cggttagctc agcgtcgacc 360

aaaggtccaa gcgtgtttcc gctggctccg agcagcaaaa gcaccagcgg cggcacggct 420

gccctgggct gcctggttaa agattatttc ccggaaccag tcaccgtgag ctggaacagc 480

ggggcgctga ccagcggcgt gcatacctt ccggcggtgc tgcaaagcag cggcctgtat 540

agcctgagca gcgttgtgac cgtgccgagc agcagcttag gcactcagac ctatatttgc 600

aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagtggaacc gaaaagcn 658

<210> 234

<211> 640

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (640)..(640)

<223> n puede ser TGCAGC ó GCC

<400> 234

gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatattggt acttataatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgatt ctaatcgtcc ctcaggcgtg 180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc cagtcttatg attctcagtc tattgtgttt 300

ggcggcggca cgaagttaac cgttcttggc cagccgaaag ccgcaccgag tgtgacgctg 360

tttccgccga gcagcgaaga attgcaggcg aacaaagcga ccctggtgtg cctgattagc 420

gacttttatc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg 480

ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540

ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat 600

gaggggagca ccgtggaaaa aaccgttgcg ccgactgagn 640

<210> 235

<211> 7

<212> PRT

<213> homo sapiens

<400> 235

Thr Ser Gly Met Ser Val Gly

1 5

<210> 236

<211> 16

<212> PRT

<213> homo sapiens

<400> 236

Leu Ile Asp Trp Asp Glu Asp Lys Ser Tyr Ser Thr Ser Leu Lys Thr

1 5 10 15

<210> 237

<211> 11

<212> PRT

<213> homo sapiens

<400> 237

Tyr Asn Trp Tyr Asn Pro Pro Gly Phe Asp Asn

1 5 10

<210> 238

<211> 13

<212> PRT

<213> homo sapiens

<400> 238

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Tyr Val Ser

1 5 10

<210> 239

<211> 7

<212> PRT

<213> homo sapiens

<400> 239

Arg Asn Asp Lys Arg Pro Ser

1 5

<210> 240

<211> 9

<212> PRT

<213> homo sapiens

<400> 240

Gln Ser Ala Asp Ser Ser Ser Met Val

1 5

<210> 241

<211> 121

<212> PRT

<213> homo sapiens

<400> 241

Gln Val Gln Leu Lys Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln

1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser

20 25 30

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

35 40 45

Trp Leu Ala Leu Ile Asp Trp Asp Glu Asp Lys Ser Tyr Ser Thr Ser

50 55 60

Leu Lys Thr Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val

65 70 75 80

1092

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Tyr Asn Trp Tyr Asn Pro Pro Gly Phe Asp Asn Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 242

<211> 108

<212> PRT

<213> homo sapiens

<400> 242

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

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Arg Asn Asp Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Ala Asp Ser Ser Ser
85 90 95

Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 243

<211> 224

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (224)..(224)

<223> X puede ser C, EF, ó CEF

<400> 243

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

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

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

Trp Leu Ala Leu Ile Asp Trp Asp Glu Asp Lys Ser Tyr Ser Thr Ser
50 55 60

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Tyr Asn Trp Tyr Asn Pro Pro Gly Phe Asp Asn Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215 220

<210> 244
<211> 213
<212> PRT
<213> homo sapiens
<220>
<221> CARACTERÍSTICAS_VARIAS
<222> (213)..(213)
<223> X puede ser CS ó A

<400> 244
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

1015

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45
Ile Tyr Arg Asn Asp Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Ala Asp Ser Ser Ser
85 90 95
Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205
Ala Pro Thr Glu Xaa
210

<210> 245

<211> 363

<212> ADN

<213> homo sapiens

<400> 245

caggtgcaat tgaaagaaag cggcccggcc ctggtgaaac cgacccaaac cctgaccctg 60

acctgtacct tttccggatt tagcctgtct acttctggta tgtctgtggg ttggattcgc 120

cagccgcctg ggaaagccct cgagtggctg gctcttatcg attgggatga ggataagtct 180

tatagcacca gcctgaaaac gcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240

gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgttat 300

aattggtata atcctcctgg ttttgataat tggggccaag gcaccctggt gacggttagc 360

tca 363

<210> 246

<211> 324

<212> ADN

<213> homo sapiens

<400> 246

gatatcgtgc tgacccagcc gccttcagtg agtggcgcac caggtcagcg tgtgaccatc 60

tcgtgtagcg gcagcagcag caacattggt tctaattatg tgtcttggta ccagcagttg 120

cccgggacgg cgccgaaact tctgatttat cgtaatgata agcgtccctc aggcgtgccg 180

gatcgtttta gcggatccaa aagcggcacc agcgcgagcc ttgcgattac gggcctgcaa 240

agcgaagacg aagcggatta ttattgccag tctgctgatt cttcttctat ggtgtttggc 300

ggcggcacga agttaaccgt tctt 324

<210> 247

<211> 670

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (670)..(670)

<223> n puede ser TGC, GAATTC, ó TGCGAATTC

<400> 247

caggtgcaat tgaaagaaag cggcccggcc ctggtgaaac cgacccaaac cctgaccctg 60

acctgtacct tttccggatt tagcctgtct acttctggta tgtctgtggg ttggattcgc 120

cagccgcctg ggaaagccct cgagtggctg gctcttatcg attgggatga ggataagtct 180

tatagcacca gcctgaaaac gcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240

gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgttat 300

aattggtata atcctcctgg ttttgataat tggggccaag gcaccctggt gacggttagc 360

tcagcgtcga ccaaaggtcc aagcgtgttt ccgctggctc cgagcagcaa aagcaccagc 420

ggcggcacgg ctgccctggg ctgcctggtt aaagattatt tccccgaacc agtcaccgtg 480

agctggaaca gcggggcgct gaccagcggc gtgcatacct ttccggcggt gctgcaaagc 540

agcggcctgt atagcctgag cagcgttgtg accgtgccga gcagcagctt aggcactcag 600

acctatattt gcaacgtgaa ccataaaccg agcaacacca aagtggataa aaaagtggaa 660

ccgaaaagcn 670

<210> 248

<211> 637

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (637)..(637)

<223> n puede ser TGCAGC ó GCC

<400> 248

gatatcgtgc tgacccagcc gccttcagtg agtggcgcac caggtcagcg tgtgaccatc 60

tcgtgtagcg gcagcagcag caacattggt tctaattatg tgtcttggta ccagcagttg 120

cccgggacgg cgccgaaact tctgatttat cgtaatgata agcgtccctc aggcgtgccg 180

gatcgtttta gcggatccaa aagcggcacc agcgcgagcc ttgcgattac gggcctgcaa 240

agcgaagacg aagcggatta ttattgccag tctgctgatt cttcttctat ggtgtttggc 300

ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt 360

ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac 420

ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600

gggagcaccg tggaaaaaac cgttgcgccg actgagn 637

<210> 249

<211> 219

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (219)..(219)

<223> X puede ser C, EF, ó CEF

<400> 249

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

1 5 10 15

1099

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Asn Ile Gly Pro Phe Phe Gly Ile Ala Asn Tyr Ala Gln Lys Phe
50 55 60
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Thr Pro Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa

210 215

<210> 250

<211> 655

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (655)..(655)

<223> n puede ser TGC, GAATTC, ó TGCGAATTC

<400> 250

caggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60

agctgcaaag cctccggagg cacttttttct tcttatgcca tttcttgggt gcgccaagcc 120

cctgggcagg gtctcgagtg gatgggcaat atcggtccgt tttttggcat tgcgaattac 180

gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag cacgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300

ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360

ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420

ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg 480

gcgctgacca gcggcgtgca taccttttccg gcggtgctgc aaagcagcgg cctgtatagc 540

ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600

gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagcn 655

<210> 251

<211> 213

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (213)..(213)

<223> X puede ser CS ó A

<400> 251

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val
20 25 30

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

Asp Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Asp Asp Gly Ser Thr Ala
85 90 95

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205
Ala Pro Thr Glu Xaa
210

<210> 252
<211> 637
<212> ADN
<213> homo sapiens
<220>
<221> características_varias
<222> (637)..(637)
<223> n puede ser TGCAGC ó GCC
<400> 252

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60
tcgtgtagcg gcgattctat tcctaattat tatgtttatt ggtaccagca gaaacccggg 120
caggcgccag ttcttgtgat ttatgatgat tctaatcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ccagacttat gatgatggtt ctactgctga ggtgtttggc 300

ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt 360

ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac 420

ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcgggg 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600

gggagcaccg tggaaaaaac cgttgcgccg actgagn 637

<210> 253

<211> 117

<212> PRT

<213> homo sapiens

<400> 253

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Thr Asp Ser Gln Thr Ala Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser

115

<210> 254

<211> 220

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (220)..(220)

<223> X puede ser C, EF, ó CEF

<400> 254

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Thr Asp Ser Gln Thr Ala Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140
Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160
Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175
Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190
Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215 220

<210> 255
<211> 351
<212> ADN
<213> homo sapiens
<400> 255

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60
agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120
cctgggaagg gtctcgagtg gatgggcatt attgatccta ctgattctca gactgcttat 180
tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240
cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300
atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc a 351

<210> 256

<211> 658

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (658)..(658)

<223> n puede ser TGC, GAATTC, ó TGCGAATTC

<400> 256

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt attgatccta ctgattctca gactgcttat 180

tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc agcgtcgacc 360

aaaggtccaa gcgtgtttcc gctggctccg agcagcaaaa gcaccagcgg cggcacggct 420

gccctgggct gcctggttaa agattatttc ccggaaccag tcaccgtgag ctggaacagc 480

ggggcgctga ccagcggcgt gcataccttt ccggcggtgc tgcaaagcag cggcctgtat 540

agcctgagca gcgttgtgac cgtgccgagc agcagcttag gcactcagac ctatatttgc 600

aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagtggaacc gaaaagcn 658

<210> 257

<211> 117

<212> PRT

<213> homo sapiens

<400> 257

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

<210> 258
<211> 220
<212> PRT
<213> homo sapiens
<220>
<221> CARACTERÍSTICAS_VARIAS
<222> (220)..(220)
<223> X puede ser C, EF, ó CEF

<400> 258

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

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

Gly Ile Ile Asp Pro Thr Asp Ser Tyr Thr Val Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

1099

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215 220

<210> 259

<211> 351

<212> ADN

<213> homo sapiens

<400> 259

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata tcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt attgatccta ctgattctta tactgtttat 180

tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc a 351

<210> 260

<211> 658

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (658)..(658)

<223> n puede ser TGC, GAATTC, ó TGCGAATTC

<400> 260

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact tcttattata ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt attgatccta ctgattctta tactgtttat 180

tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtggtt ttgatcattg gggccaaggc accctggtga cggttagctc agcgtcgacc 360

aaaggtccaa gcgtgtttcc gctggctccg agcagcaaaa gcaccagcgg cggcacggct 420

gccctgggct gcctggttaa agattatttc ccggaaccag tcaccgtgag ctggaacagc 480

ggggcgctga ccagcggcgt gcataccttt ccggcggtgc tgcaaagcag cggcctgtat 540

agcctgagca gcgttgtgac cgtgccgagc agcagcttag gcactcagac ctatatttgc 600

aacgtgaacc ataaaccgag caacaccaaa gtggataaaa aagtggaacc gaaaagcn 658

<210> 261

<211> 107

<212> PRT

<213> homo sapiens

<400> 261

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln

1 5 10 15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala

20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr

35 40 45

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser

50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu

65 70 75 80

1031

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Thr Gly Glu Ser Gly
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 262

<211> 212

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (212)..(212)

<223> X puede ser CS ó A

<400> 262

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Thr Gly Glu Ser Gly
85 90 95

1032

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110

Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125

Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140

Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160

Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
165 170 175

Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
180 185 190

Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
195 200 205

Pro Thr Glu Xaa
210

<210> 263

<211> 321

<212> ADN

<213> homo sapiens

<400> 263

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttgg gatactggtg agtctggtgt gtttggcggc 300

ggcacgaagt taaccgttct t 321

<210> 264

<211> 634

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (634)..(634)

<223> n puede ser TGCAGC ó GCC

<400> 264

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttgg gatactggtg agtctggtgt gtttggcggc 300

ggcacgaagt taaccgttct tggccagccg aaagccgcac cgagtgtgac gctgtttccg 360

ccgagcagcg aagaattgca ggcgaacaaa gcgaccctgg tgtgcctgat tagcgacttt 420

tatccgggag ccgtgacagt ggcctggaag gcagatagca gccccgtcaa ggcgggagtg 480

gagaccacca caccctccaa acaaagcaac aacaagtacg cggccagcag ctatctgagc 540

ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgagggg 600

agcaccgtgg aaaaaaccgt tgcgccgact gagn 634

<210> 265

<211> 108

<212> PRT

<213> homo sapiens

<400> 265

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

<210> 266

<211> 213

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (213)..(213)

<223> X puede ser CS ó A

<400> 266

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Ile Leu Pro His Gly
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Xaa
210

<210> 267
<211> 324
<212> ADN
<213> homo sapiens
<400> 267

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60
tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120
caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ccagacttgg gatattcttc ctcatggtct tgtgtttggc 300
ggcggcacga agttaaccgt tctt 324

<210> 268
<211> 637
<212> ADN
<213> homo sapiens
<220>
<221> características_varias
<222> (637)..(637)
<223> n puede ser TGCAGC ó GCC
<400> 268

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttgg gatattcttc ctcatggtct tgtgtttggc 300

ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt 360

ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac 420

ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600

gggagcaccg tggaaaaaac cgttgcgccg actgagn 637

<210> 269

<211> 108

<212> PRT

<213> homo sapiens

<400> 269

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln

1 5 10 15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala

20 25 30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr

35 40 45

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser

50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu

65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Thr Asp Ser Pro Thr Gly
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 270

<211> 213

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (213)..(213)

<223> X puede ser CS ó A

<400> 270

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
20 25 30

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

Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Thr Asp Ser Pro Thr Gly
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110
Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140
Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160
Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175
Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190
Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205
Ala Pro Thr Glu Xaa
210

<210> 271
<211> 324
<212> ADN
<213> homo sapiens
<400> 271

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60
tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120
caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccaggcttgg actgattctc ctactggtct tgtgtttggc 300

ggcggcacga agttaaccgt tctt 324

<210> 272

<211> 637

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (637)..(637)

<223> n puede ser TGCAGC ó GCC

<400> 272

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccaggcttgg actgattctc ctactggtct tgtgtttggc 300

ggcggcacga agttaaccgt tcttggccag ccgaaagccg caccgagtgt gacgctgttt 360

ccgccgagca gcgaagaatt gcaggcgaac aaagcgaccc tggtgtgcct gattagcgac 420

ttttatccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgag 600

gggagcaccg tggaaaaaac cgttgcgccg actgagn 637

<210> 273

<211> 116

<212> PRT

<213> homo sapiens

<400> 273

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 274

<211> 219

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (219)..(219)

<223> X puede ser C, EF, ó CEF

<400> 274

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215

<210> 275

<211> 348

<212> ADN

<213> homo sapiens

<400> 275

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctgatg attcttatac tgagtattct 180

ccttctttte agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 276

<211> 655

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (655)..(655)

<223> n puede ser TGC, GAATTC, ó TGCGAATTC

<400> 276

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctgatg attcttatac tgagtattct 180

ccttctttte agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360

ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420

ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg 480

gcgctgacca gcggcgtgca tacctttccg gcggtgctgc aaagcagcgg cctgtatagc 540

ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600

gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagcn 655

<210> 277

<211> 116

<212> PRT

<213> homo sapiens

<400> 277

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr

20 25 30

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

35 40 45

Ile Ile Asp Pro Gln Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln

50 55 60

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

<210> 278
<211> 219
<212> PRT
<213> homo sapiens
<220>
<221> CARACTERÍSTICAS_VARIAS
<222> (219)..(219)
<223> X puede ser C, EF, ó CEF

<400> 278
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15
Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30
Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
35 40 45
Ile Ile Asp Pro Gln Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95
Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215

<210> 279
<211> 348
<212> ADN
<213> homo sapiens
<400> 279

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctcagg attcttatac tgagtattct 180

ccttcttttc agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 280

<211> 655

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (655)..(655)

<223> n puede ser TGC, GAATTC, TGCGAATTC

<400> 280

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctcagg attcttatac tgagtattct 180

ccttcttttc agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360

ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420

ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg 480

gcgctgacca gcggcgtgca taccttccg gcggtgctgc aaagcagcgg cctgtatagc 540

ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600

gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagcn 655

<210> 281

<211> 116

<212> PRT

<213> homo sapiens

<400> 281

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Glu Asp Ser His Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 282

<211> 219

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (219)..(219)

<223> X puede ser C, EF, ó CEF

<400> 282

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Glu Asp Ser His Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

1050

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190
Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205
Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa
210 215

<210> 283
<211> 348
<212> ADN
<213> homo sapiens
<400> 283

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60
agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120
gggaagggtc tcgagtggat gggcattatt gatcctgagg attctcatac tgagtattct 180
ccttctttte agggtcaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240
caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300
ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 284
<211> 655
<212> ADN
<213> homo sapiens

<220>

<221> características_varias

<222> (655)..(655)

<223> n puede ser TGC, GAATTC, ó TGCGAATTC

<400> 284

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatattt cttgggtgcg ccagatgcct 120

gggaagggtc tcgagtggat gggcattatt gatcctgagg attctcatac tgagtattct 180

ccttcttttc agggtcaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc gtcgaccaaa 360

ggtccaagcg tgtttccgct ggctccgagc agcaaaagca ccagcggcgg cacggctgcc 420

ctgggctgcc tggttaaaga ttatttcccg gaaccagtca ccgtgagctg gaacagcggg 480

gcgctgacca gcggcgtgca tacctttccg gcggtgctgc aaagcagcgg cctgtatagc 540

ctgagcagcg ttgtgaccgt gccgagcagc agcttaggca ctcagaccta tatttgcaac 600

gtgaaccata aaccgagcaa caccaaagtg gataaaaaag tggaaccgaa aagcn 655

<210> 285

<211> 106

<212> PRT

<213> homo sapiens

<400> 285

Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln

1 5 10 15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val

20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Gly Ser Glu Asp Gln Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 286

<211> 211

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (211)..(211)

<223> X puede ser CS ó A

<400> 286

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80
Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Gly Ser Glu Asp Gln Val
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140
Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160
Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175
Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190
Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205
Thr Glu Xaa
210

<210> 287

<211> 318

<212> ADN

<213> homo sapiens

<400> 287

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cgctacttgg ggttctgagg atcaggtgtt tggcggcggc 300

acgaagttaa ccgttctt 318

<210> 288

<211> 631

<212> ADN

<213> homo sapiens

<220>

<221> características_varias

<222> (631)..(631)

<223> n puede ser TGCAGC ó GCC

<400> 288

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cgctacttgg ggttctgagg atcaggtgtt tggcggcggc 300

acgaagttaa ccgttcttgg ccagccgaaa gccgcaccga gtgtgacgct gtttccgccg 360

agcagcgaag aattgcaggc gaacaaagcg accctggtgt gcctgattag cgacttttat 420

ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag 480

accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg 540

acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaggggagc 600

accgtggaaa aaaccgttgc gccgactgag n 631

<210> 289

<211> 107

<212> PRT

<213> homo sapiens

<400> 289

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ser Thr Trp Asp Ile Glu Pro Thr Tyr
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 290

<211> 212

1055

<212> PRT

<213> homo sapiens

<220>

<221> CARACTERÍSTICAS_VARIAS

<222> (212)..(212)

<223> X puede ser CS ó A

<400> 290

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ser Thr Trp Asp Ile Glu Pro Thr Tyr
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110

Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125

Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140

Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160
Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
165 170 175
Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
180 185 190
Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
195 200 205
Pro Thr Glu Xaa
210

<210> 291
<211> 321
<212> ADN
<213> homo sapiens
<400> 291

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60
tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120
caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180
tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
gacgaagcgg attattattg ctctacttgg gatattgagc ctacttatgt gtttggcggc 300
ggcacgaagt taaccgttct t 321

<210> 292
<211> 634
<212> ADN
<213> homo sapiens

1057

<220>

<221> características_varias

<222> (634)..(634)

<223> n puede ser TGCAGC ó GCC

<400> 292

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ctctacttgg gatattgagc ctacttatgt gtttggcggc 300

ggcacgaagt taaccgttct tggccagccg aaagccgcac cgagtgtgac gctgtttccg 360

ccgagcagcg aagaattgca ggcgaacaaa gcgaccctgg tgtgcctgat tagcgacttt 420

tatccgggag ccgtgacagt ggcctggaag gcagatagca gccccgtcaa ggcgggagtg 480

gagaccacca caccctccaa acaaagcaac aacaagtacg cggccagcag ctatctgagc 540

ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgagggg 600

agcaccgtgg aaaaaaccgt tgcgccgact gagn 634

<210> 293

<211> 228

<212> PRT

<213> homo sapiens

<400> 293

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala

1 5 10 15

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu

20 25 30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
35 40 45
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
50 55 60
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65 70 75 80
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
85 90 95
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
100 105 110
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
115 120 125
Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
130 135 140
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1061

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<211> 1676

<212> PRT

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Glu Asp Ile Phe Leu Asn Gly Cys
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1081

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/060052

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 C07K16/18

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

B. FIELDS SEARCHED

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

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, BIOSIS, EMBASE, WPI Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/115476 A1 (TEDESCO FRANCESCO [IT] ET AL) 1 June 2006 (2006-06-01) examples 1-12	1-33
Y		34-39

X	CICCHETTI F ET AL: "Immune parameters relevant to neural xenograft survival in the primate brain" XENOTRANSPLANTATION, MUNKSGAARD, DE, vol. 10, no. 1, 1 January 2003 (2003-01-01), pages 41-49, XP002410883 ISSN: 0908-665X page 42 table 1 pages 44-46 figures 1,2	1-33
Y		34-39

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier 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
6 November 2009	16/11/2009
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	**Authorized officer** Bumb, Peter

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/060052

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/29697 A (ALEXION PHARMA INC [US]; EVANS MARK J [US]; MATIS LOUIS [US]; MUELLER) 9 November 1995 (1995-11-09) examples 1-15	1-33,36, 37,39
Y		34,35,38
X	WO 02/30985 A (TANOX INC [US]) 18 April 2002 (2002-04-18) figure 2 examples 1-3	1-33
Y		34-39
X	ROTHER RUSSELL P ET AL: "Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria." NATURE BIOTECHNOLOGY NOV 2007, vol. 25, no. 11, November 2007 (2007-11), pages 1256-1264, XP002553743 ISSN: 1087-0156 the whole document	1-33,38
Y		34-37,39
Y	US 2007/196367 A1 (DINU VALENTIN [US]) 23 August 2007 (2007-08-23) paragraphs [0061] - [0063]	34,35
Y	HOLERS V MICHAEL: "The spectrum of complement alternative pathway-mediated diseases." IMMUNOLOGICAL REVIEWS JUN 2008, vol. 223, June 2008 (2008-06), pages 300-316, XP002553744 ISSN: 1600-065X the whole document	34-39
X	WO 02/086085 A (BAYER AG [US]; MORPHOSYS AG [DE]; PAN CLARK [US]; KNORR ANDREAS M [DE]) 31 October 2002 (2002-10-31) sequence 115 paragraphs [0082], [0083], [0120]	29-33

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2009/060052

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 allsearchable 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 reportcovers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

Invention 1: claims 1-39 (all in part)

Isolated monoclonal antibody or an antigen binding fragment thereof which binds complement C5 protein with a KA of at least 10 7 M (-1), wherein the antibody comprises partial structural features from Ab 8109, 7086, 7865, 8091 or 7821, i.e. wherein the structural features are (i.e. 95% identical) CDRs, VH, VL, heavy chain or light chain as defined in claims 15-26 or corresponding nucleic acids as defined in claims 28-29, and where this Ab's structural features are SEQ ID NOs as defined in Table 1.

Invention 2: claims 1-39 (all in part)

same as for invention 1, except that the Abs are Ab 8110, 7832, 8113, 8128, 7092, 7876, 7878, 8129, 8130, 7909, 8131, 7910 or 8132.

Invention 3: claims 1-39 (all in part)

same as for invention 1, except that the Abs are Ab 8111 or 7093.

Invention 4: claims 1-39 (all in part)

same as for invention 1, except that the Abs are Ab 8114, 8126, 7829, 8112, 8125, 7091, 7871, 7872, 7873, 8127 or 7830.

Inventions 5-10: claims 1-39 (all in part)

same as for invention 1, except that the Ab is Ab 6525, 6756, 5757, 5763, 7087 or 7094, respectively.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/060052

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006115476 A1	01-06-2006	AU 2003246676 A1	02-02-2004
		WO 2004007553 A1	22-01-2004
		EP 1529063 A1	11-05-2005
		IT MI20021527 A1	12-01-2004
WO 9529697 A	09-11-1995	AU 2474795 A	29-11-1995
		BR 9507594 A	16-09-1997
		CA 2189015 A1	09-11-1995
		EP 2112165 A2	28-10-2009
		EP 0758904 A1	26-02-1997
		JP 3734266 B2	11-01-2006
		JP 10500289 T	13-01-1998
		JP 4294596 B2	15-07-2009
		JP 2005185286 A	14-07-2005
		JP 2006020633 A	26-01-2006
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		US 6074642 A	13-06-2000
		US 6355245 B1	12-03-2002
WO 0230985 A	18-04-2002	AU 9659401 A	22-04-2002
		CA 2424379 A1	18-04-2002
		EP 1325033 A2	09-07-2003
		EP 2113516 A1	04-11-2009
US 2007196367 A1	23-08-2007	NONE	
WO 02086085 A	31-10-2002	AU 2002307494 A1	05-11-2002
		CA 2445168 A1	31-10-2002
		EP 1381631 A2	21-01-2004
		JP 2004529647 T	30-09-2004
		JP 2009195233 A	03-09-2009

ANEXO INFORMATIVO

Presentación

El resumen debe ser claro y tan conciso como lo permita la descripción. No debe exceder de 250 palabras, debiendo contener preferentemente de 50 a 150 palabras y puede incluir fórmulas químicas y matemáticas, cuadros o figuras, en tamaño 12x12.

Contenido

El resumen debe tratar esencialmente de lo que es nuevo y aporta la invención al estado de la técnica al que pertenece. De esta manera, si la naturaleza de la invención es la modificación de un aparato, o la presentación de un procedimiento, producto o compuesto, el resumen debe enfocarse hacia la descripción técnica de la modificación.

En el caso de que el documento de patente reivindique un producto, particularmente un compuesto o componente y también contenga un procedimiento o método de preparación, éste también debe ser incluido en el resumen.

En lo que concierne a los compuestos o composiciones químicas, el resumen debe contener la naturaleza química del compuesto o de la composición, así como el campo de aplicación. El resumen debe indicar la fórmula química que mejor caracterice la invención.

En lo que respecta a los procedimientos, el resumen debe explicar el tipo de reacción, los reactivos y las condiciones para llevar a cabo el procedimiento.

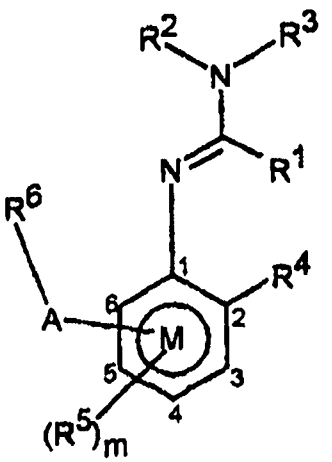
El resumen no debe contener declaraciones relativas a las ventajas asociadas a la invención.

Ejemplo:

Objeto de la Invención: Derivados de fenilamidina de fórmula (I) con aplicación como antifúngicos.

Características de la Invención: Compuestos fungicidas de fórmula (I) y sales donde: R1 es hidrógeno, alquilo, alquenilo, alquinilo, carbocíclico o heterocíclico cada uno de los cuales se encuentra sustituido; R2 y R3 son iguales o diferentes y se eligen entre: ciano, acilo, -ORa o –OSRa donde Ra es alquilo, alquenilo, alquinilo, carbociclilo o heterociclilo, o bien, R2 y R3 forman conjuntamente con el átomo al cual se unen un anillo que puede sustituirse por R4 que es alquilo, alquenilo, alquinilo, carbocicliclo o heterociclilo y que pueden sustituirse por hidroxi, mercapto, azido, nitro, halógeno, ciano, acilo. R5 es igual a la definición contemplada para R4, R6 es un anillo carbocíclico o heterocíclico opcionalmente sustituido y A es un grupo enlazante o AR6 y AR5 forman un anillo fusionado con el anillo de benceno M.

Figura característica:



Campo de aplicación: Producción de agentes antifúngicos con aplicación farmacéutica

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Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
NOVARTIS AG

REFERENCIA	Radicación No.	11 011416
	Solicitud internacional	PCT/EP2009/060052
	Fecha inicio fase nacional	05/03/2001
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	№ 06093

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 título primero de la Circular Única N° 10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (e)

El anterior requerimiento fue notificado por fijación en lista de fecha 08 ABR. 2011.

adpa11

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Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
CLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
NOVARTIS AG

REFERENCIA	Radicación No.	11 011416
	Solicitud internacional	PCT/EP2009/060052
	Fecha inicio fase nacional	05/03/2001
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	06092

Como resultado del examen de forma, realizado con fundamento en el artículo 39 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. Con respecto al resumen y de conformidad con lo dispuesto en el artículo 31 D. 486 en el cual se establece que el resumen consiste en una síntesis de la divulgación técnica contenida en la solicitud de patente, debe adecuar el resumen a los dispuesto en dicha norma, teniendo en cuenta que el extracto permitirá precisar el objeto de la invención, sus elementos característicos y el campo de aplicación.
Anexo al presente requerimiento se sugieren los lineamientos principales para la presentación adecuada del resumen.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 08 ABR. 2011.
adpa11