SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-111121- -00007-0000

Fecha: 2013-12-26 16:58:25 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 851 DIVISIONAL Folios: 6

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO8

No. 13-300529- -00000-0000

Fecha: 2013-12-26 16:58:25 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 6

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DIVISIONAL

DE PATENTE DE

INVENCIÓN

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

SOLICITANTE: GLAXO GROUP LIMITED

EXPEDIENTE No. 11-1121

DIRECCIÓN: Glaxo wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN. Reino Unido.

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 26 de diciembre de 2013

P2011/000155A

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-111121- -00007-0000

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DIRECCIÓN DE NUEVAS CREACIONES
CONVERSIÓN, DIVISIÓN Y FUSIÓN DE SOLICITUDES **P2011/000155A**

1. **Identificación del Tramite**

[ ] Conversión [X] División [ ] Fusión

[X] Patente de Invención
[ ] Patente de Modelo de Utilidad

2. **Datos del solicitante**

[ ] Persona Natural [X] Persona Juridica

GLAXO GROUP LIMITED LLC

Nombre o denominación / Nombre o razón social

MARCUS JONATHAN WILLIAM DALTON

Nombre del representante legal

Tipo de empresa [ ] Micro [ ] Pequeña [ ] Mediana [ ] Otra

Documento de Identificación [ ] C.C. [ ] C.E. [ ] NIT [ ] Otro Número _____

Nacionalidad/Pais de constitución	Dirección del titular	Ciudad
Inglaterra	980 Great West Road, Brentford Middlesex	Middlesex
Dirección electrónica	**No. Fax**	**Número telefónico**
office@olartemoure.com	6017799	6017700

[ ] **Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico**

3. **Datos del apoderado:**

CARLOS R. OLARTE	79.782.747 Bta	74.295
Apellidos y Nombre	Documento de identificación	Tarjeta profesional

Dirección y domicilio	Dirección del titular	Ciudad
Carrera 5 No 34-03 Bogotá D.C.	Cra 5 No. 34-03	Bogotá
Dirección electrónica	**No. Fax**	**Número telefónico**
office@olartemoure.com	601-7799	601-7700

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo de poder general _____

4. Datos del trámite:

CONVERSION	DIVISION	FUSION
Expediente No.	Expediente No. 11-111,121	Expediente No.
De:	No. de divisionales 1	Expediente No.
A:		

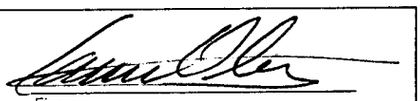
5. Comprobante de Pago No _____ **Fecha** [ ] [11] [2013]

6. Anexos

X	Comprobante de pago de la tasa para la presentación de la corrección y/o modificación
X	Poder, si fuere el caso con el que se acredita la representación
	Número de documento que ordena la comisión o fusión o división
X	Documento que contiene la conversión, división o fusión de la solicitud
X	Copia de la solicitud y sus anexos en formato magnético

7. Firma

CARLOS R. OLARTE
Nombre y apellidos


Firma

79.782.747
C.C.

74.295
Tarjeta Profesional

OLARTEMOURE

OLARTE MOURE & ASOCIADOS LTDA.

Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación.

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2011/000155A**

SOLICITUD DE:

(1)

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2)

SOLICITANTE (71)

Nombre: GLAXO GRUP LIMITED

Dirección: Glaxo Wellcome House, Berkeley Avenue, Greeford, Middlesex UB6 ONN. Reino Unido.

Nacionalidad o Domicilio: Británica

Lugar de Constitución: Gran Bretaña

Teléfono: _____ **Fax:** _____

E-mail: _____

IDENTIFICACIÓN

C.C. [ ] **NIT** [ ]

C.E. [ ] **Otro** [ ]

Cual _____

Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: Carrera 5 No. 34-03 Bogotá, Colombia

Teléfono: 601-7700 **Fax:** 601-7799

E-mail: office@olartemoure.com

IDENTIFICACIÓN

C.C. [X] **NIT** [ ]

C.E. [ ] **Otro** [ ]

Cual _____

Número 79.782.747Bta

TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA.

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA.

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2010/052008 Fecha Febrero 17, 2010

Publicación Internacional No. WO 2010/094723 Fecha Agosto 26, 2010

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

Clasificación Internacional (51) A61K 39/00.

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Febrero 19,2009	61/153,746
US	Marzo 27,2009	61/163,987
US	Septiembre 30,2009	61/247,136

(9) **Comprobante de pago No.** 13- **Fecha** _____

(10) **ANEXOS**

X	Comprobante de pago de la tasa de presentación de la solicitud.
	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica. Poderes, si fuere el caso.
	} Poderes, si fuere el caso.
	Documento de cesión del inventor al solicitante o a su causante.
	Declaraciones. Declaración bajo la Regla 417(ii) del PCT. Ver expediente original
X	Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
X	Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
	Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
	Traducción del examen preliminar internacional efectuado por la IPEA.
	De ser el caso, copia del contrato de acceso.
	De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
	De ser el caso, certificado de depósito del material biológico.
	Arte final 12 x 12.
	De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
	De ser el caso, modificaciones efectuadas a la solicitud internacional.
X	Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 134139

Bogotá D.C., Diciembre 26 de 2013 - 16:50:02

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
RECIBO DE CA	999999999	134137	26/12/2013		840.000.00
RECIBO DE CA	999999999	134138	26/12/2013		450.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	2205 DIVISIONAL SOLICITUD DE PATENTE DE INVENCION CONT. DERE	450.000.00	450.000.00
				$450.000.00

SON: **CUATROCIENTOS CINCUENTA MIL PESOS MONEDA CORRIENTE*

Responsable: _____
-*-
Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO8
No. 13-300529- -00000-0000
Fecha: 2013-12-26 16:58:25 Dep. 2020 DIR.NUEVASCR
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6

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 134141

Bogotá D.C., Diciembre 26 de 2013 - 16:50:02

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870 RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
RECIBO DE CA	999999999	134137	26/12/2013		840.000.00
RECIBO DE CA	999999999	134138	26/12/2013		450.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
3	50005-01-01 SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	30.000.00	90.000.00
10	50005-01-01 SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INICIALES	30.000.00	300.000.00
				$390.000.00

SON: **TRESCIENTOS NOVENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-****-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO8

No. 13-300529- -00000-0000

Fecha: 2013-12-26 16:58:25 Dep. 2020 DIR.NUEVASCR
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Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha: 2013 / 12 / 26 / (AAAA / MM / DD)	Recorrido:
2020		

Tipo de Radicación: Entrada: ☒ Salida: ☐ Traslado: ☐ Convenio: ☐

Radicador: | Planilla:

ID	No. Radicación	Consecutivo	Item
1	13 - 300529	0	7
2	11 - 111121	7	
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			

Item	Unidad de Conservación
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Tomo
6	Otro
Item	**Soporte Documental**
7	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	Otro

Observaciones:

El CD anexo contiene un total de 7 archivos:
7 en formato pdf, los cuales fueron procesados.

LIZETH FONSECA

ESCRITURA PÚBLICA NÚMERO: DIEZ MIL QUINIENTOS SETENTA Y DOS (10572)==========

FECHA DE OTORGAMIENTO: VEINTIUNO(21) DE NOVIEMBRE DE DOS MIL TRECE(2013)==========

NOTARIA TREINTA Y OCHO (38) DEL CÍRCULO DE BOGOTA D.C. ----------

SUPERINTENDENCIA DE NOTARIADO Y REGISTRO. ----------

CÓDIGO NOTARIAL 1100100038. ----------

FORMULARIO DE CALIFICACIÓN. ----------

CLASE DE ACTO: PROTOCOLIZACIÓN DE DOCUMENTOS. ----------

PERSONAS QUE INTERVIENEN: CARLOS REINALDO OLARTE, identificado con la cédula de ciudadanía número 79.782.747 expedida en Bogotá D.C., apoderado de **GLAXO GROUP LIMITED.**----------

En la ciudad de Bogotá, Distrito Capital, Departamento de Cundinamarca, República de Colombia, a los veintiun (21) días del mes de noviembre===== de dos mil Trece (2013), ante mí EDUARDO DURAN GOMEZ==========

NOTARIO(A) TREINTA Y OCHO (38) DEL CIRCULO DE BOGOTA D.C. --------

Compareció: **CARLOS REINALDO OLARTE,** mayor de edad, domiciliado y residente en la ciudad de Bogotá D.C., identificado con la cédula de ciudadanía número 79.782.747 expedida en Bogotá D.C., de estado civil casado con sociedad conyugal vigente, quien obra en nombre propio y manifestó: ----------

PRIMERO.- Presenta para su Protocolización en Cuatro (04) folios útiles, en los que consta El **Poder** otorgado por **GLAXO GROUP LIMITED** al señor CARLOS R. OLARTE y/o JUAN GUILLERMO MOURE, de fecha Dos (02) de Septiembre de 2013 ante el Notario Público de Londres, Inglaterra **JAMES KERR MILLIGAN**, texto en ingles y español y su respectiva Apostilla No. **J771557**.----------

SEGUNDO.- Que de conformidad con lo expuesto y atendiendo a las prescripciones del artículo 56, 57 y 58 del Decreto 960 de 1970, los documentos mencionados, contenidos en Cuatro (4) folios útiles, quedan legalmente protocolizados ante el Notario Treinta y Ocho (38) del Círculo Bogotá, de manera que desde ahora quedan bajo su custodia y guarda para que surtan los efectos legales a que haya lugar y los interesados puedan consultarlos y obtener las copias que de el solicite.----------

----------**HASTA AQUÍ LA MINUTA**----------

Eduardo Duran Gomez
NOTARIO 38 DEL CIRCULO DE BOGOTA D.C.

República de Colombia
Papel notarial para uso exclusivo de copias de escrituras públicas, certificados y documentos del archivo notarial
02/10/2013 1016266594CBaRGGB
Ca044180672
11/07/2013 10131 aC9959YBPRCC
Papel notarial para uso exclusivo en la escritura pública - No tiene costo para el usuario

SE ADVIRTIÓ al (a los) otorgante (s) de esta escritura de la **obligación que tiene (n) de leer la totalidad de su texto,** a fin de verificar la exactitud de todos los datos en ella consignados con el fin de aclarar, modificar o corregir lo que le(s) pareciere; la firma de la misma demuestra su aprobación total del texto.----------

Se advierte igualmente la necesidad de diligenciar los espacios en blanco correspondientes a la información personal y de trabajo consignados en el espacio destinado para la firma de los suscriptores del instrumento publico, con el objeto de confrontar la información solicitada con el contenido de la escritura previo a la autorización de la misma. ----------

En consecuencia, la notaria no asume ninguna responsabilidad por error o inexactitudes establecidas con posterioridad a la firma del (los) otorgante (s) y del notario.----------

En tal caso, de la existencia de estos, deben ser corregidos mediante el otorgamiento de una nueva escritura, suscrita por el (los) que intervino (eron) en la inicial y sufragada por el (ellos) mismo (s). (Articulo 35 decreto ley 960 de 1.970). ----------

ADVERTENCIA PARA TODOS LOS COMPARECIENTES QUE EXTIENDAN Y OTORGUEN INSTRUMENTOS, SEGÚN ART. 34 C.N., LEY 190 DE 1995, LEY 333 DE 1996 Y LEY 365 DE 1997. Los comparecientes bajo la gravedad del juramento manifiestan clara y expresamente que todos los dineros, bienes muebles e inmuebles contenidos en este instrumento fueron adquiridos por medios y actividades licitas. Así como el dinero con el que se efectúa el pago de los gastos notariales. ----------

OTORGAMIENTO Y AUTORIZACIÓN. Leído el presente instrumento por el otorgante y advertido de la formalidad de Ley, estuvo de acuerdo con él lo aceptó en la forma como está redactado y en testimonio de que le da su asentimiento y aprobación lo firma por ante mí y conmigo el Notario que de todo lo expuesto doy fe lo autorizo.----------

CONSTANCIA: El presente instrumento se extiende en la siguiente hoja de papel Notarial No.**********

Aa008930121, Aa008930122=----------

==========

Papel notarial para uso exclusivo en la escritura pública - No tiene costo para el usuario

ROBERTO M. OLARTE GARCÍA
Traductor e Intérprete Oficial
Resolución No. 0041
Minjusticia 1996

Este documento público es una traducción al español de un documento en idioma inglés presentado ante mí.
ROBERTO M. OLARTE GARCÍA
Traductor e Intérprete Oficial
Ministerio de Justicia
Licencia 0041/1996

10572

Eduardo Pinzón Gómez
NOTARIO 33 DEL CIRCULO DE BOGOTÁ D.C.

PRIMERA HOJA EN ESPAÑOL

APOSTILLA

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

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte

Este documento público

2. Ha sido firmado por **James Kerr Milligan**
3. Actuando en calidad de **Notario Público**
4. Lleva el sello de **dicho Notario Público**
5. en Londres
6. certifica el **4 de septiembre de 2013**
7. por el Secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Mancomunidad
8. Número **J771557**
9. Sello: (Oficina de la Mancomunidad y del Exterior – Londres)
10. Firma: **O. Matti** (firma ilegible)

Esta Apostilla no debe utilizarse en el Reino Unido y solamente confirma la autenticidad de la firma, sello o timbre sobre el documento público británico adjunto. No confirma la autenticidad del documento subyacente. Aquellas apostillas adjuntadas a documentos que hayan sido fotocopiados y certificados en el Reino Unido confirman la firma del funcionario público británico quien realizó la certificación solamente. No autentica de ninguna manera ni la firma sobre el documento original ni el contenido del documento original.

Si este documento fuera a utilizarse en un país el cual no hiciera parte de la Convención de la Haya del 5 de octubre de 1961, deberá ser presentado ante el despacho consular de la misión que represente dicho país.

República de Colombia
Papel notarial para uso exclusivo de copias de escrituras públicas, certificados y documentos del archivo notarial
02/10/2013 191619ACEaAGGEB6
Ca044180861
Cadena S.A. Nit. 890.930.534-0

PODER GENERAL

EN ESPAÑOL ***

Firma: (ilegible)
Marcus J. W. DALTON
en su calidad de Apoderado y Funcionario Autorizado

Fecha: 2 de septiembre de 2013

Ciudad, País: Brentford, Middlesex, Inglaterra

ROBERTO M. OLARTE GARCÍA
Traductor e Intérprete Oficial
Resolución No. 0041
Minjusticia 1996

DE PINNA
NOTARIES

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

C E R T I F I C O:

QUE es autentica la firma suscrita al pie del Poder General adjunto, por ser del puño y letra del Señor Don **Marcus Jonathan William DALTON**, de nacionalidad británica, nacido el 28 de mayo de 1963, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada **"GLAXO GROUP LIMITED"**, sociedad privada de responsabilidad limitada, debidamente constituida el 14 de octubre de 1935 y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número **305979**, con domicilio social en 980 Great West Road, Brentford, Middlesex TW8 9GS, Inglaterra;

Y QUE el antedicho Don **Marcus Jonathan William DALTON** está debidamente autorizado a firmar dicho Poder General en virtud de un Poder otorgado en su favor por la referida Sociedad fechado 8 de agosto de 2011, copia del cual he tenido a la vista.

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

James Kerr MILLIGAN
Notario Público de Londres, Inglaterra

JKM/56192/01
FO (Colombia) x 1

Eduardo Durán Gómez
NOTARIO 38 DEL CIRCULO DE BOGOTÁ D.C.

República de Colombia

18165aBGREGSE9PC
02/10/2013

Apostillas, legalizaciones y autenticaciones de firmas públicas, certificados y documentos del archivo notarial

cadena s.a. Nit. 890.930.534-0

LARTE

LARTE MOURE &

Gen

The undersigned,

domiciled i

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Jua

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ju

J

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Country: Pays/Pais	United Kingdom of Great Britain and Northern Ireland
This public document Le présent acte public / El presente documento público	
2. Has been signed by a été signé par ha sido firmado por	James Kerr Milligan
3. Acting in the capacity of agissant en qualité de quien actúa en calidad de	Notary Public
4. Bears the seal/stamp of est revêtu du sceau / timbre de y está revestido del sello / timbre de	The Said Notary Public

Certified
Attesté / Certificado

5. at á / en: London	**6. the** le / el día: 04 September 2013
7. by par / por	Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs
8. Number sous no / bajo el número	J771557
9. Seal / stamp: Sceau / timbre: Sello / timbre:	**10. Signature:** O. Matti Signature: Firma:

This Apostille is not to be used in the UK and only confirms the authenticity of the signature, seal or stamp on the attached UK public document. It does not confirm the authenticity of the underlying document. Apostilles attached to documents that have been photocopied and certified in the UK confirm the signature of the UK public official who conducted the certification only. It does not authenticate either the signature on the original document or the contents of the original document in any way.

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

Carlos R. Olarte
Juan G. Moure

Alexander Agudelo
Carlos A. Parra
Juan Felipe Acosta
Andrés Rincón
Mónica Guevara
Andrés Alvarado
Ella Ponce
Liliana Galindo
María Clara Calderón
Mauricio Avila
Laura Escobar
José Jairo Dangond
Gina Cáceres
Isabella Herrera
Zaava Rojas

Mentor
María Clara Múnera

OLARTEMOURE

OLARTE MOURE & ASOCIADOS LTDA.

General Power

The undersigned,

GLAXO GROUP LIMITED

domiciled in

980 Great West Road, Brentford Middlesex TW8 9GS, England

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GLAXO GROUP LIMITED

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10572

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Nombre o denominación / Nombre o razón social

MARCUS JONATHAN WILLIAM DALTON

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Nombre y apellidos

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

(57) **Abstract**: The invention relates to improved variants of the anti-serum albumin immunoglobulin single variable domain DOM7h-11, as well as ligands and drug conjugates comprising such variants, compositions, nucleic acids, vectors and hosts.

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IMPROVED ANTI-SERUM ALBUMIN BINDING VARIANTS

The invention relates to improved variants of the anti-serum albumin immunoglobulin single variable domain DOM7h-11, as well as ligands and drug conjugates comprising such variants, compositions, nucleic acids, vectors and hosts.

BACKGROUND OF THE INVENTION

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

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

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

WO2008/096158 discloses DOM7h-11, which is a good anti-SA dAb. It would be desirable to provide improved dAbs that are variants of DOM7h-11 and that specifically bind serum albumin, preferably albumins from human and non-human species, which would provide utility in animal models of disease as well as for human

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

SUMMARY OF THE INVENTION

Aspects of the present invention solve these problems.

To this end, the present inventors surprisingly found that beneficial mutations can be targeted to the FW2/CDR2 junction (positions 49 to 51, numbering according to Kabat) of DOM7h-11.

In one aspect the invention, therefore, provides an anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-11, wherein the variant comprises at least one mutation in the FW2/CDR2 junction (positions 49 to 51, numbering according to Kabat) compared to DOM7h-11, and wherein the variant has from 2 to 8 changes compared to the amino acid sequence of DOM7h-11.

In one aspect the invention provides an anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-11, wherein the variant comprises a Met at position 32 (numbering according to Kabat) compared to DOM7h-11, and wherein the variant has from 0 to 4 further changes compared to the amino acid sequence of DOM7h-11.

Embodiments of either aspect of the invention provide DOM7h-11 variants of good anti-serum albumin affinities. The choice of variant can allow for tailoring of half-life according to the desired therapeutic and/or prophylactic setting. For example, in one embodiment, the affinity of the variant for serum albumin is relatively high, such that the variant would be useful for inclusion in products that find utility in treating and/or preventing chronic or persistent diseases, conditions, toxicity or other chronic indications. In one embodiment, the affinity of the variant for serum albumin is relatively modest, such that the variant would be useful for inclusion in products that find utility in treating and/or preventing acute diseases, conditions, toxicity or other acute indications. In one embodiment, the affinity of the variant for serum albumin is intermediate, such that the variant would be useful for inclusion in products that find utility in treating and/or preventing acute or chronic diseases, conditions, toxicity or other acute or chronic indications.

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

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

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

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

An aspect of the invention provides a fusion product, eg, a fusion protein or fusion with a peptide or NCE (new chemical entity) drug, comprising a polypeptide, protein, peptide or NCE drug fused or conjugated (for an NCE) to any variant as described above, wherein the variant is DOM7h-11-15 or DOM7h-11-15^{S12P} (or a variant having an amino acid that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of DOM7h-11-15) or DOM7h-11-12 (or a variant having an amino acid that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of DOM7h-11-12). DOM7h-11-15 and DOM7h-11-12 give only a modest drop in affinity when fused or conjugated to partner making them useful in fusion products. DOM7h-11-15^{S12P} is identical to DOM7h-11-15, with the exception that position 12 (numbering according to Kabat) is a proline instead of a serine. This provides advantages set out in WO08052933, including to reduce binding to Protein-L of fusion proteins containing this domain antibody and to facilitate purification. The entire disclosure of WO08052933 is incorporated herein by reference. Similarly, the invention provides a DOM7h-11 variant as disclosed herein wherein the variant comprises an amino acid sequence as set out below with the exception that position 12 (numbering according to Kabat) is a proline. The invention also provides fusion proteins, conjugates or composition comprising such DOM7h-11 variants.

One aspect of the invention provides a variant of DOM7h-11 that comprises an amino acid sequence that is identical to the amino acid sequence of DOM7h-11-15^{S12P}or has up to 4 changes compared to the amino acid sequence of DOM7h-11-15^{S12P}, provided that the amino acid sequence of the variant has at least one mutation in the FW2/CDR2 junction (positions 49 to 51, numbering according to Kabat).

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

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

An aspect of the invention provides a polypeptide fusion or conjugate comprising an anti-serum albumin dAb as disclosed herein (eg, DOM7h-11-15 or DOM7h-11-3 or DOM7h-11-15^{S12P}or DOM7h-11-15^{S12P} with up to 4 changes compared to the amino acid sequence of DOM7h-11-15^{S12P}) and an incretin or insulinotropic agent, eg, exendin-4, GLP-1(7-37), GLP-1(6-36) or any incretin or insulinotropic agent disclosed in WO06/059106, these agents being explicitly incorporated herein by reference as though written herein for inclusion in the present invention and claims below.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Amino-acid sequence alignment for DOM7h-11 variant dAbs. A "." at a particular position indicates the same amino as found in DOM7h-11 at that position. The CDRs are indicated by underlining and bold text (the first underlined sequence is CDR1, the second underlined sequence is CDR2 and the third underlined sequence is CDR3).

Figure 2: Kinetic parameters of DOM7h-11 variants. KD units = nM; Kd units = sec^{-1}; Ka units = M^{-1} sec^{-1}. The notation A e-B means A x 10^{-B} and C e D means C x 10^{D}. The overall kinetic ranges in various species, as supported by the examples below, are indicated. Optional ranges are also provided for use in particular therapeutic settings (acute or chronic indications, conditions or diseases and "intermediate" for use in both chronic and acute settings). High affinity dAbs and products comprising these are useful for chronic settings. Medium affinity dAbs and products comprising these are useful for intermediate settings. Low affinity dAbs and products comprising these are useful for acute settings. The affinity in this respect is the affinity for serum albumin. Various example anti-serum dAbs and fusion proteins are listed, and these support the

ranges disclosed. Many of the examples have favourable kinetics in human and one or more non-human animals (eg, in human and *Cynomolgus* monkey and/or mouse). Choice of dAb or product comprising this can be tailored, according to the invention, depending on the setting (eg, chronic or acute) to be treated therapeutically.

DETAILED DESCRIPTION OF THE INVENTION

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

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art (e.g., in cell culture, molecular genetics, nucleic acid chemistry, hybridization techniques and biochemistry). Standard techniques are used for molecular, genetic and biochemical methods (see generally, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2d ed. (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. and Ausubel *et al.*, Short Protocols in Molecular Biology (1999) 4th Ed, John Wiley & Sons, Inc. which are incorporated herein by reference) and chemical methods.

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

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

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

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

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

As used herein, "antibody format" refers to any suitable polypeptide structure in which one or more antibody variable domains can be incorporated so as to confer binding specificity for antigen on the structure. A variety of suitable antibody formats are known in the art, such as, chimeric antibodies, humanized antibodies, human antibodies, single chain antibodies, bispecific antibodies, antibody heavy chains, antibody light chains, homodimers and heterodimers of antibody heavy chains and/or light chains, antigen-binding fragments of any of the foregoing (*e.g.*, a Fv fragment (*e.g.*, single chain Fv (scFv), a disulfide bonded Fv), a Fab fragment, a Fab' fragment, a $F(ab')_2$ fragment), a single antibody variable domain (*e.g.*, a dAb, V_H, V_{HH}, V_L), and modified versions of any of the foregoing (*e.g.*, modified by the covalent attachment of polyethylene glycol or other suitable polymer or a humanized V_{HH}).

The phrase "immunoglobulin single variable domain" refers to an antibody variable domain (V_H, V_{HH}, V_L) that specifically binds an antigen or epitope independently of different V regions or domains. An immunoglobulin single variable domain can be present in a format (*e.g.,* homo- or hetero-multimer) with other variable regions or variable domains where the other regions or domains are not required for antigen binding by the single immunoglobulin variable domain (*i.e.*, where the immunoglobulin single variable domain binds antigen independently of the additional variable domains). A "domain antibody" or "dAb" is the same as an "immunoglobulin single variable domain" as the term is used herein. A "single immunoglobulin variable

domain" is the same as an "immunoglobulin single variable domain" as the term is used herein. A "single antibody variable domain" or an "antibody single variable domain" is the same as an "immunoglobulin single variable domain" as the term is used herein. An immunoglobulin single variable domain is in one embodiment a human antibody variable domain, but also includes single antibody variable domains from other species such as rodent (for example, as disclosed in WO 00/29004, the contents of which are incorporated herein by reference in their entirety), nurse shark and *Camelid* V_{HH} dAbs. Camelid V_{HH} are immunoglobulin single variable domain polypeptides that are derived from species including camel, llama, alpaca, dromedary, and guanaco, which produce heavy chain antibodies naturally devoid of light chains. The V_{HH} may be humanized.

A "domain" is a folded protein structure which has tertiary structure independent of the rest of the protein. Generally, domains are responsible for discrete functional properties of proteins, and in many cases may be added, removed or transferred to other proteins without loss of function of the remainder of the protein and/or of the domain. A "single antibody variable domain" is a folded polypeptide domain comprising sequences characteristic of antibody variable domains. It therefore includes complete antibody variable domains and modified variable domains, for example, in which one or more loops have been replaced by sequences which are not characteristic of antibody variable domains, or antibody variable domains which have been truncated or comprise N- or C-terminal extensions, as well as folded fragments of variable domains which retain at least the binding activity and specificity of the full-length domain.

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

As used herein, the term "dose" refers to the quantity of ligand administered to a subject all at one time (unit dose), or in two or more administrations over a defined time

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

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

Half lives (t½ alpha and t½ beta) and AUC can be determined from a curve of serum concentration of ligand against time. The WinNonlin analysis package, eg version 5.1 (available from Pharsight Corp., Mountain View, CA94040, USA) can be used, for example, to model the curve. When two-compartment modeling is used, in a first phase (the alpha phase) the ligand is undergoing mainly distribution in the patient, with some elimination. A second phase (beta phase) is the phase when the ligand has

been distributed and the serum concentration is decreasing as the ligand is cleared from the patient. The t alpha half life is the half life of the first phase and the t beta half life is the half life of the second phase. Thus, in one embodiment, in the context of the present invention, the variable domain, fusion protein or ligand has a tα half–life in the range of (or of about) 15 minutes or more. In one embodiment, the lower end of the range is (or is about) 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 10 hours, 11 hours or 12 hours. In addition, or alternatively, the variable domain, fusion protein or ligand according to the invention will have a tα half life in the range of up to and including 12 hours (or about 12 hours). In one embodiment, the upper end of the range is (or is about) 11, 10, 9, 8, 7, 6 or 5 hours. An example of a suitable range is (or is about) 1 to 6 hours, 2 to 5 hours or 3 to 4 hours.

In one embodiment, the present invention provides the variable domain, fusion protein or ligand according to the invention has a tβ half–life in the range of (or of about) 2.5 hours or more. In one embodiment, the lower end of the range is (or is about) 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 10 hours , 11 hours, or 12 hours. In addition, or alternatively, the tβ half–life is (or is about) up to and including 21 or 25 days. In one embodiment, the upper end of the range is (or is about)12 hours, 24 hours, 2 days, 3 days, 5 days, 10 days, 15 days, 19 days, 20 days, 21 days or 22 days. For example, the variable domain, fusion protein or ligand according to the invention will have a tβ half life in the range 12 to 60 hours (or about 12 to 60 hours). In a further embodiment, it will be in the range 12 to 48 hours (or about 12 to 48 hours). In a further embodiment still, it will be in the range 12 to 26 hours (or about 12 to 26 hours).

As an alternative to using two-compartment modeling, the skilled person will be familiar with the use of non-compartmental modeling, which can be used to determine terminal half-lives (in this respect, the term “terminal half-life” as used herein means a terminal half-life determined using non-compartmental modeling). The WinNonlin analysis package, eg version 5.1 (available from Pharsight Corp., Mountain View, CA94040, USA) can be used, for example, to model the curve in this way. In this instance, in one embodiment the single variable domain, fusion protein or ligand has a terminal half life of at least (or at least about) 8 hours, 10 hours, 12 hours, 15 hours, 28

hours, 20 hours, 1 day, 2 days, 3 days, 7 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days or 25 days. In one embodiment, the upper end of this range is (or is about) 24 hours, 48 hours, 60 hours or 72 hours or 120 hours. For example, the terminal half-life is (or is about) from 8 hours to 60 hours, or 8 hours to 48 hours or 12 to 120 hours, eg, in man.

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

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

it can be a molecule that is structurally and/or functionally similar to a cognate partner or target.

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

In one aspect, the invention provides an anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-11, wherein the variant comprises at least one mutation in the FW2/CDR2 junction (positions 49 to 51, numbering according to Kabat) compared to DOM7h-11, and wherein the variant has from 2 to 8 changes compared to the amino acid sequence of DOM7h-11. Optionally, position 49 (according to Kabat) is Leu. Additionally or alternatively, position 50 (according to Kabat) is optionally Ala or Trp. Additionally or alternatively, position 51 (according to Kabat) is optionally Phe or Asn. In one embodiment, the variant comprises a mutation at each of positions 49, 50 and 51 (numbering according to Kabat) compared to DOM7h-11. In one embodiment, the variant comprises a LFG motif, where L is at position 49 (numbering according to Kabat), wherein L, F and G are Leu, Phe and Gly respectively.

In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-3, DOM7h-11-15, DOM7h-11-12 and DOM7h-11-19 or has up to 4 changes

compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has at least one mutation in the FW2/CDR2 junction as defined above. In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of DOM7h-11-15^{S12P}or has up to 4 changes compared to the amino acid sequence of DOM7h-11-15^{S12P}, provided that the amino acid sequence of the variant has at least one mutation in the FW2/CDR2 junction (positions 49 to 51, numbering according to Kabat). In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-3, or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has L at position 49, W at position 50 and N at position 51. In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-12, or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has M at position 32 and L at position 49. In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-15 or DOM7h-11-15^{S12P}, or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has M at position 32, L at position 49, A at position 50 and F at position 51. In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-18, or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has M at position 32 and H at position 87. In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-19, or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has M at position 32, L at position 49 and T at position 91. All numbering in this paragraph is according to Kabat.

An aspect of the invention provides an anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-11, wherein the variant

comprises a Met at position 32 (numbering according to Kabat) compared to DOM7h-11, and wherein the variant has from 0 to 4 further changes compared to the amino acid sequence of DOM7h-11. Optionally, the variant comprises at least one mutation in the FW2/CDR2 junction (positions 49 to 51, numbering according to Kabat) compared to DOM7h-11.

In one embodiment of any aspect of the invention, the variant comprises at least one mutation compared to DOM7h-11 selected from the following

Position 49 = L,
Position 50 = A or W,
Position 51 = F or N,
Position 87 = H, and
Position 91 = T.

In one embodiment, the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-12, DOM7h-11-15, DOM7h-11-15^{S12P}, DOM7h-11-18 and DOM7h-11-19 or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has Met at position 32.

In one embodiment, the variant comprises one or more of the following kinetic characteristics:-

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

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

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

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

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

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

(g) The variant comprises a binding site that specifically binds rat SA with a dissociation constant (KD) from (or from about) 1 to (or to about) 10000 nM, optionally from (or from about) 20 to (or to about) 6000 nM, as determined by surface plasmon resonance;

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

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

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

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

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

Optionally, the variant has

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

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

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

IV: kinetics according to I and II; or

V: kinetics according to I and III; or

VI: kinetics according to I, II and III.

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

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

In one embodiment of the multispecific ligand, the target antigen may be, or be part of, polypeptides, proteins or nucleic acids, which may be naturally occurring or synthetic. In this respect, the ligand of the invention may bind the target antigen and act as an antagonist or agonist (e.g., EPO receptor agonist). One skilled in the art will appreciate that the choice is large and varied. They may be for instance, human or animal proteins, cytokines, cytokine receptors, where cytokine receptors include receptors for cytokines, enzymes, co-factors for enzymes or DNA binding proteins. Suitable cytokines and growth factors include, but are preferably not limited to: ApoE, Apo-SAA, BDNF, Cardiotrophin-1, EGF, EGF receptor, ENA-78, Eotaxin, Eotaxin-2, Exodus-2, EpoR, FGF-acidic, FGF-basic, fibroblast growth factor-10, FLT3 ligand,

Fractalkine (CX3C), GDNF, G-CSF, GM-CSF, GF-β1, insulin, IFN-γ, IGF-I, IGF-II, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8 (72 a.a.), IL-8 (77 a.a.), IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-16, IL-17, IL-18 (IGIF), Inhibin α, Inhibin β, IP-10, keratinocyte growth factor-2 (KGF-2), KGF, Leptin, LIF, Lymphotactin, Mullerian inhibitory substance, monocyte colony inhibitory factor, monocyte attractant protein, M-CSF, MDC (67 a.a.), MDC (69 a.a.), MCP-1 (MCAF), MCP-2, MCP-3, MCP-4, MDC (67 a.a.), MDC (69 a.a.), MIG, MIP-1α, MIP-1β, MIP-3α, MIP-3β, MIP-4, myeloid progenitor inhibitor factor-1 (MPIF-1), NAP-2, Neurturin, Nerve growth factor, β-NGF, NT-3, NT-4, Oncostatin M, PDGF-AA, PDGF-AB, PDGF-BB, PF-4, RANTES, SDF1α, SDF1β, SCF, SCGF, stem cell factor (SCF), TARC, TGF-α, TGF-β, TGF-β2, TGF-β3, tumour necrosis factor (TNF), TNF-α, TNF-β, TNF receptor I, TNF receptor II, TNIL-1, TPO, VEGF, VEGF receptor 1, VEGF receptor 2, VEGF receptor 3, GCP-2, GRO/MGSA, GRO-β, GRO-γ, HCC1, 1-309, HER 1, HER 2, HER 3 and HER 4, CD4, human chemokine receptors CXCR4 or CCR5, non-structural protein type 3 (NS3) from the hepatitis C virus, , TNF-alpha, IgE, IFN-gamma, MMP-12, CEA, H. pylori, TB, influenza, Hepatitis E, MMP-12, internalizing receptors that are over-expressed on certain cells, such as the epidermal growth factor receptor (EGFR), ErBb2 receptor on tumor cells, an internalising cellular receptor, LDL receptor, FGF2 receptor, ErbB2 receptor, transferrin receptor, PDGF receptor, VEGF receptor, PsmAr, an extracellular matrix protein, elastin, fibronectin, laminin, α1-antitrypsin, tissue factor protease inhibitor, PDK1, GSK1, Bad, caspase-9, Forkhead, an antigen of Helicobacter pylori, an antigen of Mycobacterium tuberculosis, and an antigen of influenza virus. It will be appreciated that this list is by no means exhaustive.

In one embodiment, the multispecific ligand comprises an anti-SA dAb variant of the invention and an anti-TNFR1 binding moiety, eg, an anti-TNFR1 dAb. Optionally, the ligand has only one anti-TNFR1 binding moiety (eg, dAb) to reduce the chance of receptor cross-linking. In one embodiment, the anti-SA dAb variant is DOM7h-11-3 or DOM7h-11-15 or DOM7h-11-15^{S12P}.

In one embodiment, the anti-TNFR1 binding moiety is DOM1h-131-206 disclosed in WO2008149148 (the amino acid sequence of which and the nucleotide sequence of which, as disclosed in that PCT application, are expressly incorporated herein by reference as though explicitly written herein and for use with the present invention, and it is contemplated that any part of such disclosure can be incorporated into one or more claims herein). In one embodiment, the multispecific ligand comprises or consists of the amino acid sequence of DOM1h-131-206 and the amino acid sequence of DOM7h-11-3 or DOM7h-11-15 or DOM7h-11-15^{S12P}.

In one embodiment, the anti-TNFR1 binding moiety or dAb is any such moiety or dAb disclosed in co-pending application USSN 61/153,746, the disclosure of which is incorporated herein by reference. In one embodiment, the anti-TNFR1 binding moiety comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of DOM1h-574-156, DOM1h-574-72, DOM1h-574-109, DOM1h-574-138, DOM1h-574-162 or DOM1h-574-180 or the amino acid sequence of any anti-TNFR1 dAb disclosed in Table 3. In one embodiment, the multispecific ligand comprises or consists of the amino acid sequence of DOM1h-574-156 and the amino acid sequence of DOM7h-11-3 or DOM7h-11-15 or DOM7h-11-15^{S12P}.

In one embodiment, the ligand of the invention is a fusion protein comprising a variant of the invention fused directly or indirectly to one or more polypeptides. For example, the fusion protein can be a “drug fusion” as disclosed in WO2005/118642 (the disclosure of which is incorporated herein by reference), comprising a variant of the invention and a polypeptide drug as defined in that PCT application.

As used herein, "drug" refers to any compound (e.g., small organic molecule, nucleic acid, polypeptide) that can be administered to an individual to produce a beneficial, therapeutic or diagnostic effect through binding to and/or altering the function of a biological target molecule in the individual. The target molecule can be an endogenous target molecule encoded by the individual's genome (e.g. an enzyme, receptor, growth factor, cytokine encoded by the individual's genome) or an exogenous target molecule encoded by the genome of a pathogen (e. g. an enzyme encoded by the genome of a virus, bacterium, fungus, nematode or other pathogen). Suitable drugs for

use in fusion proteins and conjugates comprising an anti-SA dAb variant of the invention are disclosed in WO2005/118642 and WO2006/059106 (the entire disclosures of which are incorporated herein by reference, and including the entire list of specific drugs as though this list were expressly written herein, and it is contemplated that such incorporation provides disclosure of specific drugs for inclusion in claims herein). For example, the drug can be glucagon-like peptide 1 (GLP-1) or a variant, interferon alpha 2b or a variant or exendin-4 or a variant.

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

A ligand which contains one single variable domain (monomer) variant of the invention or more than one single variable domain (multimer, fusion protein, conjugate, and dual specific ligand as defined herein) which specifically binds to serum albumin, can further comprise one or more entities selected from, but preferably not limited to a label, a tag , an additional single variable domain, a dAb, an antibody, an antibody fragment, a marker and a drug. One or more of these entities can be located at either the

COOH terminus or at the N terminus or at both the N terminus and the COOH terminus of the ligand comprising the single variable domain, (either immunoglobulin or non-immunoglobulin single variable domain). One or more of these entities can be located at either the COOH terminus, or the N terminus, or both the N terminus and the COOH terminus of the single variable domain which specifically binds serum albumin of the ligand which contains one single variable domain (monomer) or more than one single variable domains (multimer, fusion protein, conjugate, and dual specific ligand as defined herein). Non-limiting examples of tags which can be positioned at one or both of these termini include a HA, his or a myc tag. The entities, including one or more tags, labels and drugs, can be bound to the ligand which contains one single variable domain (monomer) or more than one single variable domain (multimer, fusion protein, conjugate, and dual specific ligand as defined herein), which binds serum albumin, either directly or through linkers as described above.

An aspect of the invention provides a fusion product, eg, a fusion protein or fusion with a peptide or conjugate with an NCE (new chemical entity) drug, comprising a polypeptide drug fused or conjugated (for an NCE) to any variant as described above, optionally wherein the variant is DOM7h-11-15 or DOM7h-11-15^{S12P} (or a variant having an amino acid that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of DOM7h-11-15 or DOM7h-11-15^{S12P}) or DOM7h-11-12 (or a variant having an amino acid that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of DOM7h-11-15 or DOM7h-11-15^{S12P}). DOM7h-11-15, DOM7h-11-15^{S12P} and DOM7h-11-12 give only a modest drop in affinity when fused or conjugated to partner, making them useful in fusion products.

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

Also encompassed herein is an isolated nucleic acid encoding any of the variants, fusion proteins, conjugates or ligands described herein, e.g., a ligand which contains one single variable domain (monomer) variant of the invention or more than one single variable domain (e.g., multimer, fusion protein, conjugate, and dual specific

ligand as defined herein) variant which specifically binds to serum albumin, or which specifically binds both human serum albumin and at least one non-human serum albumin, or functionally active fragments thereof. Also encompassed herein is a vector and/or an expression vector, a host cell comprising the vector, e.g., a plant or animal cell and/or cell line transformed with a vector, a method of expressing and/or producing one or more variants, fusion proteins or ligands which contains one single variable domain (monomer) varuiant or more than one single variable domain variants (e.g., multimer, fusion protein, conjugate, and dual specific ligand as defined herein) which specifically binds to serum albumin, or fragment(s) thereof encoded by said vectors, including in some instances culturing the host cell so that the one or more variants, fusion proteins or ligands or fragments thereof are expressed and optionally recovering the ligand which contains one single variable domain (monomer) or more than one single variable domain (e.g., multimer, fusion protein, conjugate, and dual specific ligand as defined herein) which specifically binds to serum albumin, from the host cell culture medium. Also encompassed are methods of contacting a ligand described herein with serum albumin, including serum albumin and/or non-human serum albumin(s), and/or one or more targets other than serum albumin, where the targets include biologically active molecules, and include animal proteins, cytokines as listed above, and include methods where the contacting is in vitro as well as administering any of the variants, fusion proteins or ligands described herein to an individual host animal or cell *in vivo* and/or *ex vivo*. Preferably, administering ligands described herein which comprises a single variable domain (immunoglobulin or non-immunoglobulin) directed to serum albumin and/or non-human serum albumin(s), and one or more domains directed to one or more targets other than serum albumin, will increase the half life, including the T beta and/or terminal half life, of the anti-target ligand. Nucleic acid molecules encoding the variants, fusion proteins or single domain containing ligands or fragments thereof, including functional fragments thereof, are contemplated herein. Vectors encoding the nucleic acid molecules, including but preferably not limited to expression vectors, are contemplated herein, as are host cells from a cell line or organism containing one or more of these expression vectors. Also

contemplated are methods of producing any variant, fusion protein or ligand, including, but preferably not limited to any of the aforementioned nucleic acids, vectors and host cells.

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

An aspect of the invention provides a nucleic acid comprising the nucleotide sequence of a DOM7h-11 variant selected from DOM7h-11-3, DOM7h-11-15, DOM7h-11-15^{S12P}, DOM7h-11-12, DOM7h-11-18 and DOM7h-11-19 or a nucleotide sequence that is at least 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99% identical to said selected sequence.

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

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

DOM7h-14 variant sequences, which are not according to the invention, are disclosed in a co-pending US provisional patent application entitled IMPROVED ANTI-SERUM ALBUMIN BINDING VARIANTS, filed on the same day as the present application. These sequences of DOM7h-14 variants (SEQ ID NO:s 1-10 in the co-pending application) are incorporated herein by reference as though explicitly written herein.

SEQUENCES

Table 1: Amino Acid Sequences of DOM7h-11 Variant dAbs

DOM7h-11-12 (SEQ ID NO: 1)
DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILFGSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

DOM7h-11-15 (SEQ ID NO: 2)
DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

DOM7h-11-18 (SEQ ID NO: 3)
DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLIWFGSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYHCAQAGTHPTTFGQGTKVEIKR

DOM7h-11-19 (SEQ ID NO: 4)
DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILFGSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQTGTHPTTFGQGTKVEIKR

DOM7h-11-3 (SEQ ID NO: 5)
DIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPKLLILWNSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Table 2: Nucleotide Sequences of DOM7h-11 Variant dAbs

DOM7h-11-12 (SEQ ID NO: 6)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT
CACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGTACCA GC
AGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTTGTTT GGTTCCCGGT TGCAAAGT
GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCAT
CAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCGCAG GCTGGGACGC
ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-11-15 (SEQ ID NO: 7)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT
CACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGTACCA GC
AGAAACCA GGGAAAGCCC CTAAGCTCCT GATCCTTGCT TTTTCCCGTT TGCAAAGT
GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCAT
CAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGCGCGCAG GCTGGGACGC
ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-11-18 (SEQ ID NO: 8)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT
CACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGTACCA GC
AGAAACCA GGGAAAGCCC CAAAGCTCCT GATCTGGTTT GGTTCCCGGT TGCAAAGT
GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCAT
CAGCAG TCTGCAACCT GAAGATTTTG CTACGTACCA CTGTGCGCAG GCGGGGACGC
ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-11-19 (SEQ ID NO: 9)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT
CACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGTACCA GC
AGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTTGTTT GGTTCCCGGT TGCAAAGT
GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACGGAT TTCACTCTCA CCAT
CAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCGCAG ACTGGGACGC
ATCCCACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-11-3 (SEQ ID NO: 10)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGT
CACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGACGTTAA GTTGGTACCA GC
AGAAACCA GGGAAAGCCC CTAAGCTCCT GATCCTTTGG AATTCCCGTT TGCAAAGT
GG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCAT
CAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCGCAG GCTGGGACGC
ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

Table 3: Amino Acid Sequences of anti-TNFR1 dAbs

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

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

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

>DOM1h-549 (SEQ ID NO: 14)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVDYEMHWVRQAPGKGLEWVSSISESGTTT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKRRFSASTFDYWGQGTLVT
VSS

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDHWGQGTLVT
VSS

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

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNSLYLQMNSLRAEDTAVYYCAIYTGRWVPFDNWGQGTLVT
VSS

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

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

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

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAAYYCAIYTGRWPDFEYWGQGTLVT
VSS

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

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDKGTRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

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

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCALYTGRWVPFEYWGQGTLVT
VSS

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIVNTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

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

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWGPFVYWGQGTLVT
VSS

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

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

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

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

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

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

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

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

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 4: Nucleotide sequences of anti-TNFR1 dAbs

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

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

>DOM1h-543 (SEQ ID NO: 159)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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ACCGTCTCGAGC

>DOM1h-549 (SEQ ID NO: 160)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTAGTGAGAGTGGTACGACGACA

TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAACGTCGTTTTTCTGCTTCTACGTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574 (SEQ ID NO: 161)
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GTCTCGAGC

>DOM1h-574-1 (SEQ ID NO: 162)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

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

>DOM1h-574-4 (SEQ ID NO: 164)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAATATACGGGTCGTTGGGAGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-180 (SEQ ID NO: 165)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA

TACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-7 (SEQ ID NO: 166)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-8 (SEQ ID NO: 167)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

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

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

>DOM1h-574-11 (SEQ ID NO: 170)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA

GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAATATACGGGTCGTTGGGAGCCTTTTGACCACTGGGGTCAGGGGACCCTGGTCACC
GTCTCGAGC

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

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

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

>DOM1h-574-15 (SEQ ID NO: 174)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-16 (SEQ ID NO: 175)

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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-17 (SEQ ID NO: 176)
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GGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-18 (SEQ ID NO: 177)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-19 (SEQ ID NO: 178)
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GGCTCCAGGGAAGGATCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-25 (SEQ ID NO: 179)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-26 (SEQ ID NO: 180)

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

>DOM1h-574-28 (SEQ ID NO: 182)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-29 (SEQ ID NO: 183)
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-30 (SEQ ID NO: 184)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGATCGTAGA
TACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGCATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-31 (SEQ ID NO: 185)

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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GATATATACGGGTCGTTGGGAGCCTTTTAACTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-32 (SEQ ID NO: 186)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-33 (SEQ ID NO: 187)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACT
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>DOM1h-574-35 (SEQ ID NO: 188)
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>DOM1h-574-36 (SEQ ID NO: 189)
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TACTACGCGGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
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>DOM1h-574-37 (SEQ ID NO: 190)

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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

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

>DOM1h-574-39 (SEQ ID NO: 192)
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TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-40 (SEQ ID NO: 193)
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTAAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-53 (SEQ ID NO: 194)
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TACTACGCAGACTCAGTGAAGGGCCGGTTCACCATCTCCCGCGACAATCCCAAGAACA
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>DOM1h-574-54 (SEQ ID NO: 195)

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TACTACGCGGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCACGAGC

>DOM1h-574-65 (SEQ ID NO: 196)
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TACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGATAATTCCAAGAACA
CACTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-66 (SEQ ID NO: 197)
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-67 (SEQ ID NO: 198)
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GTCTCGAGC

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

>DOM1h-574-69 (SEQ ID NO: 200)
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GTCTCGAGC

>DOM1h-574-70 (SEQ ID NO: 201)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGTACA
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>DOM1h-574-71 (SEQ ID NO: 202)
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GTCTCGAGC

>DOM1h-574-72 (SEQ ID NO: 203)
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GTCTCGAGC

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

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

>DOM1h-574-75 (SEQ ID NO: 206)
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GTCTCGAGC

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

>DOM1h-574-77 (SEQ ID NO: 208)
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GTCTCGAGC

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

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

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

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

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

>DOM1h-574-87 (SEQ ID NO: 214)
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TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-88 (SEQ ID NO: 215)
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TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

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

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

>DOM1h-574-92 (SEQ ID NO: 218)
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>DOM1h-574-93 (SEQ ID NO: 219)
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TACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

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

>DOM1h-574-95 (SEQ ID NO: 221)
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>DOM1h-574-96 (SEQ ID NO: 222)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-97 (SEQ ID NO: 223)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-98 (SEQ ID NO: 224)
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>DOM1h-574-99 (SEQ ID NO: 225)
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>DOM1h-574-100 (SEQ ID NO: 226)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-101 (SEQ ID NO: 227)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-102 (SEQ ID NO: 228)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-103 (SEQ ID NO: 229)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-104 (SEQ ID NO: 230)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-105 (SEQ ID NO: 231)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

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

>DOM1h-574-107 (SEQ ID NO: 233)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-108 (SEQ ID NO: 234)
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>DOM1h-574-109 (SEQ ID NO: 235)
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>DOM1h-574-110 (SEQ ID NO: 236)
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>DOM1h-574-111 (SEQ ID NO: 237)
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>DOM1h-574-112 (SEQ ID NO: 238)
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>DOM1h-574-113 (SEQ ID NO: 239)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGCAGA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC

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GTCTCGAGC

>DOM1h-574-114 (SEQ ID NO: 240)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTTGAATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-115 (SEQ ID NO: 241)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

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

>DOM1h-574-119 (SEQ ID NO: 245)
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>DOM1h-574-120 (SEQ ID NO: 246)
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GTCTCGAGC

>DOM1h-574-121 (SEQ ID NO: 247)
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>DOM1h-574-122 (SEQ ID NO: 248)
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>DOM1h-574-123 (SEQ ID NO: 249)
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>DOM1h-574-124 (SEQ ID NO: 250)
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TACTACGCACACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-125 (SEQ ID NO: 251)
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TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-126 (SEQ ID NO: 252)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGATCGTAGA
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>DOM1h-574-127 (SEQ ID NO: 253)
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GTCTCGAGC

>DOM1h-574-128 (SEQ ID NO: 254)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGCTGATCGTAGA
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>DOM1h-574-129 (SEQ ID NO: 255)
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TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-130 (SEQ ID NO: 256)
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GTCTCGAGC

>DOM1h-574-131 (SEQ ID NO: 257)
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>DOM1h-574-132 (SEQ ID NO: 258)
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>DOM1h-574-133 (SEQ ID NO: 259)
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>DOM1h-574-134 (SEQ ID NO: 260)
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GTCTCGAGC

>DOM1h-574-137 (SEQ ID NO: 262)
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>DOM1h-574-138 (SEQ ID NO: 263)
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>DOM1h-574-139 (SEQ ID NO: 264)
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>DOM1h-574-140 (SEQ ID NO: 265)
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>DOM1h-574-141 (SEQ ID NO: 266)
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>DOM1h-574-142 (SEQ ID NO: 267)
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>DOM1h-574-143 (SEQ ID NO: 268)
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>DOM1h-574-144 (SEQ ID NO: 269)
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>DOM1h-574-145 (SEQ ID NO: 270)
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>DOM1h-574-146 (SEQ ID NO: 271)
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>DOM1h-574-147 (SEQ ID NO: 272)
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>DOM1h-574-148 (SEQ ID NO: 273)
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>DOM1h-574-149 (SEQ ID NO: 274)
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>DOM1h-574-150 (SEQ ID NO: 275)
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>DOM1h-574-151 (SEQ ID NO: 276)
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>DOM1h-574-152 (SEQ ID NO: 277)
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-153 (SEQ ID NO: 278)
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>DOM1h-574-154 (SEQ ID NO: 279)
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GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

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

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

>DOM1h-574-158 (SEQ ID NO: 283)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-159 (SEQ ID NO: 284)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA

TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

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

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

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

>DOM1h-574-163 (SEQ ID NO: 288)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACACACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-164 (SEQ ID NO: 289)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACACACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

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

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

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

>DOM1h-574-168 (SEQ ID NO: 293)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACCGGTGATCGTAGA
TACTACGATCACTCTGTGAAGGGCCGGTTCACTATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-169 (SEQ ID NO: 294)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGCGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

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

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

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

>DOM1h-574-173 (SEQ ID NO: 298)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTAGA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-174 (SEQ ID NO: 299)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTAGA
TACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

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

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

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

>DOM1h-574-178 (SEQ ID NO: 303)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTAGA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-179 (SEQ ID NO: 304)

GAGGTGCAGCTGCTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTAGA
TACTACGATGACGCGGTGAAGGGCCGGTTCACCATCACCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

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

(used in Rat studies):-

DOM7h-14/Exendin-4 fusion DMS number 7138

Amino acid sequence (SEQ ID NO: 305)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRS
SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGAALPRTFGQGTKVEIK
R

Nucleotide sequence (SEQ ID NO: 306)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGT
CTCAGTTATCTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCTCAGGGTGCGGCGTTGCCTAGGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

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

Amino acid sequence (SEQ ID NO: 307)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRS
SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIK
R

Nucleotide sequence (SEQ ID NO: 308)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGT
CTCAGTTATCTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

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

Amino acid sequence (SEQ ID NO: 309)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRS
SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLMKPMTFGQGTKVEIK
R

Nucleotide sequence (SEQ ID NO: 310)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGT
CTCAGTTATCTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCTCAGGGTCTTATGAAGCCTATGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

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

Amino acid sequence (SEQ ID NO: 311)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTISCRASQWIGSQLSWYQQKPGEAPKLLIMWRS

SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGAALPRTFGQGTKVEIK
R

Nucleotide sequence (SEQ ID NO: 312)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCTCTTGCCGGGCAAGTCAGTGGATTGGGTC
TCAGTTATCTTGGTACCAGCAGAAACCAGGGGAAGCCCCTAAGCTCCTGAT
CATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGT
GGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATT
TTGCTACGTACTACTGTGCTCAGGGTGCGGCGTTGCCTAGGACGTTCGGCCA
AGGGACCAAGGTGGAAATCAAACGG

DOM7h-11/Exendin-4 fusion DMS number 7142

Amino acid sequence (SEQ ID NO: 313)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPKLLIWFGSR
LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Nucleotide sequence (SEQ ID NO: 314)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGA
CGACGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCTGGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

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

Amino acid sequence (SEQ ID NO: 315)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILFGSR

LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Nucleotide sequence (SEQ ID NO: 316)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGA
CGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCTTGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

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

Amino acid sequence (SEQ ID NO: 317)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSR
LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Nucleotide sequence (SEQ ID NO: 318)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGA
CGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCCTTGCTTTTTCCCGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGT
GGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATT
TTGCTACGTACTACTGCGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCA
AGGGACCAAGGTGGAAATCAAACGG

DOM7h14-10/ G4SC-NCE fusion

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

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSL
QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKRG
GGGSC

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

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

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTC
CTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGAC
AGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTAC
TACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCCAAGGGACCAAG
GTGGAAATCAAACGGGGTGGCGGAGGGGGTTCCTGT

DOM7h14-10/TVAAPSC fusion

Amino acid sequence (SEQ ID NO: 321)

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSL
QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKRT
VAAPSC

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

Nucleotide sequence (SEQ ID NO: 322)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTC
CTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGAC
AGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTAC
TACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCCAAGGGACCAAG
GTGGAAATCAAACGGACCGTCGCTGCTCCATCTTGT

(used in mouse studies):-

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

Amino acid sequence (SEQ ID NO: 323)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLS
WYQQKPGKAPKLLIWFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
AQAGTHPTTFGQGTKVEIKR

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLS
WYQQKPGKAPKLLIWFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
AQAGTHPTTFGQGTKVEIKRAAAEQKLISEEDLN

Nucleotide sequence (SEQ ID NO: 325)

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

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

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

ACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACG
ACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAACA
AAAACTCATCTCAGAAGAGGATCTGAATTAA

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

Amino acid sequence (SEQ ID NO: 327)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS
WYQQKPGKAPKLLILFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA
QAGTHPTTFGQGTKVEIKR

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS
WYQQKPGKAPKLLILFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA
QAGTHPTTFGQGTKVEIKRAAAEQKLISEEDLN

Nucleotide sequence (SEQ ID NO: 329)

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

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

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

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

Amino acid sequence (SEQ ID NO: 331)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS
WYQQKPGKAPKLLILAFSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA
QAGTHPTTFGQGTKVEIKR

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS
WYQQKPGKAPKLLILAFSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA
QAGTHPTTFGQGTKVEIKRAAAEQKLISEEDLN

Nucleotide sequence (SEQ ID NO: 333)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC
CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA
GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC

CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCCTTGCTTTTTCCCGTTTGCAAAGTGGGGTCCCATCACGTTTC
AGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAA
CCTGAAGATTTTGCTACGTACTACTGCGCGCAGGCTGGGACGCATCCTACGA
CGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

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

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC
CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA
GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC
CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCCTTGCTTTTTCCCGTTTGCAAAGTGGGGTCCCATCACGTTTC
AGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAA
CCTGAAGATTTTGCTACGTACTACTGCGCGCAGGCTGGGACGCATCCTACGA
CGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAACAA
AAACTCATCTCAGAAGAGGATCTGAATTAA

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

EXEMPLIFICATION

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

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

EXAMPLE 1: Vk Affinity Maturation

Selections:

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

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

Affinity maturation libraries:

Both error-prone and CDR libraries were created using DOM7h-11 and DOM7h-14 parental dAbs (see WO2008/096158 for the sequences of DOM7h-11 and DOM7h-14). The CDR libraries were generated in the pDOM4 vector and the error prone libraries were generated in the pDOM33 vector (to allow for selection with or without protease treatment). Vector pDOM4, is a derivative of the Fd phage vector in which the *gene III* signal peptide sequence is replaced with the yeast glycolipid anchored surface protein (GAS) signal peptide. It also contains a *c-myc* tag between the leader sequence and *gene III*, which puts the *gene III* back in frame. This leader sequence functions well both in phage display vectors but also in other prokaryotic expression vectors and can be universally used. pDOM33 is a modified version of the pDOM4 vector where the the c-myc tag has been removed which renders the dAb-phage fusion resistant to the protease trypsin. This allows the use of trypsin within the phage selection to select for dAbs that are more protease stable (see WO2008149143).

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

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

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

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

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

	Library size	
	DOM7h-11	DOM7h-14

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

Example 2: Selection strategies:

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

1) Selections against HSA only:

Three rounds of selection against HSA were carried out. The error prone libraries and each CDR library were selected as an individual pool in all rounds. The first round of selection was performed against HSA passively coated onto an immunotube at 1mg/ml. Round 2 was performed against 100nM HSA and round 3 against 10nM (CDR selections) or 20 or 100nM (Error prone selections) HSA, both as soluble selections followed by a fourth round of selection with the error prone libraries against 1.5 nM HSA as a soluble selection. The error prone libraries were eluted with 0.1M glycine pH 2.0 before neutralisation with 1M Tris pH 8.0 and the CDR libraries were eluted with 1mg/ml trypsin before infection into log phase TG1 cells. The third round of each selection was subcloned into pDOM5 for screening. Soluble selections used biotinylated HSA.

2) Trypsin selections against HSA:

In order to select dAbs with increased protease resistance compared to the parental clone and with potentially improved biophysical properties, trypsin was used in phage selections (see WO2008149143). Four rounds of selection were preformed against HSA. The first round of selection of error prone libraries was performed against passively coated HSA at 1mg/ml without trypsin; the second round against

passively coated HSA at 1mg/ml with 20µg/ml trypsin for 1hour at 37°C; the third round selection was performed by soluble selection using biotinylated HSA against 100 nM HSA with 20 µg/ml or 100 µg/ml trypsin for 1hour at 37°C. The final round of selection was performed by soluble selection using biotinylated HSA against 100nM HSA with 100 µg/ml trypsin overnight at 37°C.

3) Cross-over selections against HSA (round 1) and RSA (rounds 2-4):
The first round selection was carried out against 1mg/ml passively coated HSA or 1 µM HSA (soluble selection), followed by a further three rounds of soluble selections against biotinylated RSA at concentrations of 1 µM for round 1, 100nm for round 2 and 20nM, 10nM or 1nM for round 3.

Screening strategy and affinity determination:

In each case after selection a pool of phage DNA from the appropriate round of selection is prepared using a QIAfilter midiprep kit (Qiagen), the DNA is digested using the restriction enzymes Sal1 and Not1 and the enriched V genes are ligated into the corresponding sites in pDOM5 the soluble expression vector which expresses the dAb with a myc tag (see PCT/EP2008/067789). The ligated DNA is used to electro-transform *E. coli* HB 2151 cells which are then grown overnight on agar plates containing the antibiotic carbenicillin. The resulting colonies are individually assessed for antigen binding. In each case at least 96 clones were tested for binding to HSA, CSA (*Cynomlgus* monkey Serum Albumin), MSA (mouse serum albumin) and RSA by BIAcore™ (surface plasmon resonance). MSA antigen was obtained from Sigma (essentially fatty acid free, ~99% (agarose gel electrophoresis), lyophilized powder Cat. No. A3559) and CSA was purified from *Cynomolgus* serum albumin using prometic blue resin (Amersham). Soluble dAb fragments were produced in bacterial culture in ONEX culture media (Novagen) overnight at 37°C in 96 well plates. The culture supernatant containing soluble dAb was centrifuged and analysed by BIAcore for

binding to high density HSA, CSA, MSA and RSA CM5 chips. Clones were found to bind to all these species of serum albumin by off-rate screening. The clones were sequenced revealing unique dAb sequences.

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

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

Unique dAbs were expressed as bacterial supernatants in 2.5L shake flasks in Onex media at 30°C for 48hrs at 250rpm. dAbs were purified from the culture media by absorption to protein L agarose followed by elution with 10mM glycine pH2.0. Binding to HSA, CSA, MSA and RSA by BIAcore was confirmed using purified protein at 3 concentrations 1μM, 500nM and 50nM. To determine the binding affinity (K_D) of the AlbudAbs to each serum albumin; purified dAbs were analysed by BIAcore over albumin concentration range from 5000nM to 39nM (5000nM, 2500nM, 1250nM, 625nM, 312nM, 156nM, 78nM, 39nM).

Table 6

AlbudAb	**Affinity (K_D) to SA (nM)**	**Kd**	**Ka**
	Rat		
DOM7h-14	60	2.095E-01	4.00E+06
DOM7h-14-10	4	9.640E-03	4.57E+06

DOM7h-14-18	410	2.275E-01	5.60E+05
DOM 7h-14-19	890	2.870E-01	3.20E+05
DOM 7h-14-28	45 (140)	7.0E-02 (1.141e-1)	2.10E+06 (8.3e5)
DOM 7h-14-36	30 (6120)	2.9E-02 (5.54e-2)	1.55E+06 (9e3)
DOM 7h-11	2100	1.00E-01	4.80E+04
DOM 7h-11-3	10000 (88000)	(7.18e-1)	(8.11e3)
DOM 7h-11-12	200	5.22E-01	2.76E+06
DOM 7h-11-15	20	2.10E-02	1.10E+06
DOM 7h-11-18	80 (29000)	6.0E-02 (3.7e-1)	1.64E+06 (1.3e4)
DOM 7h-11-19	28 (17000)	9.1e-02 (1.4e-1)	9.80E+05 (8.1e3)
	Cyno		
DOM 7h-14	66	9.65E-02	1.50E+06
DOM 7h-14-10	9	1.15E-02	1.60E+06
DOM 7h-14-18	180	1.05E-01	6.30E+5
DOM 7h-14-19	225	1.56E-01	7.00E+05
DOM 7h-14-28	66 (136)	1.3E-01 (1.34e-1)	2.50E+06 (9.8e5)
DOM 7h-14-36	35 (7830)	1.9E-02 (1.1e-1)	9.80E+06 (1.43e4)
DOM 7h-11	1000	6.82E-01	8.00E+05
DOM 7h-11-3	670 (200)	9.6E-02	2.90E+05

		(1.5e-1)	(7.26e5)
DOM 7h-11-12	≥6000		
DOM 7h-11-15	3	5.57E-03	5.80E+06
DOM 7h-11-18	10000 (65000)	1.36 (4.8e-1)	2.25E+05 (7.3e3)
DOM 7h-11-19	≥10000 (375000)	(6.2e-1)	(1.7e3)
	Mouse		
DOM 7h-14	12	4.82E-02	4.10E+06
DOM 7h-14-10	30	3.41E-02	1.29E+06
DOM 7h-14-18	65	9.24E-02	2.28E+06
DOM 7h-14-19	60	5.76E-02	1.16E+06
DOM 7h-14-28	26 (31)	3.4E-02 (7.15e-2)	1.60E+06 (2.28e6)
DOM 7h-14-36	35 (33)	2.3E-02 (7.06e-2)	8.70E+05 (2.11e6)
DOM 7h-11	5000	9.00E-01	
DOM 7h-11-3	≥10000 (36000)	(6.12e-1)	(1.67e4)
DOM 7h-11-12	130	1.89E-01	1.53E+06
DOM 7h-11-15	10	9.40E-03	1.10E+06
DOM 7h-11-18	150 (1600)	2.4E-02 (6.23e-2)	4.40E+05 (4e4)
DOM 7h-11-19	100 (18000)	3.7E-02 (8.8e-2)	1.40E+06 (4.9e3)
	Human		

DOM 7h-14	33	4.17E-02	1.43E+06
DOM 7h-14-10	12	1.39E-02	1.50E+06
DOM 7h-14-18	280	3.39E-02	1.89E+05
DOM 7h-14-19	70	5.25E-02	8.26E+05
DOM 7h-14-28	30 (8260)	3.3E-02 (5.6e-2)	1.24E+06 (6.78e3)
DOM 7h-14-36	28 (1260)	2.4E-02 (6.7e-2)	1.23E+06 (5.4e4)
DOM 7h-11	2800	6.41E-01	7.00E+05
DOM 7h-11-3	32 (130)	1.6E-02 (2.35e-2)	6.50E+05 (1.86e5)
DOM 7h-11-12	350	4.13E-01	1.26E+06
DOM 7h-11-15	1	1.84E-03	2.00E+06
DOM 7h-11-18	36 (32000)	5.1E-02 (2.7e-1)	3.40E+06 (8.39e3)
DOM 7h-11-19	65 (38000)	1.1E-01 (2.09e-1)	1.80E+06 (5.4e3)

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

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

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

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

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

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

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

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

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

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

AlbudAb	CDR		
	CDR1	CDR2	CDR3
DPK9 Vk dummy	SQSISSYLN (SEQ ID NO: 335)	YAASSLQS (SEQ ID NO: 336)	QQSYSTPNT (SEQ ID NO: 337)
DOM7h-11	SRPIGTTLS (SEQ ID NO: 338)	WFGSRLQS (SEQ ID NO: 339)	AQAGTHPTT (SEQ ID NO: 340)
DOM7h-11-12	SRPIGTMLS	LFGSRLQS	AQAGTHPTT

	(SEQ ID NO: 341)	(SEQ ID NO: 342)	(SEQ ID NO: 343)
DOM 7h-11-15	SRPIGTMLS (SEQ ID NO: 344)	LAFSRLQS (SEQ ID NO: 345)	AQAGTHPTT (SEQ ID NO: 346)
DOM 7h-11-18	SRPIGTMLS (SEQ ID NO: 347)	WFGSRLQS (SEQ ID NO: 348)	AQAGTHPTT (SEQ ID NO: 349)
DOM 7h-11-19	SRPIGTMLS (SEQ ID NO: 350)	LFGSRLQS (SEQ ID NO: 351)	AQTGTHPTT (SEQ ID NO: 352)
DOM 7h-11-3	SRPIGTTLS (SEQ ID NO: 353)	LWFSRLQS (SEQ ID NO: 354)	AQAGTHPTT (SEQ ID NO: 355)

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

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

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

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

AlbudAb	CDR		
	CDR1	CDR2	CDR3
DPK9 Vk dummy	SQSISSYLN (SEQ ID NO: 335)	YAASSLQS (SEQ ID NO: 336)	QQSYSTPNT (SEQ ID NO: 337)
DOM 7h-14	SQWIGSQLS (SEQ ID NO: 356)	MWRSSLQS (SEQ ID NO: 357)	AQGAALPRT (SEQ ID NO: 358)
DOM 7h-14-10	SQWIGSQLS (SEQ ID NO: 359)	MWRSSLQS (SEQ ID NO: 360)	AQGLRHPKT (SEQ ID NO: 361)

DOM 7h-14-18	SQWIGSQLS (SEQ ID NO: 362)	MWRSSLQS (SEQ ID NO: 363)	AQGLMKPMT (SEQ ID NO: 364)
DOM 7h-14-19	SQWIGSQLS (SEQ ID NO: 365)	MWRSSLQS (SEQ ID NO: 366)	AQGAALPRT (SEQ ID NO: 367)
DOM 7h-14-28	SQWIGSQLS (SEQ ID NO: 368)	MWRSSLQS (SEQ ID NO: 369)	AQGAALPKT (SEQ ID NO: 370)
DOM 7h-14-36	SQWIGSQLS (SEQ ID NO: 371)	MWRSSLQS (SEQ ID NO: 372)	AQGFKKPRT (SEQ ID NO: 373)

Example 5: Expression and Biophysical Characterisation:

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

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

DSC (Differential Scanning Calorimetry): briefly, the protein is heated at a constant rate of 180 °C/hrs (at 1mg/mL in PBS) and a detectable heat change associated with thermal denaturation measured. The transition midpoint ($_{app}T_m$) is determined, which is described as the temperature where 50% of the protein is in its native conformation and the other 50% is denatured. Here, DSC determined the apparent transition midpoint

(appTm) as most of the proteins examined do not fully refold. The higher the Tm, the more stable the molecule. Unfolding curves were analysed by non-2-state equations. The software package used was Origin^R v7.0383.

Table 9

AlbudAb	Biophysical parameters	
	SEC MALLS	DSC Tm(^{o}C)
DOM7h-14	M	60
DOM 7h-14-10	M	59
DOM 7h-14-18	M	58
DOM 7h-14-19	M	59
DOM 7h-14-28	M	58.3/60.2
DOM 7h-14-36	M	59.2
DOM 7h-11	M	66.9-72.2
DOM 7h-11-3	M (95%)*	66.6/70.5
DOM 7h-11-12	M (<2%D)	71.7
DOM 7h-11-15	M (<5%D)	58.5-60.5
DOM 7h-11-18	M (98%)	58.9/65.8
DOM 7h-11-19	M	71.8/76.6

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

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

For DOM7h-14 and DOM7h-11 variants, favorable biophysical parameters (monomeric in solution as determined by SEC MALLs and appTm of >55°C as determined by DSC) and expression levels were maintained during affinity maturation. Monomeric state is

advantageous because it avoids dimerisation and the risk of products that may cross-link targets such as cell-surface receptors.

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

AlbudAbs DOM7h-14-10, DOM7h-14-18, DOM7h-14-19, DOM7h-11, DOM7h11-12 and DOM7h-11-15 were cloned into the pDOM5 vector. For each AlbudAb™, 20-50mg quantities were expressed in E. coli and purified from bacterial culture supernatant using protein L affinity resin and eluted with 100mM glycine pH2. The proteins were concentred to greater than 1mg/ml, buffer exchanged into PBS and endotoxin depleted using using Q spin columns (Vivascience). For Rat pharmacokinetic (PK) analysis, AlbudAbs were dosed as single i.v injections at 2.5mg/kg using 3 rats per compound. Serum samples were taken at 0.16, 1, 4, 12, 24, 48, 72, 120, 168hrs. Analysis of serum levels was by anti-myc ELISA as per the method described below.

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

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

Anti-myc ELISA method

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

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

Table 10: Single AlbudAb™ PK

Species	AlbudAb	Albumin K_D (nM)	PK parameters			
			AUC h x µg/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
Rat	**DOM7h-14***	60				

	DOM7h-14-10	4	2134.6	1.2	42.1	71.2
	DOM7h-14-18	410	617.3	4.1	38.4	228.1
	DOM 7h-14-19	890	632.6	4.1	36.3	213.3
	DOM 7h-11	2100	320.1	7.8	23.3	263.9
	DOM 7h-11-12	200	398.7	6.4	35.5	321.2
	DOM 7h-11-15	20	843.4	3.0	30.3	130.7
mouse	**DOM 7h-11**	5000	304.7	8.2	18.3	216.8
	DOM 7h-11-12	130	646.6	3.9	43.9	244.8
	DOM 7h-11-15	10	499.2	5.0	33.7	243.4
Cyno	**DOM 7h-14***	66			217.5	
	DOM 7h-14-10	9	6174.6	0.4	200.8	117.8
	DOM 7h-11*	3300			135.1	
	DOM 7h-11-15	3	4195	0.6	198.1	170.3

* Historical data

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

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

Example 7: AlbudAb™ IFN fusions

Cloning and expression

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

Interferon alpha 2b amino acid sequence:

CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIP VLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTET PLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRS KE (SEQ ID NO:374)

Interferon alpha 2b nucleotide sequence:

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

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

the TVAAPS linker region. The primers used are as follows:-

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

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

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

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

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

Leader sequence (nucleotide):

ATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTGCTGTGGGTGCCCGGA TCCACCGGGC (SEQ ID NO:383)

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

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

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

	aa + myc	**nt + myc**	**aa no tag**	**nt no tag**
DMS7321 (IFNα2b-DOM7h-14)	CDLPQTHSLGSRRT	TGCGACTTGCC	CDLPQTHSLG	TGCGACTTGCC
	LMLLAQMRRISLFS	ACAGACACAT	SRRTLMLLA	ACAGACACAT
	CLKDRHDFGFPQE	AGTTTGGGATC	QMRRISLFSC	AGTTTGGGATC
	EFGNQFQKAETIPV	AAGAAGAACA	LKDRHDFGFP	AAGAAGAACA
	LHEMIQQIFNLFST	TTGATGTTATT	QEEFGNQFQ	TTGATGTTATT
	KDSSAAWDETLLD	AGCACAAATG	KAETIPVLHE	AGCACAAATG
	KFYTELYQQLNDL	CGTAGAATTTC	MIQQIFNLFS	CGTAGAATTTC
	EACVIQGVGVTETP	TTTGTTCTCTT	TKDSSAAWD	TTTGTTCTCTT
	LMKEDSILAVRKY	GTCTAAAGGAC	ETLLDKFYTE	GTCTAAAGGA
	FQRITLYLKEKKYS	CGTCACGACTT	LYQQLNDLE	CCGTCACGACT
	PCAWEVVRAEIMR	CGGATTCCCTC	ACVIQGVGV	TCGGATTCCCT
	SFSLSTNLQESLRS	AGGAAGAGTTT	TETPLMKEDS	CAGGAAGAGT

	KETVAAPSDIQMT	GGAAACCAATT	ILAVRKYFQR	TTGGAAACCA
	QSPSSLSASVGDRV	CCAAAAAGCA	ITLYLKEKKY	ATTCCAAAAA
	TITCRASQWIGSQL	GAAACTATTCC	SPCAWEVVR	GCAGAAACTA
	SWYQQKPGKAPKL	TGTCTTGCACG	AEIMRSFSLS	TTCCTGTCTTG
	LIMWRSSLQSGVPS	AAATGATCCAG	TNLQESLRSK	CACGAAATGA
	RFSGSGSGTDFTLT	CAAATATTCAA	ETVAAPSDIQ	TCCAGCAAATA
	ISSLQPEDFATYYC	TTTGTTTTCTA	MTQSPSSLSA	TTCAATTTGTT
	AQGAALPRTFGQG	CAAAGGACTC	SVGDRVTITC	TTCTACAAAGG
	TKVEIKR	ATCAGCCGCTT	RASQWIGSQL	ACTCATCAGCC
	AAAEQKLISEEDL	GGGATGAAAC	SWYQQKPGK	GCTTGGGATGA
	N* (SEQ ID NO:384)	TCTGTTAGATA	APKLLIMWR	AACTCTGTTAG
		AATTCTACACT	SSLQSGVPSR	ATAAATTCTAC
		GAACTATATCA	FSGSGSGTDF	ACTGAACTATA
		ACAACTGAAC	TLTISSLQPED	TCAACAACTGA
		GATCTAGAGGC	FATYYCAQG	ACGATCTAGA
		TTGCGTTATTC	AALPRTFGQ	GGCTTGCGTTA
		AGGGTGTAGG	GTKVEIKR	TTCAGGGTGTA
		AGTTACTGAAA	(SEQ ID	GGAGTTACTGA
		CTCCCCTAATG	NO:386)	AACTCCCCTAA
		AAAGAAGATT		TGAAAGAAGA
		CAATTCTAGCC		TTCAATTCTAG
		GTTAGAAAATA		CCGTTAGAAA
		CTTTCAGCGTA		ATACTTTCAGC
		TCACATTGTAT		GTATCACATTG
		TTAAAGGAAA		TATTTAAAGGA
		AGAAATACTCC		AAAGAAATAC
		CCATGTGCATG		TCCCCATGTGC
		GGAGGTGGTTA		ATGGGAGGTG
		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG

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

		CTCAGGGTGCG GCGTTGCCTAG GACGTTCGGCC AAGGGACCAA GGTGGAAATC AAACGG**GCGG CCGCAGAACA AAAACTCATC TCAGAAGAGG ATCTGAATTA A** (SEQ ID NO:385)		TACTGTGCTCA GGGTGCGGCG TTGCCTAGGAC GTTCGGCCAAG GGACCAAGGT GGAAATCAAA CGG (SEQ ID NO:387)
DMS732 (IFNα2b-DOM7h-14-10)	CDLPQTHSLGSRRT LMLLAQMRRISLFS CLKDRHDFGFPQE EFGNQFQKAETIPV LHEMIQQIFNLFST KDSSAAWDETLLD KFYTELYQQLNDL EACVIQGVGVTETP LMKEDSILAVRKY FQRITLYLKEKKYS PCAWEVVRAEIMR SFSLSTNLQESLRS KETVAAPSDIQMT QSPSSLSASVGDRV TITCRASQWIGSQL SWYQQKPGKAPKL LIMWRSSLQSGVPS RFSGSGSGTDFTLT	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG CGTAGAATTTC TTTGTTCTCTT GTCTAAAGGAC CGTCACGACTT CGGATTCCCTC AGGAAGAGTTT GGAAACCAATT CCAAAAAGCA GAAACTATTCC TGTCTTGCACG AAATGATCCAG CAAATATTCAA	CDLPQTHSLG SRRTLMLLA QMRRISLFSC LKDRHDFGFP QEEFGNQFQ KAETIPVLHE MIQQIFNLFS TKDSSAAWD ETLLDKFYTE LYQQLNDLE ACVIQGVGV TETPLMKEDS ILAVRKYFQR ITLYLKEKKY SPCAWEVVR AEIMRSFSLS TNLQESLRSK ETVAAPSDIQ	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG CGTAGAATTTC TTTGTTCTCTT GTCTAAAGGA CCGTCACGACT TCGGATTCCCT CAGGAAGAGT TTGGAAACCA ATTCCAAAAA GCAGAAACTA TTCCTGTCTTG CACGAAATGA TCCAGCAAATA

	ISSLQPEDFATYYC	TTTGTTTTCTA	MTQSPSSLSA	TTCAATTTGTT
	AQGLRHPKTFGQG	CAAAGGACTC	SVGDRVTITC	TTCTACAAAGG
	TKVEIKR	ATCAGCCGCTT	RASQWIGSQL	ACTCATCAGCC
	AAAEQKLISEEDL	GGGATGAAAC	SWYQQKPGK	GCTTGGGATGA
	N* (SEQ ID NO:388)	TCTGTTAGATA	APKLLIMWR	AACTCTGTTAG
		AATTCTACACT	SSLQSGVPSR	ATAAATTCTAC
		GAACTATATCA	FSGSGSGTDF	ACTGAACTATA
		ACAACTGAAC	TLTISSLQPED	TCAACAACTGA
		GATCTAGAGGC	FATYYCAQG	ACGATCTAGA
		TTGCGTTATTC	LRHPKTFGQ	GGCTTGCGTTA
		AGGGTGTAGG	GTKVEIKR	TTCAGGGTGTA
		AGTTACTGAAA	(SEQ ID	GGAGTTACTGA
		CTCCCCTAATG	NO:390)	AACTCCCCTAA
		AAAGAAGATT		TGAAAGAAGA
		CAATTCTAGCC		TTCAATTCTAG
		GTTAGAAAATA		CCGTTAGAAA
		CTTTCAGCGTA		ATACTTTCAGC
		TCACATTGTAT		GTATCACATTG
		TTAAAGGAAA		TATTTAAAGGA
		AGAAATACTCC		AAAGAAATAC
		CCATGTGCATG		TCCCCATGTGC
		GGAGGTGGTTA		ATGGGAGGTG
		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG
		TCTCTCTTTCT		GTCCTTCTCTC
		ACGAATTTGCA		TTTCTACGAAT
		AGAATCTTTGA		TTGCAAGAATC
		GATCTAAGGA		TTTGAGATCTA
		AACCGTCGCTG		AGGAAACCGT
		CTCCATCTGAC		CGCTGCTCCAT

		ATCCAGATGAC		CTGACATCCAG
		CCAGTCTCCAT		ATGACCCAGTC
		CCTCCCTGTCT		TCCATCCTCCC
		GCATCTGTAGG		TGTCTGCATCT
		AGACCGTGTCA		GTAGGAGACC
		CCATCACTTGC		GTGTCACCATC
		CGGGCAAGTC		ACTTGCCGGGC
		AGTGGATTGGG		AAGTCAGTGG
		TCTCAGTTATC		ATTGGGTCTCA
		TTGGTACCAGC		GTTATCTTGGT
		AGAAACCAGG		ACCAGCAGAA
		GAAAGCCCCTA		ACCAGGGAAA
		AGCTCCTGATC		GCCCCTAAGCT
		ATGTGGCGTTC		CCTGATCATGT
		CTCGTTGCAAA		GGCGTTCCTCG
		GTGGGGTCCCA		TTGCAAAGTGG
		TCACGTTTCAG		GGTCCCATCAC
		TGGCAGTGGAT		GTTTCAGTGGC
		CTGGGACAGAT		AGTGGATCTGG
		TTCACTCTCAC		GACAGATTTCA
		CATCAGCAGTC		CTCTCACCATC
		TGCAACCTGAA		AGCAGTCTGCA
		GATTTTGCTAC		ACCTGAAGATT
		GTACTACTGTG		TTGCTACGTAC
		CTCAGGGTTTG		TACTGTGCTCA
		AGGCATCCTAA		GGGTTTGAGGC
		GACGTTCGGCC		ATCCTAAGACG
		AAGGGACCAA		TTCGGCCAAGG
		GGTGGAAATC		GACCAAGGTG
		AAACGG**GCGG**		GAAATCAAAC

		CCGCAGAACA AAAACTCATC TCAGAAGAGG ATCTGAATTA A (SEQ ID NO:389)		GG (SEQ ID NO:391)
DMS7323 (IFNα2b-DOM7h-14-18)	CDLPQTHSLGSRRT LMLLAQMRRISLFS CLKDRHDFGFPQE EFGNQFQKAETIPV LHEMIQQIFNLFST KDSSAAWDETLLD KFYTELYQQLNDL EACVIQGVGVTETP LMKEDSILAVRKY FQRITLYLKEKKYS PCAWEVVRAEIMR SFSLSTNLQESLRS KETVAAPSDIQMT QSPSSLSASVGDRV TITCRASQWIGSQL SWYQQKPGKAPKL LIMWRSSLQSGVPS RFSGSGSGTDFTLT ISSLQPEDFATYYC AQGLMKPMTFGQ GTKVEIKR**AAAEQ KLISEEDLN*** (SEQ ID NO:392)	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG CGTAGAATTTC TTTGTTCTCTT GTCTAAAGGAC CGTCACGACTT CGGATTCCCTC AGGAAGAGTTT GGAAACCAATT CCAAAAAGCA GAAACTATTCC TGTCTTGCACG AAATGATCCAG CAAATATTCAA TTTGTTTTCTA CAAAGGACTC ATCAGCCGCTT GGGATGAAAC TCTGTTAGATA AATTCTACACT	CDLPQTHSLG SRRTLMLLA QMRRISLFSC LKDRHDFGFP QEEFGNQFQ KAETIPVLHE MIQQIFNLFS TKDSSAAWD ETLLDKFYTE LYQQLNDLE ACVIQGVGV TETPLMKEDS ILAVRKYFQR ITLYLKEKKY SPCAWEVVR AEIMRSFSLS TNLQESLRSK ETVAAPSDIQ MTQSPSSLSA SVGDRVTITC RASQWIGSQL SWYQQKPGK APKLLIMWR SSLQSGVPSR	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG CGTAGAATTTC TTTGTTCTCTT GTCTAAAGGA CCGTCACGACT TCGGATTCCCT CAGGAAGAGT TTGGAAACCA ATTCCAAAAA GCAGAAACTA TTCCTGTCTTG CACGAAATGA TCCAGCAAATA TTCAATTTGTT TTCTACAAAGG ACTCATCAGCC GCTTGGGATGA AACTCTGTTAG ATAAATTCTAC

		GAACTATATCA	FSGSGSGTDF	ACTGAACTATA
		ACAACTGAAC	TLTISSLQPED	TCAACAACTGA
		GATCTAGAGGC	FATYYCAQG	ACGATCTAGA
		TTGCGTTATTC	LMKPMTFGQ	GGCTTGCGTTA
		AGGGTGTAGG	GTKVEIKR	TTCAGGGTGTA
		AGTTACTGAAA	(SEQ ID	GGAGTTACTGA
		CTCCCCTAATG	NO:394)	AACTCCCCTAA
		AAAGAAGATT		TGAAAGAAGA
		CAATTCTAGCC		TTCAATTCTAG
		GTTAGAAAATA		CCGTTAGAAA
		CTTTCAGCGTA		ATACTTTCAGC
		TCACATTGTAT		GTATCACATTG
		TTAAAGGAAA		TATTTAAAGGA
		AGAAATACTCC		AAAGAAATAC
		CCATGTGCATG		TCCCCATGTGC
		GGAGGTGGTTA		ATGGGAGGTG
		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG
		TCTCTCTTTCT		GTCCTTCTCTC
		ACGAATTTGCA		TTTCTACGAAT
		AGAATCTTTGA		TTGCAAGAATC
		GATCTAAGGA		TTTGAGATCTA
		AACCGTCGCTG		AGGAAACCGT
		CTCCATCTGAC		CGCTGCTCCAT
		ATCCAGATGAC		CTGACATCCAG
		CCAGTCTCCAT		ATGACCCAGTC
		CCTCCCTGTCT		TCCATCCTCCC
		GCATCTGTAGG		TGTCTGCATCT
		AGACCGTGTCA		GTAGGAGACC
		CCATCACTTGC		GTGTCACCATC

		CGGGCAAGTC AGTGGATTGGG TCTCAGTTATC TTGGTACCAGC AGAAACCAGG GAAAGCCCTA AGCTCCTGATC ATGTGGCGTTC CTCGTTGCAAA GTGGGGTCCCA TCACGTTTCAG TGGCAGTGGAT CTGGGACAGAT TTCACTCTCAC CATCAGCAGTC TGCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTCTT ATGAAGCCTAT GACGTTCGGCC AAGGGACCAA GGTGGAAATC AAACGG**GCGG CCGCAGAACA AAAACTCATC TCAGAAGAGG ATCTGAATTA A** (SEQ ID NO:393)		ACTTGCCGGGC AAGTCAGTGG ATTGGGTCTCA GTTATCTTGGT ACCAGCAGAA ACCAGGGAAA GCCCCTAAGCT CCTGATCATGT GGCGTTCCTCG TTGCAAAGTGG GGTCCCATCAC GTTTCAGTGGC AGTGGATCTGG GACAGATTTCA CTCTCACCATC AGCAGTCTGCA ACCTGAAGATT TTGCTACGTAC TACTGTGCTCA GGGTCTTATGA AGCCTATGACG TTCGGCCAAGG GACCAAGGTG GAAATCAAAC GG (SEQ ID NO:395)

DMS7324 (IFNα2b-DOM7h-14-19)	CDLPQTHSLGSRRT	TGCGACTTGCC	CDLPQTHSLG	TGCGACTTGCC
	LMLLAQMRRISLFS	ACAGACACAT	SRRTLMLLA	ACAGACACAT
	CLKDRHDFGFPQE	AGTTTGGGATC	QMRRISLFSC	AGTTTGGGATC
	EFGNQFQKAETIPV	AAGAAGAACA	LKDRHDFGFP	AAGAAGAACA
	LHEMIQQIFNLFST	TTGATGTTATT	QEEFGNQFQ	TTGATGTTATT
	KDSSAAWDETLLD	AGCACAAATG	KAETIPVLHE	AGCACAAATG
	KFYTELYQQLNDL	CGTAGAATTTC	MIQQIFNLFS	CGTAGAATTTC
	EACVIQGVGVTETP	TTTGTTCTCTT	TKDSSAAWD	TTTGTTCTCTT
	LMKEDSILAVRKY	GTCTAAAGGAC	ETLLDKFYTE	GTCTAAAGGA
	FQRITLYLKEKKYS	CGTCACGACTT	LYQQLNDLE	CCGTCACGACT
	PCAWEVVRAEIMR	CGGATTCCCTC	ACVIQGVGV	TCGGATTCCCT
	SFSLSTNLQESLRS	AGGAAGAGTTT	TETPLMKEDS	CAGGAAGAGT
	KETVAAPSDIQMT	GGAAACCAATT	ILAVRKYFQR	TTGGAAACCA
	QSPSSLSASVGDRV	CCAAAAAGCA	ITLYLKEKKY	ATTCCAAAAA
	TISCRASQWIGSQL	GAAACTATTCC	SPCAWEVVR	GCAGAAACTA
	SWYQQKPGEAPKL	TGTCTTGCACG	AEIMRSFSLS	TTCCTGTCTTG
	LIMWRSSLQSGVPS	AAATGATCCAG	TNLQESLRSK	CACGAAATGA
	RFSGSGSGTDFTLT	CAAATATTCAA	ETVAAPSDIQ	TCCAGCAAATA
	ISSLQPEDFATYYC	TTTGTTTTCTA	MTQSPSSLSA	TTCAATTTGTT
	AQGAALPRTFGQG	CAAAGGACTC	SVGDRVTISC	TTCTACAAAGG
	TKVEIKR	ATCAGCCGCTT	RASQWIGSQL	ACTCATCAGCC
	AAAEQKLISEEDL	GGGATGAAAC	SWYQQKPGE	GCTTGGGATGA
	N* (SEQ ID NO:396)	TCTGTTAGATA	APKLLIMWR	AACTCTGTTAG
		AATTCTACACT	SSLQSGVPSR	ATAAATTCTAC
		GAACTATATCA	FSGSGSGTDF	ACTGAACTATA
		ACAACTGAAC	TLTISSLQPED	TCAACAACTGA
		GATCTAGAGGC	FATYYCAQG	ACGATCTAGA
		TTGCGTTATTC	AALPRTFGQ	GGCTTGCGTTA
		AGGGTGTAGG	GTKVEIKR	TTCAGGGTGTA
		AGTTACTGAAA	(SEQ ID	GGAGTTACTGA

		CTCCCCTAATG AAAGAAGATT CAATTCTAGCC GTTAGAAAATA CTTTCAGCGTA TCACATTGTAT TTAAAGGAAA AGAAATACTCC CCATGTGCATG GGAGGTGGTTA GAGCAGAAAT TATGAGGTCCT TCTCTCTTTCT ACGAATTTGCA AGAATCTTTGA GATCTAAGGA AACCGTCGCTG CTCCATCTGAC ATCCAGATGAC CCAGTcTCCAT CCTCCCTGTCT GCATCTGTAGG AGACCGTGTCA CCATCTCTTGC CGGGCAAGTC AGTGGATTGGG TCTCAGTTATC TTGGTACCAGC AGAAACCAGG GGAAGCCCCTA	NO:398)	AACTCCCCTAA TGAAAGAAGA TTCAATTCTAG CCGTTAGAAA ATACTTTCAGC GTATCACATTG TATTTAAAGGA AAAGAAATAC TCCCCATGTGC ATGGGAGGTG GTTAGAGCAG AAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT CGCTGCTCCAT CTGACATCCAG ATGACCCAGTc TCCATCCTCCC TGTCTGCATCT GTAGGAGACC GTGTCACCATC TCTTGCCGGGC AAGTCAGTGG ATTGGGTCTCA GTTATCTTGGT ACCAGCAGAA ACCAGGGGAA

		AGCTCCTGATC ATGTGGCGTTC CTCGTTGCAAA GTGGGGTCCCA TCACGTTTCAG TGGCAGTGGAT CTGGGACAGAT TTCACTCTCAC CATCAGCAGTC TGCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTGCG GCGTTGCCTAG GACGTTCGGCC AAGGGACCAA GGTGGAAATC AAACGG**GCGG CCGCAGAACA AAAACTCATC TCAGAAGAGG ATCTGAATTA A** (SEQ ID NO:397)		GCCCCTAAGCT CCTGATCATGT GGCGTTCCTCG TTGCAAAGTGG GGTCCCATCAC GTTTCAGTGGC AGTGGATCTGG GACAGATTTCA CTCTCACCATC AGCAGTCTGCA ACCTGAAGATT TTGCTACGTAC TACTGTGCTCA GGGTGCGGCG TTGCCTAGGAC GTTCGGCCAAG GGACCAAGGT GGAAATCAAA CGG (SEQ ID NO:399)
DMS7325 (IFNα2b-DOM7h-11)	CDLPQTHSLGSRRT LMLLAQMRRISLFS CLKDRHDFGFPQE EFGNQFQKAETIPV LHEMIQQIFNLFST KDSSAAWDETLLD	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG	CDLPQTHSLG SRRTLMLLA QMRRISLFSC LKDRHDFGFP QEEFGNQFQ KAETIPVLHE	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG

	KFYTELYQQLNDL	CGTAGAATTTC	MIQQIFNLFS	CGTAGAATTTC
	EACVIQGVGVTETP	TTTGTTCTCTT	TKDSSAAWD	TTTGTTCTCTT
	LMKEDSILAVRKY	GTCTAAAGGAC	ETLLDKFYTE	GTCTAAAGGA
	FQRITLYLKEKKYS	CGTCACGACTT	LYQQLNDLE	CCGTCACGACT
	PCAWEVVRAEIMR	CGGATTCCCTC	ACVIQGVGV	TCGGATTCCCT
	SFSLSTNLQESLRS	AGGAAGAGTTT	TETPLMKEDS	CAGGAAGAGT
	KETVAAPSDIQMT	GGAAACCAATT	ILAVRKYFQR	TTGGAAACCA
	QSPSSLSASVGDRV	CCAAAAAGCA	ITLYLKEKKY	ATTCCAAAAA
	TITCRASRPIGTTLS	GAAACTATTCC	SPCAWEVVR	GCAGAAACTA
	WYQQKPGKAPKLL	TGTCTTGCACG	AEIMRSFSLS	TTCCTGTCTTG
	IWFGSRLQSGVPSR	AAATGATCCAG	TNLQESLRSK	CACGAAATGA
	FSGSGSGTDFTLTIS	CAAATATTCAA	ETVAAPSDIQ	TCCAGCAAATA
	SLQPEDFATYYCA	TTTGTTTTCTA	MTQSPSSLSA	TTCAATTTGTT
	QAGTHPTTFGQGT	CAAAGGACTC	SVGDRVTITC	TTCTACAAAGG
	KVEIKR	ATCAGCCGCTT	RASRPIGTTL	ACTCATCAGCC
	AAAEQKLISEEDL	GGGATGAAAC	SWYQQKPGK	GCTTGGGATGA
	N* (SEQ ID NO:400)	TCTGTTAGATA	APKLLIWFGS	AACTCTGTTAG
		AATTCTACACT	RLQSGVPSRF	ATAAATTCTAC
		GAACTATATCA	SGSGSGTDFT	ACTGAACTATA
		ACAACTGAAC	LTISSLQPEDF	TCAACAACTGA
		GATCTAGAGGC	ATYYCAQAG	ACGATCTAGA
		TTGCGTTATTC	THPTTFGQGT	GGCTTGCGTTA
		AGGGTGTAGG	KVEIKR (SEQ	TTCAGGGTGTA
		AGTTACTGAAA	ID NO:402)	GGAGTTACTGA
		CTCCCCTAATG		AACTCCCCTAA
		AAAGAAGATT		TGAAAGAAGA
		CAATTCTAGCC		TTCAATTCTAG
		GTTAGAAAATA		CCGTTAGAAA
		CTTTCAGCGTA		ATACTTTCAGC
		TCACATTGTAT		GTATCACATTG

		TTAAAGGAAA		TATTTAAAGGA
		AGAAATACTCC		AAAGAAATAC
		CCATGTGCATG		TCCCCATGTGC
		GGAGGTGGTTA		ATGGGAGGTG
		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG
		TCTCTCTTTCT		GTCCTTCTCTC
		ACGAATTTGCA		TTTCTACGAAT
		AGAATCTTTGA		TTGCAAGAATC
		GATCTAAGGA		TTTGAGATCTA
		AACCGTCGCTG		AGGAAACCGT
		CTCCATCTGAC		CGCTGCTCCAT
		ATCCAGATGAC		CTGACATCCAG
		CCAGTCTCCAT		ATGACCCAGTC
		CCTCCCTGTCT		TCCATCCTCCC
		GCATCTGTAGG		TGTCTGCATCT
		AGACCGTGTCA		GTAGGAGACC
		CCATCACTTGC		GTGTCACCATC
		CGGGCAAGTC		ACTTGCCGGGC
		GTCCGATTGGG		AAGTCGTCCGA
		ACGACGTTAAG		TTGGGACGAC
		TTGGTACCAGC		GTTAAGTTGGT
		AGAAACCAGG		ACCAGCAGAA
		GAAAGCCCCTA		ACCAGGGAAA
		AGCTCCTGATC		GCCCCTAAGCT
		TGGTTTGGTTC		CCTGATCTGGT
		CCGGTTGCAAA		TTGGTTCCCGG
		GTGGGGTCCCA		TTGCAAAGTGG
		TCACGTTTCAG		GGTCCCATCAC
		TGGCAGTGGAT		GTTTCAGTGGC

		CTGGGACAGAT TTCACTCTCAC CATCAGCAGTC TGCAACCTGAA GATTTTGCTAC GTACTACTGTG CGCAGGCTGG GACGCATCCTA CGACGTTCGGC CAAGGGACCA AGGTGGAAAT CAAACGG**GCG GCCGCAGAAC AAAAACTCAT CTCAGAAGAG GATCTGAATT AA** (SEQ ID NO:401)		AGTGGATCTGG GACAGATTTCA CTCTCACCATC AGCAGTCTGCA ACCTGAAGATT TTGCTACGTAC TACTGTGCGCA GGCTGGGACG CATCCTACGAC GTTCGGCCAAG GGACCAAGGT GGAAATCAAA CGG (SEQ ID NO:403)
DMS7326 (IFNα2b-DOM7h-11-12)	CDLPQTHSLGSRRT LMLLAQMRRISLFS CLKDRHDFGFPQE EFGNQFQKAETIPV LHEMIQQIFNLFST KDSSAAWDETLLD KFYTELYQQLNDL EACVIQGVGVTETP LMKEDSILAVRKY FQRITLYLKEKKYS PCAWEVVRAEIMR SFSLSTNLQESLRS	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG CGTAGAATTTC TTTGTTCTCTT GTCTAAAGGAC CGTCACGACTT CGGATTCCCTC AGGAAGAGTTT	CDLPQTHSLG SRRTLMLLA QMRRISLFSC LKDRHDFGFP QEEFGNQFQ KAETIPVLHE MIQQIFNLFS TKDSSAAWD ETLLDKFYTE LYQQLNDLE ACVIQGVGV TETPLMKEDS	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG CGTAGAATTTC TTTGTTCTCTT GTCTAAAGGA CCGTCACGACT TCGGATTCCCT CAGGAAGAGT

	KETVAAPSDIQMT	GGAAACCAATT	ILAVRKYFQR	TTGGAAACCA
	QSPSSLSASVGDRV	CCAAAAAGCA	ITLYLKEKKY	ATTCCAAAAA
	TITCRASRPIGTML	GAAACTATTCC	SPCAWEVVR	GCAGAAACTA
	SWYQQKPGKAPKL	TGTCTTGCACG	AEIMRSFSLS	TTCCTGTCTTG
	LILFGSRLQSGVPS	AAATGATCCAG	TNLQESLRSK	CACGAAATGA
	RFSGSGSGTDFTLT	CAAATATTCAA	ETVAAPSDIQ	TCCAGCAAATA
	ISSLQPEDFATYYC	TTTGTTTTCTA	MTQSPSSLSA	TTCAATTTGTT
	AQAGTHPTTFGQG	CAAAGGACTC	SVGDRVTITC	TTCTACAAAGG
	TKVEIKR	ATCAGCCGCTT	RASRPIGTML	ACTCATCAGCC
	AAAEQKLISEEDL	GGGATGAAAC	SWYQQKPGK	GCTTGGGATGA
	N* (SEQ ID NO:404)	TCTGTTAGATA	APKLLILFGS	AACTCTGTTAG
		AATTCTACACT	RLQSGVPSRF	ATAAATTCTAC
		GAACTATATCA	SGSGSGTDFT	ACTGAACTATA
		ACAACTGAAC	LTISSLQPEDF	TCAACAACTGA
		GATCTAGAGGC	ATYYCAQAG	ACGATCTAGA
		TTGCGTTATTC	THPTTFGQGT	GGCTTGCGTTA
		AGGGTGTAGG	KVEIKR (SEQ	TTCAGGGTGTA
		AGTTACTGAAA	ID NO:406)	GGAGTTACTGA
		CTCCCCTAATG		AACTCCCCTAA
		AAAGAAGATT		TGAAAGAAGA
		CAATTCTAGCC		TTCAATTCTAG
		GTTAGAAAATA		CCGTTAGAAA
		CTTTCAGCGTA		ATACTTTCAGC
		TCACATTGTAT		GTATCACATTG
		TTAAAGGAAA		TATTTAAAGGA
		AGAAATACTCC		AAAGAAATAC
		CCATGTGCATG		TCCCCATGTGC
		GGAGGTGGTTA		ATGGGAGGTG
		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG

		TCTCTCTTTCT		GTCCTTCTCTC
		ACGAATTTGCA		TTTCTACGAAT
		AGAATCTTTGA		TTGCAAGAATC
		GATCTAAGGA		TTTGAGATCTA
		AACCGTCGCTG		AGGAAACCGT
		CTCCATCTGAC		CGCTGCTCCAT
		ATCCAGATGAC		CTGACATCCAG
		CCAGTCTCCAT		ATGACCCAGTC
		CCTCCCTGTCT		TCCATCCTCCC
		GCATCTGTAGG		TGTCTGCATCT
		AGACCGTGTCA		GTAGGAGACC
		CCATCACTTGC		GTGTCACCATC
		CGGGCAAGTC		ACTTGCCGGGC
		GTCCGATTGGG		AAGTCGTCCGA
		ACGATGTTAAG		TTGGGACGATG
		TTGGTACCAGC		TTAAGTTGGTA
		AGAAACCAGG		CCAGCAGAAA
		GAAAGCCCCTA		CCAGGGAAAG
		AGCTCCTGATC		CCCCTAAGCTC
		TTGTTTGGTTC		CTGATCTTGTT
		CCGGTTGCAAA		TGGTTCCCGGT
		GTGGGGTCCCA		TGCAAAGTGG
		TCACGTTTCAG		GGTCCCATCAC
		TGGCAGTGGAT		GTTTCAGTGGC
		CTGGGACAGAT		AGTGGATCTGG
		TTCACTCTCAC		GACAGATTTCA
		CATCAGCAGTC		CTCTCACCATC
		TGCAACCTGAA		AGCAGTCTGCA
		GATTTTGCTAC		ACCTGAAGATT
		GTACTACTGTG		TTGCTACGTAC

		CGCAGGCTGG GACGCATCCTA CGACGTTCGGC CAAGGGACCA AGGTGGAAAT CAAACGG**GCG GCCGCAGAAC AAAAACTCAT CTCAGAAGAG GATCTGAATT AA** (SEQ ID NO:405		TACTGTGCGCA GGCTGGGACG CATCCTACGAC GTTCGGCCAAG GGACCAAGGT GGAAATCAAA CGG (SEQ ID NO:407)
DMS7327 (IFNα2b-DOM7h-11-15)	CDLPQTHSLGSRRT LMLLAQMRRISLFS CLKDRHDFGFPQE EFGNQFQKAETIPV LHEMIQQIFNLFST KDSSAAWDETLLD KFYTELYQQLNDL EACVIQGVGVTETP LMKEDSILAVRKY FQRITLYLKEKKYS PCAWEVVRAEIMR SFSLSTNLQESLRS KETVAAPSDIQMT QSPSSLSASVGDRV TITCRASRPIGTML SWYQQKPGKAPKL LILAFSRLQSGVPS RFSGSGSGTDFTLT	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG CGTAGAATTTC TTTGTTCTCTT GTCTAAAGGAC CGTCACGACTT CGGATTCCCTC AGGAAGAGTTT GGAAACCAATT CCAAAAAGCA GAAACTATTCC TGTCTTGCACG AAATGATCCAG CAAATATTCAA	CDLPQTHSLG SRRTLMLLA QMRRISLFSC LKDRHDFGFP QEEFGNQFQ KAETIPVLHE MIQQIFNLFS TKDSSAAWD ETLLDKFYTE LYQQLNDLE ACVIQGVGV TETPLMKEDS ILAVRKYFQR ITLYLKEKKY SPCAWEVVR AEIMRSFSLS TNLQESLRSK ETVAAPSDIQ	TGCGACTTGCC ACAGACACAT AGTTTGGGATC AAGAAGAACA TTGATGTTATT AGCACAAATG CGTAGAATTTC TTTGTTCTCTT GTCTAAAGGA CCGTCACGACT TCGGATTCCCT CAGGAAGAGT TTGGAAACCA ATTCCAAAAA GCAGAAACTA TTCCTGTCTTG CACGAAATGA TCCAGCAAATA

	ISSLQPEDFATYYC	TTTGTTTTCTA	MTQSPSSLSA	TTCAATTTGTT
	AQAGTHPTTFGQG	CAAAGGACTC	SVGDRVTITC	TTCTACAAAGG
	TKVEIKR	ATCAGCCGCTT	RASRPIGTML	ACTCATCAGCC
	AAAEQKLISEEDL	GGGATGAAAC	SWYQQKPGK	GCTTGGGATGA
	N* (SEQ ID NO:408)	TCTGTTAGATA	APKLLILAFS	AACTCTGTTAG
		AATTCTACACT	RLQSGVPSRF	ATAAATTCTAC
		GAACTATATCA	SGSGSGTDFT	ACTGAACTATA
		ACAACTGAAC	LTISSLQPEDF	TCAACAACTGA
		GATCTAGAGGC	ATYYCAQAG	ACGATCTAGA
		TTGCGTTATTC	THPTTFGQGT	GGCTTGCGTTA
		AGGGTGTAGG	KVEIKR (SEQ	TTCAGGGTGTA
		AGTTACTGAAA	ID NO:410)	GGAGTTACTGA
		CTCCCCTAATG		AACTCCCCTAA
		AAAGAAGATT		TGAAAGAAGA
		CAATTCTAGCC		TTCAATTCTAG
		GTTAGAAAATA		CCGTTAGAAA
		CTTTCAGCGTA		ATACTTTCAGC
		TCACATTGTAT		GTATCACATTG
		TTAAAGGAAA		TATTTAAAGGA
		AGAAATACTCC		AAAGAAATAC
		CCATGTGCATG		TCCCCATGTGC
		GGAGGTGGTTA		ATGGGAGGTG
		GAGCAGAAAT		GTTAGAGCAG
		TATGAGGTCCT		AAATTATGAG
		TCTCTCTTTCT		GTCCTTCTCTC
		ACGAATTTGCA		TTTCTACGAAT
		AGAATCTTTGA		TTGCAAGAATC
		GATCTAAGGA		TTTGAGATCTA
		AACCGTCGCTG		AGGAAACCGT
		CTCCATCTGAC		CGCTGCTCCAT

		ATCCAGATGAC		CTGACATCCAG
		CCAGTCTCCAT		ATGACCCAGTC
		CCTCCCTGTCT		TCCATCCTCCC
		GCATCTGTAGG		TGTCTGCATCT
		AGACCGTGTCA		GTAGGAGACC
		CCATCACTTGC		GTGTCACCATC
		CGGGCAAGTC		ACTTGCCGGGC
		GTCCGATTGGG		AAGTCGTCCGA
		ACGATGTTAAG		TTGGGACGATG
		TTGGTACCAGC		TTAAGTTGGTA
		AGAAACCAGG		CCAGCAGAAA
		GAAAGCCCCTA		CCAGGGAAAG
		AGCTCCTGATC		CCCCTAAGCTC
		CTTGCTTTTTC		CTGATCCTTGC
		CCGTTTGCAAA		TTTTTCCCGTT
		GTGGGGTCCCA		TGCAAAGTGG
		TCACGTTTCAG		GGTCCCATCAC
		TGGCAGTGGAT		GTTTCAGTGGC
		CTGGGACAGAT		AGTGGATCTGG
		TTCACTCTCAC		GACAGATTTCA
		CATCAGCAGTC		CTCTCACCATC
		TGCAACCTGAA		AGCAGTCTGCA
		GATTTTGCTAC		ACCTGAAGATT
		GTACTACTGCG		TTGCTACGTAC
		CGCAGGCTGG		TACTGCGCGCA
		GACGCATCCTA		GGCTGGGACG
		CGACGTTCGGC		CATCCTACGAC
		CAAGGGACCA		GTTCGGCCAAG
		AGGTGGAAAT		GGACCAAGGT
		CAAACGG**GCG**		GGAAATCAAA

		GCCGCAGAAC AAAAACTCAT CTCAGAAGAG GATCTGAATT AA (SEQ ID NO:409)		CGG (SEQ ID NO:411)

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

Affinity Determination and Biophysical Characterisation:

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

Table 12: Affinity to SA

AlbudAb	**Fusion**	**Affinity to SA (nM)**	**Kd**	**Ka**
		Rat		
DOM7h-14	IFNα2b	350	4.500E-02	1.28E+05
DOM7h-14-10	IFNα2b	16	4.970E-03	5.90E+05
DOM 7h-14-18	IFNα2b	780	2.127E-01	5.80E+05
DOM 7h-14-19	IFNα2b	1900	1.206E-01	7.96E+04
DOM 7h-11	IFNα2b	6000	7.500E-01	nd
DOM 7h-11-12	IFNα2b	1700	3.100E-01	1.30E+05

DOM 7h-11-15	IFNα2b	200	1.660E-02	1.50E+05
		Cyno		
DOM 7h-14	IFNα2b	60	1.32E-02	5.0E+05
DOM 7h-14-10	IFNα2b	19	7.05E-03	4.50E+05
DOM 7h-14-18	IFNα2b	no binding	no binding	no binding
DOM 7h-14-19	IFNα2b	520	8.47E-02	2.73E+05
DOM 7h-11	IFNα2b	3300	3.59E-01	1.20E+05
DOM 7h-11-12	IFNα2b	630	3.45E-01	7.00E+05
DOM 7h-11-15	IFNα2b	15	4.86E-03	3.60E+05
		Mouse		
DOM 7h-14	IFNα2b	240	3.21E-02	1.50E+06
DOM 7h-14-10	IFNα2b	60	3.45E-02	6.86E+05
DOM 7h-14-18	IFNα2b	180	1.50E-01	9.84E+05
DOM 7h-14-19	IFNα2b	490	4.03E-02	1.19E+05
DOM 7h-11	IFNα2b	6000	1.55E-01	nd
DOM 7h-11-12	IFNα2b	150	9.49E-02	6.30E+05
DOM 7h-11-15	IFNα2b	28	6.69E-03	2.80E+05
		Human		
DOM 7h-14	IFNα2b	244	2.21E-02	9.89E+04
DOM 7h-14-10	IFNα2b	32	6.58E-03	3.48E+05
DOM 7h-14-18	IFNα2b	470	2.75E-01	6.15E+05
DOM 7h-14-19	IFNα2b	350	4.19E-02	1.55E+05
DOM 7h-11	IFNα2b	670	2.02E-01	7.00E+05

DOM 7h-11-12	IFNα2b	500	1.66E-01	3.90E+05
DOM 7h-11-15	IFNα2b	10	1.87E-03	3.50E+05

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

Table 13: Biophysical Characterisation

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

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

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

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

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

PK Determination for AlbudAb-IFNα2bfusions

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

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

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

Table 14:

Species	AlbudAb	Fusion	Albumin K_D (nM)	PK parameters			
				AUC h x ug/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
Rat	**7h-14**	IFNα2b	350	832.1	2.4	27	94.5
	7h-14-10	IFNα2b	16	1380.7	1.5	35.8	75.2
	7h-14-18	IFNα2b	780	691.2	2.9	22.4	93.7
	7h-14-19	IFNα2b	1900	969.4	2.2	25	78.7
	7h-11	IFNα2b	6000	327.9	6.5	11	101.9
	7h-11-12	IFNα2b	1700	747.1	2.8	25.8	104.7
	7h-11-15	IFNα2b	200	1118.7	1.8	39.5	103.6
mouse	**7h-14**	IFNα2b	240	761.2	2.6	30.4	115.3
	7h-14-10	IFNα2b	60	750.5	2.7	30.9	118.6
	7h-11	IFNα2b	6000	493.9	4.0	8.8	51.2
	7h-11-12	IFNα2b	150	439.6	4.5	21.5	140.9
	7h-11-15	IFNα2b	28	971.8	2.1	33.6	99.6

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

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

IFNα2b-DOM7h-14-10 variants, the improvement in *in vitro* K_D to serum albumin also correlated to an improvement in t1/2 in rat.

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

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

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

Table 15:

Species	AlbudAb	Fusion	Albumin K_D (nM)	PK parameters			
				AUC h x ug/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
Rat	DOM7h-14	Exendin-4	2400	18	57.1	11	901.9
	DOM7h-14-10	Exendin-4	19	43.6	23.1	22.1	740.3
	DOM7h-14-18	Exendin-4	16000	16.9	75.7	9.4	1002.5
	DOM7h-14-19	Exendin-4	17000	31.4	32.5	11.9	556.7
	DOM7h-11	Exendin-4	24000	6.1	168	7.1	1684.1
	DOM7h-11-12	Exendin-4	1400	24.2	59.9	13	1068.7

	DOM7h-11-15	Exendin-4	130	36.3	27.6	19.3	765.7
	DOM7h14-10	NCE-GGGGSC	62				
	DOM7h14-10	NCE-TVAAPSC	35				
Human	DOM7h-14	NCE	204				
mouse	DOM7h-11	DOM1m-21-23		234	10.7	4.7	72.5
	DOM7h-11-12	DOM1m-21-23		755	3.3	18	86.2
	DOM7h-11-15	DOM1m-21-23		1008	2.5	17.4	62.4

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

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

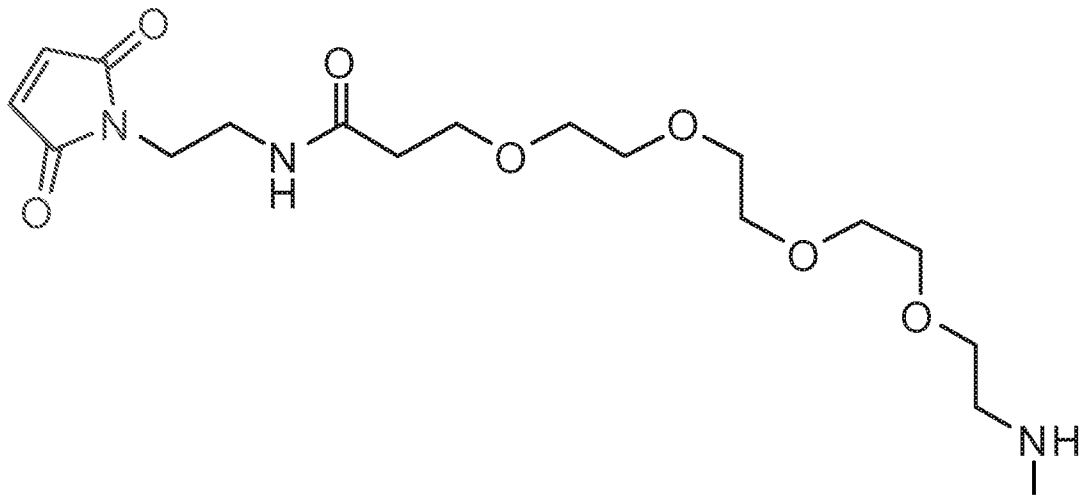
To produce genetic fusions of exendin-4 or with DOM7h-14 (or other AlbudAb) which binds serum albumin, the exendin-4-linker-AlbudAb sequence was cloned into the pTT-5 vector (obtainable from CNRC, Canada). In each case the exendin-4 was at the 5' end

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

NCE Albudab fusions:

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

PEG linker:



Sequences:

DOM7h-14 R108C:

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSL QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKC (SEQ ID NO:412)

Nucleotide:

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

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

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

dAb-Albudab fusion: the 2 DOM7h-11 AlbudAbs with the highest affinity to RSA experience a 2-fold decrease in affinity to RSA as on BIAcore when fused to a

therapeutic domain antibody (DOM1m-21-23) compared to the unfused AlbudAb. The DOM7h-11 clone shows a micromolar K_D when fused (2.8uM) as well as when unfused (~5uM).

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

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

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

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

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

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

DIQMTQSPSSLPASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR
(SEQ ID NO: 414)

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

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

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

GCAACAGCGTCGACGGACATCCAGATGACCCAGTCTCCATCCTCCCTGCCTG
CATCTGTAGG (SEQ ID NO: 416).

An alternative aspect of the invention provides a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 415 or a nucleotide sequence that is at least 80% identical to said selected sequence. In one embodiment, DOM7h-11-15^{S12P} is encoded by, and expressed from, a vector that contains a linker region and a C-terminal sequence encoding a protein or peptide drug or a single variable domain or other antibody fragment to make the in-line protein fusion product. The linker, in one embodiment,

comprises the amino acid sequence TVA, eg, TVAAPS. Other aspects of the invention are a vector comprising the nucleic acid; and an isolated host cell comprising the vector. The invention also provides a method of treating or preventing a disease or disorder in a patient, comprising administering at least one dose of DOM7h-11-15^{S12P} to said patient.

5

CLAIMS:

1. An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-11 (DOM7h-11 as shown in Figure 1), wherein the variant comprises at least one mutation in the FW2/CDR2 junction (positions 49 to 51, numbering according to Kabat) compared to DOM7h-11, and wherein the variant has from 2 to 8 changes compared to the amino acid sequence of DOM7h-11.

2. The variant of claim 1, wherein position 49 (according to Kabat) is Leu.

3. The variant of claim 1 or 2, wherein position 50 (according to Kabat) is Ala or Trp.

4. The variant of claim 1, 2 or 3, wherein position 51 (according to Kabat) is Phe or Asn.

5. The variant of claim 1, wherein the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-3 (SEQ ID NO: 5), DOM7h-11-15 (SEQ ID NO: 2), DOM7h-11-12 (SEQ ID NO: 1) and DOM7h-11-19 (SEQ ID NO: 4)or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has at least one mutation in the FW2/CDR2 junction as defined in any one of claims 1 to 4.

6. The variant of claim 1, wherein the variant comprises an amino acid sequence that is identical to the amino acid sequence of DOM7h-11-15^{S12P}(SEQ ID NO: 414) or has up to 4 changes compared to the amino acid sequence of DOM7h-11-15^{S12P}, provided that the amino acid sequence of the variant has at least one

mutation in the FW2/CDR2 junction as defined in any one of claims 1 to 4.

7. An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-11, wherein the variant comprises a Met at position 32 (numbering according to Kabat) compared to DOM7h-11 (as shown in Figure 1), and wherein the variant has from 0 to 4 further changes compared to the amino acid sequence of DOM7h-11.

8. The variant of claim 7, wherein the variant comprises at least one mutation in the FW2/CDR2 junction (positions 49 to 51, numbering according to Kabat) compared to DOM7h-11 (as shown in Figure 1).

9. The variant of claim 7, wherein the variant comprises at least one mutation compared to DOM7h-11 (as shown in Figure 1) selected from the following

Position 49 = L,
Position 50 = A or W,
Position 51 = F or N,
Position 87 = H, and
Position 91 = T.

10. The variant of claim 7, wherein the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-12 (SEQ ID NO: 1), DOM7h-11-15 (SEQ ID NO: 2), DOM7h-11-18 (SEQ ID NO: 3) and DOM7h-11-19 (SEQ ID NO: 4) or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has Met at position 32 .

11. The variant of claim 7, wherein the variant comprises an amino acid sequence that is identical to the amino acid sequence of DOM7h-11-15^{S12P} (SEQ ID NO:

414) or has up to 4 changes compared to the selected amino acid sequence, provided that the amino acid sequence of the variant has Met at position 32 .

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

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

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

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

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

17. The variant of any preceding claim, wherein the variant comprises a binding site that specifically binds *Cynomolgus* monkey SA with an on-rate constant (K_a) of

from about 2 x 10^6 to about 1 x 10^4 $M^{-1}sec^{-1}$, optionally from about 1 x 10^6 to about 5 x 10^3 $M^{-1}sec^{-1}$ as determined by surface plasmon resonance.

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

19. An anti-SA variant single variable domain of any one of claims 1 to 17, wherein the variable domain is conjugated to a drug (optionally an NCE drug), optionally wherein the selected variant is DOM7h-11-15 (SEQ ID NO: 2), DOM7h-11-15^{S12P} (SEQ ID NO: 414) or DOM7h-11-12 (SEQ ID NO: 1).

20. A fusion protein comprising a polypeptide or peptide drug fused to a variant according to any one of claims 1 to 17, optionally wherein the selected variant is DOM7h-11-15 (SEQ ID NO: 2), DOM7h-11-15^{S12P} (SEQ ID NO: 414) or DOM7h-11-12 (SEQ ID NO: 1).

21. A fusion protein according to claim 20, wherein the fusion protein comprises a linker (eg, a linker comprising the amino acid sequence TVA, optionally TVAAPS) between the variant and the drug.

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

23. A nucleic acid comprising a nucleotide sequence encoding a variant according to any one of claims 1 to 17 or a multispecific ligand of claim 18 or fusion protein of claim 20 or 21.

24. A nucleic acid comprising the nucleotide sequence of a DOM7h-11 variant selected from the nucleotide sequence of DOM7h-11-3 (SEQ ID NO: 5), DOM7h-11-15 (SEQ ID NO: 2), DOM7h-11-12 (SEQ ID NO: 1), DOM7h-11-

18 (SEQ ID NO: 3) and DOM7h-11-19 (SEQ ID NO: 4) or a nucleotide sequence that is at least 80% identical to said selected sequence.

25. A nucleic acid comprising the nucleotide sequence of DOM7h-11-15^{S12P} (SEQ ID NO: 414) or a nucleotide sequence that is at least 80% identical to said selected sequence.

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

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

28. A method of treating or preventing a disease or disorder in a patient, comprising administering at least one dose of a variant according to any one of claims 1 to 22 to said patient.

Kabat Residue	'	'	'	'	5	'	'	'	'	10	'	'	'	'	15	'	'	'	'	20
DOM7h-11	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T
DOM7h-11-12	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-11-15	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-11-18	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-11-19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-11-3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	25	'	'	'	'	30	'	'	'	'	35	'	'	'	'	40
DOM7h-11	I	T	C	**R**	**A**	**S**	**R**	**P**	**I**	**G**	**T**	**T**	**L**	**S**	W	Y	Q	Q	K	P
DOM7h-11-12	.	.	.	-	-	-	-	-	-	-	-	**M**	-	-	.	.	.	.	.	.
DOM7h-11-15	.	.	.	-	-	-	-	-	-	-	-	**M**	-	-	.	.	.	.	.	.
DOM7h-11-18	.	.	.	-	-	-	-	-	-	-	-	**M**	-	-	.	.	.	.	.	.
DOM7h-11-19	.	.	.	-	-	-	-	-	-	-	-	**M**	-	-	.	.	.	.	.	.
DOM7h-11-3	.	.	.	-	-	-	-	-	-	-	-	-	-	-	.	.	.	.	.	.

Kabat Residue	'	'	'	'	45	'	'	'	'	50	'	'	'	'	55	'	'	'	'	60
DOM7h-11	G	K	A	P	K	L	L	I	W	**F**	**G**	**S**	**R**	**L**	**Q**	**S**	G	V	P	S
DOM7h-11-12	.	.	.	.	.	.	.	.	L	-	-	-	-	-	-	-	.	.	.	.
DOM7h-11-15	.	.	.	.	.	.	.	.	L	**A**	**F**	-	-	-	-	-	.	.	.	.
DOM7h-11-18	.	.	.	.	.	.	.	.	.	-	-	-	-	-	-	-	.	.	.	.
DOM7h-11-19	.	.	.	.	.	.	.	.	L	-	-	-	-	-	-	-	.	.	.	.
DOM7h-11-3	.	.	.	.	.	.	.	.	L	**W**	**N**	-	-	-	-	-	.	.	.	.

Kabat Residue	'	'	'	'	65	'	'	'	'	70	'	'	'	'	75	'	'	'	'	80
DOM7h-11	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P
DOM7h-11-12	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

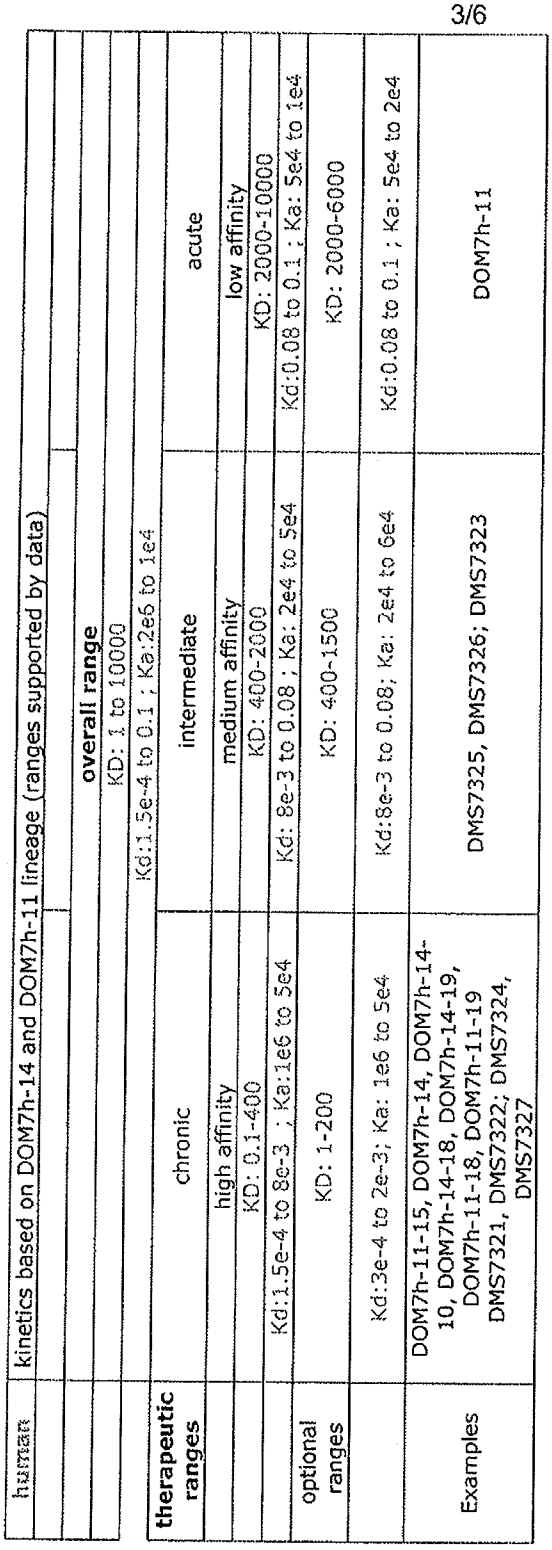
Figure 1A

DOM7h-11-15	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-11-18	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-11-19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-11-3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	85	'	'	'	'	90	'	'	'	'	95	'	'	'	'	100
DOM7h-11	E	D	F	A	T	Y	Y	C	A	Q	A	G	T	H	P	T	T	F	G	Q
DOM7h-11-12	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-11-15	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-11-18	.	.	.	.	.	.	H	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-11-19	.	.	.	.	.	.	.	.	.	.	T	.	.	.	.	.	.	.	.	.
DOM7h-11-3	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Kabat Residue	'	'	'	'	105	'	'	'
DOM7h-11	G	T	K	V	E	I	K	R
DOM7h-11-12	.	.	.	.	.	.	.	.
DOM7h-11-15	.	.	.	.	.	.	.	.
DOM7h-11-18	.	.	.	.	.	.	.	.
DOM7h-11-19	.	.	.	.	.	.	.	.
DOM7h-11-3	.	.	.	.	.	.	.	.

Figure 1B



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

Figure 2A

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

Figure 2B

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

Figure 2C

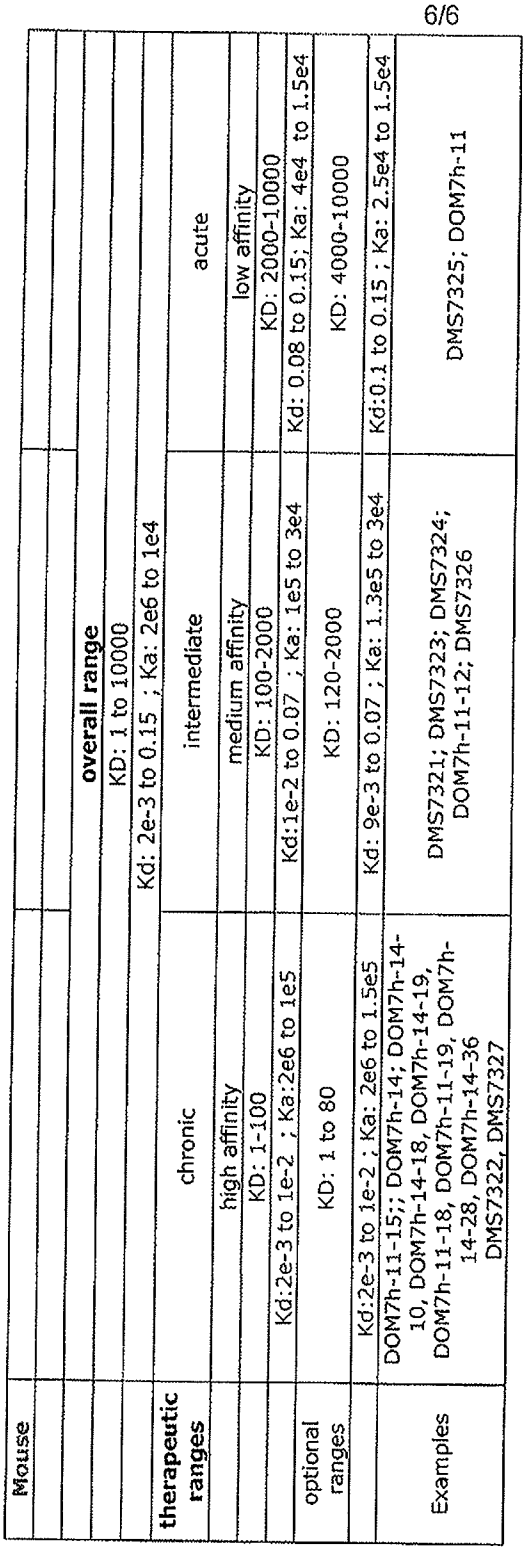

Mouse
overall range
KD: 1 to 10000
Kd: 2e-3 to 0.15 ; Ka: 2e6 to 1e4
therapeutic ranges
chronic
intermediate
acute
high affinity
medium affinity
low affinity
KD: 1-100
KD: 100-2000
KD: 2000-10000
Kd:2e-3 to 1e-2 ; Ka:2e6 to 1e5
Kd:1e-2 to 0.07 ; Ka: 1e5 to 3e4
Kd: 0.08 to 0.15; Ka: 4e4 to 1.5e4
optional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

Figure 2D

VARIANTES DE UNION A ANTI-ALBÚMINA DE SUERO MEJORADAS

La invención se refiere a variantes mejoradas del dominio variable sencillo de inmunoglobulina anti-albúmina de suero DOM7h-11, así como a ligandos y fármacos conjugados que comprenden dichas variantes, composiciones, ácido nucleicos, vectores y huéspedes.

ANTECEDENTES DE LA INVENCIÓN

Los documentos WO04003019 y WO2008/096158 describen restos de unión anti-albúmina de suero (SA), tales como dominios variables sencillos de inmunoglobulina (dAbs) anti-SA, que tienen semividas terapéuticamente útiles. Estos documentos describen dAbs anti-SA así como ligandos multiespecíficos que comprenden dichos dAbs, por ejemplo, ligandos que comprenden un dAb y un dAb anti-SA que se une específicamente a un antígeno diana, tal como TNFR1. Se describen restos de unión que se unen específicamente a albúminas de suero de más de una especie, por ejemplo dAbs anti-SA de reactividad cruzada de ser humano/ratón.

Los documentos WO05118642 y WO2006/059106 describen el concepto de conjugar o asociar un resto de unión anti-SA, tal como un dominio variable sencillo de inmunoglobulina anti-SA, a un fármaco, para aumentar la semivida del fármaco. Se describen y ejemplifican proteínas, péptidos y fármacos NCE (nueva entidad química). El documento WO2006/059106 describe el uso de este concepto para aumentar la semivida de agentes insulinotrópicos, por ejemplo, hormonas incretinas tales como el péptido similar a glucagón (GLP)-1.

También se hace referencia a Holt y col, “Anti-Serum albumin domain antibodies for extending the half-lives of short lived drugs”, Protein Engineering,

Design & Selection, vol 21, Nº 5, pág. 283-288, 2008.

El documento WO2008/096158 describe DOM7h-11, que es un buen dAb anti-SA. Sería deseable proporcionar dAbs mejorados que fueran variantes del DOM7h-11 y que la albúmina de suero se uniera específicamente, preferiblemente albúminas de especies humanas y no humanas, que proporcionarían utilidad en modelos animales de enfermedades así como para la terapia y/o diagnóstico en seres humanos. También sería deseable permitir la elección entre restos de unión (dAbs) anti-SA de afinidad relativamente moderada y elevada. Dichos restos podrían unirse a fármacos, eligiéndose el resto de unión anti-SA de acuerdo con la solicitud final contemplada. Esto permitiría al fármaco adaptarse mejor a las indicaciones crónicas o agudas del tratamiento y/o prevención, dependiendo de la elección del resto de unión anti-SA. También sería deseable proporcionar anti-dAbs, que sean monoméricos o sustancialmente lo sean en solución. Esto sería especialmente ventajoso cuando el dAb anti-SA está unido a un resto de unión, por ejemplo, un dAb, que se une específicamente a un receptor de la superficie celular, tal como TNFR1, con el propósito de antagonizar al receptor. El estado monomérico del dAb anti-SA es útil para reducir la posibilidad de entrecruzamiento del receptor, ya que es menos probable que se formen multímeros que puedan unirse y producir entrecruzamientos de los receptores (por ejemplo, TNFR1) en la superficie celular, aumentando de esta manera la probabilidad de agonismo de los receptores y la señalización perjudicial de los receptores.

SUMARIO DE LA INVENCIÓN

Aspectos de la presente invención resuelven estos problemas.

Con este fin, los presentes inventores descubren sorprendentemente que pueden dirigirse mutaciones benéficas en la unión FW2/CDR2 (posiciones 49 a 51,

numeración de acuerdo con Kabat) del DOM7h-11.

Por lo tanto, en un aspecto la invención proporciona una variante de dominio variable sencillo de inmunoglobulina anti-albúmina de suero (SA) de DOM7h-11, en el que la variante comprende al menos una mutación en la unión FW2/CDR2 (posiciones 49 a 51 numeración de acuerdo con Kabat) en comparación con DOM7h-11 y en el que la variante tiene de 2 a 8 cambios en comparación con la secuencia de aminoácidos de DOM7h-11.

En un aspecto de la invención proporciona una variante de dominio variable sencillo de inmunoglobulina anti-albúmina de suero (SA) de DOM7h-11, en el que la variante comprende una Met en la posición 32 (numeración de acuerdo con Kabat) en comparación con DOM7h-11 y en el que la variante tiene de 0 a 4 cambios adicionales en comparación con la secuencia de aminoácidos de DOM7h-11.

Realizaciones de cualquiera de los dos aspectos de la invención proporciona variantes de DOM7h-11 con buena afinidad anti-albúmina de suero. La elección de variantes puede permitir la adaptación de la semivida de acuerdo con el entorno terapéutico y/o profiláctico deseado. Por ejemplo, en una realización, la afinidad de la variante para la albúmina de suero es relativamente alta, de manera que la variante sería útil para incluir en productos que encuentren utilidad en el tratamiento y/o prevención de enfermedades, afecciones, toxicidades crónicas o persistentes, u otras indicaciones crónicas. En una realización, la afinidad de la variante para la albúmina de suero es relativamente moderada, de manera que la variante sería útil para incluir en productos que encuentren utilidad en el tratamiento y/o prevención de enfermedades, afecciones, toxicidades, agudas u otras indicaciones agudas. En una realización, la afinidad de la variante para la albúmina de suero es intermedia, de manera que la variante sería útil para incluir en productos que encuentren utilidad en

el tratamiento y/o prevención de enfermedades, afecciones, toxicidades, agudas o crónicas u otras indicaciones agudas o crónicas.

Es concebible que una molécula con una afinidad y especificidad elevada apropiada para la albúmina de suero permaneciera en circulación el suficiente tiempo para tener el efecto terapéutico deseado (Tomlinson, *Nature Biotechnology* **22**, 521 - 522 (2004)). En este caso, una variante anti-SA de elevada afinidad permanecería en la circulación en suero coincidiendo con la de la albúmina de suero de la especie (WO2008096158). Una vez en circulación, cualquier agente terapéutico fusionado a la variante AlbudAb™ (una AlbudAb es un dAb anti-albúmina de suero o dominio variable sencillo de inmunoglobulina), ya sea NCE, péptido o proteína, sería capaz por consiguiente de actuar durante más tiempo sobre su diana y presentar un efecto terapéutico más duradero. Esto permitiría dirigir enfermedades crónicas o persistentes sin necesidad de dosis frecuentes.

Una variante con afinidad moderada (pero específica para SA) permanecería únicamente en la circulación en suero durante un tiempo corto (por ejemplo, durante algunas horas o algunos días) permitiendo la dirección específica de las dianas terapéuticas implicadas en enfermedades agudas mediante el agente terapéutico fusionado.

De este modo es posible adaptar el producto que contiene anti-SA al área de enfermedad terapéutica eligiendo una variante anti-SA con la afinidad de unión a albúmina y/o semivida en suero apropiada.

Un aspecto de la invención proporciona un ligando multiespecífico que comprende una variante anti-SA como se ha descrito anteriormente y un resto de unión que se une específicamente a un antígeno diana distinto de SA.

Un aspecto de la invención proporciona un producto de fusión, por ejemplo,

una proteína de fusión o fusión con un péptido o fármaco de NCE (nueva entidad química), que comprende un polipéptido, proteína, péptido o fármaco de NCE fusionado o conjugado (para una NCE) a cualquier variante como se ha descrito anteriormente, en el que la variante es DOM7h-11-15 o DOM7h-11-15^{S12P} (o una variante que tiene una identidad de secuencia de aminoácidos de al menos el 95, 96, 97, 98 o 99% con la secuencia de aminoácidos de DOM7h-11-15) o DOM7h-11-12 (o una variante que tiene una identidad de secuencia de aminoácidos de al menos el 95, 96, 97, 98 o 99% con la secuencia de aminoácidos de DOM7h-11-12). DOM7h-11-15 y DOM7h-11-12 producen únicamente una modesta disminución de afinidad cuando se fusionan o se conjugan con el compañero haciéndoles útiles en los productos de fusión. DOM7h-11-15^{S12P} es idéntico a DOM7h-11-15, excepto que en la posición 12 (numeración de acuerdo con Kabat) hay una prolina en lugar de una serina. Esto proporciona ventajas expuestas en el documento WO08052933, que incluyen la reducción de unión a la Proteína-L de las proteínas de fusión que contienen este anticuerpo de dominio y para facilitar la purificación. Toda la descripción del documento WO08052933 se incorpora en este documento por referencia. De manera similar, la invención proporciona una variante de DOM7h-11 como se describe en este documento en la que la variante comprende una secuencia de aminoácidos como se indica a continuación con la excepción de que en la posición 12 (numeración de acuerdo con Kabat) hay una prolina. La invención también proporciona proteínas de fusión, conjugados o composiciones que comprenden dichas variantes de DOM7h-11.

Un aspecto de la invención proporciona una variante de DOM7h-11 que comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de DOM7h-11-15^{S12P} o tiene hasta 4 cambios en comparación con la secuencia de aminoácidos de DOM7h-11-15^{S12P}, mientras que la secuencia de

aminoácidos de la variante tiene al menos una mutación en la unión FW2/CDR2 (posiciones 49 a 51, numeración de acuerdo con Kabat).

Un aspecto de la invención proporciona una composición que comprende una variante, proteína o ligando de fusión de cualquier aspecto anterior y un diluyente, transportador, excipiente o vehículo farmacéuticamente aceptable.

Un aspecto de la invención proporciona un método de tratamiento o prevención de una enfermedad o trastorno en un paciente, que comprende administrar al menos una dosis de una variante de acuerdo con cualquier aspecto o realización de la invención a dicho paciente.

Un aspecto de la invención proporciona una fusión o conjugado polipeptídico que comprende un dAb anti-albúmina de suero como se ha descrito en este documento (por ejemplo, DOM7h-11-15 o DOM7h-11-3 o DOM7h-11-15^{S12P} o DOM7h-11-15^{S12P} con hasta 4 cambios en comparación con la secuencia de aminoácidos de DOM7h-11-15^{S12P}) y una incretina o agente insulinotrópico, por ejemplo, exendina-4, GLP-1(7-37), GLP-1(6-36) o cualquier incretina o agente insulinotrópico descrito en el documento WO06/059106, incorporándose explícitamente estos agentes en este documento como referencia como se ha descrito en este documento para incluir en esta invención y en las reivindicaciones a continuación.

BREVE DESCRIPCIÓN DE LOS DIBUJOS

Figura 1: Alineamiento de la secuencia de aminoácidos para dAbs de la variante DOM7h-11. Un "." en una posición particular indica que en esa posición se encuentra el mismo amino en DOM7h-11. Las CDR se indican subrayadas y en negrita (la primera secuencia subrayada es la CDR1, la segunda secuencia subrayada es la CDR2 y la tercera secuencia subrayada es la CDR3).

Figura 2: Parámetros cinéticos de variantes de DOM7h-11. Unidades KD = nM;

unidades Kd = s^{-1}; unidades Ka = M^{-1} s^{-1}. La anotación A e-B significa A x 10^{-B} y C e D significa C x 10^{D}. Se indican los intervalos cinéticos globales de diversas especies, de acuerdo con las confirmaciones de los ejemplos a continuación. También se proporcionan intervalos opcionales para usar en entornos terapéuticos particulares (indicaciones, afecciones o enfermedades agudas o crónicas e "intermedias" para usar tanto en entornos crónicos como agudos). Los dAb y productos de elevada afinidad que comprenden éstos son útiles para entornos crónicos. Los dAb y productos de afinidad media que comprenden éstos son útiles para entornos intermedios. Los dAb y productos de baja afinidad que comprenden éstos son útiles para entornos agudos. La afinidad en este aspecto es la afinidad para la albúmina de suero. Se enumeran diversos ejemplos de dAbs anti-suero y proteínas de fusión y éstos confirman los intervalos descritos. Muchos de los ejemplos tienen cinéticas favorables en seres humanos y uno o más en animales no humanos (por ejemplo, en ser humano y en mono *Cynomolgus* y/o en ratón). La elección del dAb o del producto que comprende éste puede adaptarse, de acuerdo con la invención, dependiendo del entorno (por ejemplo, crónico o agudo) a tratar terapéuticamente.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

En esta memoria descriptiva, la invención se ha descrito haciendo referencia a realizaciones, de manera que se permite realizar una memoria descriptiva clara y concisa. Se pretende y debe apreciarse que las realizaciones puedan combinarse de diversas maneras o realizarse por separado sin alejarse de la invención.

A menos que se indique otra cosa, todos los términos técnicos y científicos usados en este documento tienen el mismo significado que el habitualmente entendido por un experto en la materia (por ejemplo, en cultivos celulares, genética molecular, química de ácidos nucleicos, técnicas de hibridación y bioquímica). Para métodos

moleculares, genéticos y bioquímicos se usan técnicas convencionales (véase en líneas generales, Sambrook *y col.,* Molecular Cloning: A Laboratory Manual, 2d ed. (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. y Ausubel *y col.,* Short Protocols in Molecular Biology (1999) 4ª Ed, John Wiley & Sons, Inc. que se incorporan en este documento como referencia) y métodos químicos.

Como se usa en este documento, la expresión “antagonista del Receptor del Factor de Necrosis Tumoral I (TNFR1)” o “antagonista anti-TNFR1” o similar se refiere a un agente (por ejemplo, una molécula, un compuesto) que se une a TNFR1 y puede inhibir una (es decir, una o más) función de TNFR1. Por ejemplo, un antagonista de TNFR1 puede inhibir la unión de TNFα a TNFR1 y/o inhibir la transducción de señal mediada a través de TNFR1. Por consiguiente, con un antagonista de TNFR1 pueden inhibirse las respuestas celulares y los procedimientos mediados por TNFR1 (por ejemplo, muerte celular inducida por TNFα en un ensayo de citotoxicidad L929 convencional).

Un “paciente” es cualquier animal, por ejemplo, un mamífero, por ejemplo, un primate no humano (tal como babuino, mono *rhesus* o mono *Cynomolgus*), ratón, ser humano, conejo, rata, perro, gato o cerdo. En una realización, el paciente es un ser humano.

Como se usa en este documento, “péptido” se refiere de aproximadamente dos a aproximadamente 50 aminoácidos que están unidos entre sí mediante enlaces peptídicos.

Como se usa en este documento, “polipéptido” se refiere a al menos aproximadamente 50 aminoácidos que están unidos entre sí mediante enlaces peptídicos. Los polipéptidos generalmente comprenden estructura terciaria y plegada en los dominios funcionales.

Como se usa en este documento un anticuerpo se refiere a IgG, IgM, IgA, IgD o IgE o un fragmento (tal como un Fab, $F(ab')_2$, Fv, Fv unido por puentes disulfuro, scFv, anticuerpos multiespecíficos de conformación cerrada, scFv unido por puentes disulfuro, diacuerpo) que procede de cualquier especie que produce de manera natural un anticuerpo o creado mediante tecnología de ADN recombinante; o aislado de suero, células B, hibridomas, transfectomas, levaduras o bacterias.

Como se usa en este documento, "formato de anticuerpo" se refiere a cualquier estructura polipeptídica adecuada en la que pueden incorporarse uno o más dominios variables de anticuerpo para conferir especificidad de unión para el antígeno en la estructura. En la técnica se conoce una diversidad de formatos de anticuerpo adecuados tales como, anticuerpos quiméricos, anticuerpos humanizados, anticuerpos humanos, anticuerpos monocatenarios, anticuerpos biespecíficos, cadenas pesadas de anticuerpos, cadenas ligeras de anticuerpos, homodímeros y heterodímeros de cadenas pesadas y/o ligeras de anticuerpos, fragmentos de unión a antígeno de cualquiera de los anteriores (por ejemplo, un fragmento Fv, (por ejemplo, Fv monocatenario (scFv), Fv unido por puentes disulfuro), un fragmento Fab, un fragmento Fab', un fragmento $F(ab')_2$), un dominio variable de anticuerpo sencillo (por ejemplo, un dAb, V_H, V_{HH}, V_L) y versiones modificadas de cualquiera de los anteriores (por ejemplo, modificados por la unión covalente de polietilenglicol u otro polímero adecuado o un V_{HH} humanizado).

La frase "dominio variable sencillo de inmunoglobulina" se refiere a un dominio variable de anticuerpo (V_H, V_{HH}, V_L) que se une específicamente a un antígeno o epítope independientemente de los diferentes dominios o regiones V. Un dominio variable sencillo de inmunoglobulina puede presentarse en un formato (por ejemplo, homo- o hetero- multimérico) con otras regiones variables o dominios variables en los que las otras regiones o dominios no necesitan la unión al antígeno mediante el dominio variable

de inmunoglobulina sencillo (es decir, en el que el dominio variable sencillo de inmunoglobulina se une al antígeno independientemente de los dominios variables adicionales). Un “anticuerpo de dominio” o “dAb” es lo mismo que un “dominio variable sencillo de inmunoglobulina” como se usa el término en este documento. Un “dominio variable de inmunoglobulina sencillo” es lo mismo que un “dominio variable sencillo de inmunoglobulina” como se usa el término en este documento. Un “dominio variable de anticuerpo sencillo” o un “dominio variable sencillo de anticuerpo” es lo mismo que un “dominio variable sencillo de inmunoglobulina” como se usa el término en este documento. Un dominio variable sencillo de inmunoglobulina en una realización es un dominio variable de anticuerpo humano, pero también incluye dominios variables de anticuerpos sencillos de otras especies tales como roedores (por ejemplo, como se describe en el documento WO 00/29004, cuyo contenido se incorpora en este documento como referencia en su totalidad), tiburón nodriza y dAbs V_{HH} de *Camélidos.* Los V_{HH} de Camélidos son polipéptidos de dominio variable sencillo de inmunoglobulina que proceden de especies que incluyen camello, llama, alpaca, dromedario y guanaco, que producen de manera natural anticuerpos de cadena pesada desprovistos de cadenas ligeras. El V_{HH} puede humanizarse.

Un “dominio” es una estructura de proteína plegada que tiene una estructura terciaria independiente del resto de la proteína. Generalmente, los dominios son responsables de las propiedades funcionales específicas de las proteínas, y en muchos casos pueden añadirse, eliminarse o transferirse a otras proteínas sin que el resto de la proteína y/o del dominio pierda la función . Un “dominio variable de anticuerpo sencillo” es un dominio polipeptídico plegado que comprende secuencias características de dominios variables de anticuerpos. Por lo tanto incluye dominios variables de anticuerpo completos y dominios variables modificados, por ejemplo, en los que uno o más bucles

se han reemplazado por secuencias que no son características de dominios variables de anticuerpos, o dominios variables de anticuerpo que se han truncado o comprenden extensiones N o C-terminal, así como fragmentos plegados de dominios variables que conservan al menos la actividad y especificidad de unión del dominio de longitud completa.

En la presente solicitud, el término “prevención” y “prever” implica la administración de la composición protectora antes de la inducción de la enfermedad o afección. “Tratamiento” y “tratar” implica la administración de la composición protectora después de que comiencen a manifestarse los síntomas de la enfermedad o afección. “Supresión” o “suprimir” se refiere a la administración de la composición después de un suceso inductivo, pero antes de la aparición clínica de la enfermedad o afección.

Como se usa en este documento, el término “dosis” se refiere a la cantidad de ligando administrado a un sujeto toda al mismo tiempo (dosis unitaria) o en dos o más administraciones durante un intervalo de tiempo definido. Por ejemplo, dosis puede hacer referencia a la cantidad de ligando (por ejemplo, ligando que comprende un dominio variable sencillo de inmunoglobulina que se une al antígeno diana) administrada a un sujeto en el transcurso de un día (24 horas) (dosis diaria), dos días, una semana, dos semanas, tres semanas o uno o más meses (por ejemplo, mediante una administración única o mediante dos o más administraciones). El intervalo entre dosis puede ser cualquier cantidad de tiempo deseada. La expresión “farmacéuticamente eficaz” cuanto se refiere a una dosis significa la cantidad suficiente de ligando, dominio o agente farmacéuticamente activo para proporcionar el efecto deseado. La cantidad que es “eficaz” variará de sujeto en sujeto, dependiendo de la edad y estado general del individuo, el fármaco o agente farmacéuticamente activo particular y similar. Por tanto, no siempre es posible especificar una cantidad “eficaz” exacta que pueda aplicarse a

todos los pacientes. Sin embargo, usando experimentación rutinaria, un experto en la materia puede determinar una dosis “eficaz” apropiada en cualquier caso individual.

Para un experto en la materia serán familiares los métodos para realizar el análisis farmacocinético y para determinar la semivida del ligando (por ejemplo, dominio variable sencillo, proteína de fusión o ligando multiespecífico). Pueden encontrarse más detalles en *Kenneth, A y col*: Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists y en *Peters y col*, Pharmacokinetc analysis: A Practical Approach (1996). También se hace referencia a “Pharmacokinetics”, M Gibaldi & D Perron, publicado por Marcel Dekker, 2ª Rev. edición ex. (1982), que describe parámetros farmacocinéticos tales como semividas t alfa y t beta y el área bajo la curva (AUC). Opcionalmente, todos los parámetros y los valores farmacocinéticos indicados en este documento deben interpretarse como valores en un ser humano. Opcionalmente, todos los parámetros y valores farmacocinéticos indicados en este documento deben interpretarse como valores en ratón, rata o mono *Cynomolgus.*

Las semividas (t½ alfa y t½ beta) y el AUC pueden determinarse a partir una curva de la concentración en suero del ligando frente al tiempo. Para realizar el modelo de la curva, puede usarse, por ejemplo, el paquete de análisis WinNonlin, por ejemplo versión 5.1 (disponible de Pharsight Corp., Mountain View, CA94040, USA). Cuando se usan modelos de dos compartimentos, en una primera fase (la fase alfa) el ligando se distribuye principalmente en el paciente, con alguna eliminación. Una segunda fase (fase beta) es la fase en la que el ligando se ha distribuido y la concentración en suero va disminuyendo a medida que el paciente va eliminando el ligando. La semivida t alfa es la semivida de la primera fase y la semivida t beta es la semivida de la segunda fase. Por tanto, en una realización, en el contexto de la presente invención, el dominio variable, proteína de fusión o ligando tiene una semivida tα en el intervalo de (o de

aproximadamente) 15 minutos o más. En una realización, el límite inferior del intervalo es (o aproximadamente es) 30 minutos, 45 minutos, 1 hora, 2 horas, 3 horas, 4 horas, 5 horas, 6 horas, 7 horas, 10 horas, 11 horas o 12 horas. Adicionalmente, o de manera alternativa, el dominio variable, proteína de fusión o ligando de acuerdo con la invención tendrá una semivida $t\alpha$ en el intervalo de hasta e incluyendo 12 horas (o aproximadamente 12 horas). En una realización, el límite superior del intervalo es (o aproximadamente es) 11, 10, 9, 8, 7, 6 ó 5 horas. Un ejemplo de un intervalo adecuado es (o es aproximadamente) de 1 a 6 horas, de 2 a 5 horas o de 3 a 4 horas.

En una realización, la presente invención proporciona el dominio variable, proteína de fusión o ligando de acuerdo con la invención que tiene una semivida $t\beta$ en el intervalo de (o de aproximadamente) 2,5 horas o más. En una realización, el límite inferior del intervalo es (o es aproximadamente) 3 horas, 4 horas, 5 horas, 6 horas, 7 horas, 10 horas, 11 horas o 12 horas. Adicionalmente, o de manera alternativa, la semivida $t\beta$ es (o es aproximadamente) de hasta e incluyendo 21 ó 25 días. En una realización, el límite superior del intervalo es (o es aproximadamente) 12 horas, 24 horas, 2 días, 3 días, 5 días, 10 días, 15 días, 19 días, 20 días, 21 días o 22 días. Por ejemplo, el dominio variable, proteína de fusión o ligando de acuerdo con el invención tendrá una semivida $t\beta$ en el intervalo de 12 a 60 horas (o aproximadamente de 12 a 60 horas). En una realización adicional, estará en el intervalo de 12 a 48 horas (o aproximadamente de 12 a 48 horas). Aún en otra realización adicional, estará en el intervalo de 12 a 26 horas (o aproximadamente de 12 a 26 horas).

Como una alternativa al uso de modelos de dos compartimentos, el experto en la materia estará familiarizado con el uso de modelos no compartimentales, que pueden usarse para determinar semividas terminales (en este sentido, la expresión “semivida terminal” como se usa en este documento significa una semivida terminal determinada

usando modelos no compartimentales). Para realizar el modelo de la curva de esta manera, puede usarse, por ejemplo, el paquete de análisis WinNonlin, por ejemplo versión 5.1 (disponible de Pharsight Corp., Mountain View, CA94040, USA). En este ejemplo, en una realización el dominio variable sencillo, proteína de fusión o ligando tiene una semivida terminal de al menos (o de al menos aproximadamente) 8 horas, 10 horas, 12 horas, 15 horas, 28 horas, 20 horas, 1 día, 2 días, 3 días, 7 días, 14 días, 15 días, 16 días, 17 días, 18 días, 19 días, 20 días, 21 días, 22 días, 23 días, 24 días o 25 días. En una realización, el límite superior de este intervalo es (o es aproximadamente) 24 horas, 48 horas, 60 horas o 72 horas o 120 horas. Por ejemplo, la semivida terminal es (o es aproximadamente) 8 horas a 60 horas, o de 8 horas a 48 horas o de 12 horas a 120 horas, por ejemplo, en un ser humano.

Además, o como alternativa al criterio anterior, el dominio variable, proteína de fusión o ligando de acuerdo con la invención tiene un valor AUC (área bajo la curva) en el intervalo de (o de aproximadamente) 1 mg.min/ml o más. En una realización, el límite inferior del intervalo es (o es aproximadamente) 5, 10, 15, 20, 30, 100, 200 ó 300 mg.min/ml. Adicionalmente, o de manera alternativa, el dominio variable, proteína de fusión o ligando de acuerdo con la invención tiene una AUC en el intervalo de (o de aproximadamente) hasta 600 mg.min/ml o más. En una realización, el límite superior del intervalo es (o es aproximadamente) 500, 400, 300, 200, 150, 100, 75 ó 50 mg.min/ml. Ventajosamente, el dominio variable, proteína de fusión o ligando tendrá una AUC en (o aproximadamente en) el intervalo seleccionado del grupo que consiste en: de 15 a 150 mg.min/ml, de 15 a 100 mg.min/ml, de 15 a 75 mg.min/ml y de 15 a 50 mg.min/ml.

“Resonancia de Plasmón Superficial”: Pueden usarse ensayos de competición para determinar si un antígeno o epítope específico, tal como albúmina de suero humana, compite con otro antígeno o epítope, tal como albúmina de suero de mono

Cynomolgus, para unirse a un ligando de unión a albúmina de suero descrito en este documento, tal como un dAb específico. De manera similar pueden usarse ensayos de competición para determinar si un primer ligando tal como dAb, compite con un segundo ligando tal como un dAb de unión a un antígeno o epítope diana. El término “compite” como se usa en este documento se refiere a una sustancia, tal como una molécula, compuesto, preferiblemente una proteína, que es capaz de interferir a cualquier grado con la interacción de unión especifica entre dos o más moléculas. La frase “no se inhibe de manera competitiva” significa que la sustancia, tal como una molécula, compuesto, preferiblemente una proteína, no interfiere a ningún grado cuantificable o significativo con la interacción de unión especifica entre dos o más moléculas. La interacción de unión especifica entre dos o más moléculas incluye preferiblemente la interacción de unión específica entre un dominio variable sencillo y su compañero o diana afín. La molécula interferente o competidora puede ser otro dominio variable sencillo o puede ser una molécula que sea estructuralmente y/o funcionalmente similar a un compañero o diana afín.

La expresión “resto de unión” se refiere a un dominio que se une específicamente a un antígeno o epítope independientemente de un dominio de unión a antígeno o epítope diferente. Un resto de unión puede ser un anticuerpo de dominio (dAb) o puede ser un dominio que es un derivado de un armazón de proteína no inmunoglobulina, por ejemplo, un armazón seleccionado del grupo que consiste CTLA-4, lipocalín, SpA, una adnectina, affibody, un avímero, GroEl, transferrina, GroES y fibronectina, que se une a un ligando que no es el ligando natural (en el caso de la presente invención, en el resto se une a albúmina de suero). Véase el documento WO2008/096158, que describe ejemplos de armazones de proteínas y métodos para seleccionar dominios de unión específicos a antígeno o epítope a partir de repertorios

(véanse los Ejemplos 17 a 25). Estas descripciones específicas del documento WO2008/096158 se incorporan expresamente como referencia en esta memoria descriptiva y se describen explícitamente en esta y para usar con la presente invención y se contempla que puede incorporarse cualquier parte de dicha descripción en una o más reivindicaciones en este documento.

En un aspecto, la invención proporciona una variante de dominio variable sencilla de inmunoglobulina anti-albúmina de suero (SA) de DOM7h-11, en el que la variante comprende al menos una mutación en la unión FW2/CDR2 (posiciones 49 a 51, numeración de acuerdo con Kabat) en comparación con DOM7h-11 y en el que la variante tiene de 2 a 8 cambios en comparación con la secuencia de aminoácidos de DOM7h-11. Opcionalmente, la posición 49 (de acuerdo con Kabat) es Leu. De manera adicional o como alternativa, la posición 50 (de acuerdo con Kabat) es opcionalmente Ala o Trp. Adicionalmente o como alternativa, la posición 51 (de acuerdo con Kabat) es opcionalmente Phe o Asn. En una realización, la variante comprende una mutación en cada una de las posiciones 49, 50 y 51 (numeración de acuerdo con Kabat) en comparación con DOM7h-11. En una realización, la variante comprende un motivo LFG, en el que L está en la posición 49 (numeración de acuerdo con Kabat), en el que L, F y G son Leu, Phe y Gly respectivamente.

En una realización, la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de un dominio variable sencillo seleccionado de DOM7h-11-3, DOM7h-11-15, DOM7h-11-12 y DOM7h-11-19 o tiene hasta 4 cambios en comparación con la secuencia de aminoácidos seleccionada, mientras que la secuencia de aminoácidos de la variante tiene al menos una mutación en la unión FW2/CDR2 como se ha definido anteriormente. En una realización, la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de DOM7h-

11-15^{S12P} o tiene hasta 4 cambios en comparación con la secuencia de aminoácidos de DOM7h-11-15^{S12P}, mientras que la secuencia de aminoácidos de la variante tiene al menos una mutación en la unión FW2/CDR2 (posiciones 49 a 51, numeración de acuerdo con Kabat). En una realización, la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de un dominio variable sencillo seleccionado de DOM7h-11-3 o tiene hasta 4 cambios en comparación con la secuencia de aminoácidos seleccionada, mientras que la secuencia de aminoácidos de la variante tiene L en la posición 49, W en la posición 50 y N en la posición 51. En una realización, la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de un dominio variable sencillo seleccionado de DOM7h-11-12, o tiene hasta 4 cambios en comparación con la secuencia de aminoácidos seleccionada, mientras que la secuencia de aminoácidos de la variante tiene M en la posición 32 y L en la posición 49. En una realización, la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de un dominio variable sencillo seleccionado de DOM7h-11-15 o DOM7h-11-15^{SP12}, o tiene hasta 4 cambios en comparación con la secuencia de aminoácidos seleccionada, mientras que la secuencia de aminoácidos de la variante tiene M en la posición 32, L en la posición 49, A en la posición 50 y F en la posición 51. En una realización, la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de un dominio variable sencillo seleccionado de DOM7h-11-18, o tiene hasta 4 cambios en comparación con la secuencia de aminoácidos seleccionada, mientras que la secuencia de aminoácidos de la variante tiene M en la posición 32 y H en la posición 87. En una realización, la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de un dominio variable sencillo seleccionado de DOM7h-11-19 o tiene hasta 4 cambios en comparación con la secuencia de aminoácidos

seleccionada, mientras que la secuencia de aminoácidos de la variante tiene M en la posición 32, L en la posición 49 y T en la posición 91. Todas las numeraciones de este párrafo son de acuerdo con Kabat.

Un aspecto de la invención proporciona una variante del dominio variable sencillo de inmunoglobulina anti-albúmina de suero (SA) de DOM7h-11, en el que la variante comprende una Met en la posición 32 (numeración de acuerdo con Kabat) en comparación con DOM7h-11, y en la que la variante tiene de 0 a 4 cambios adicionales en comparación con la secuencia de aminoácidos de DOM7h-11. Opcionalmente, la variante comprende al menos una mutación en la unión FW2/CDR2 (posiciones 49 a 51, numeración de acuerdo con Kabat) en comparación con DOM7h-11.

En una realización de cualquier aspecto de la invención, la variante comprende al menos una mutación en comparación con DOM7h-11 seleccionada de las siguientes posiciones:

Posición 49 = L,

Posición 50 = A o W,

Posición 51 = F o N,

Posición 87 = H, y

Posición 91 = T.

En una realización, la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de un dominio variable sencillo seleccionado de DOM7h-11-12, DOM7h-11-15, DOM7h-11-15^{S12P}, DOM7h-11-18 y DOM7h-11-19 o tiene hasta 4 cambios en comparación con la secuencia de aminoácidos seleccionada, mientras que la secuencia de aminoácidos de la variante tiene Met en la posición 32.

En una realización, la variante comprende una más de las siguientes características cinéticas:

(a) La variante comprende un sitio de unión que se une específicamente a SA humana con una constante de disociación (KD) de (o de aproximadamente) 0,1 a (o a aproximadamente) 10.000 nM, opcionalmente de (o de aproximadamente) 1 a (o a aproximadamente) 6.000 nM, determinada de acuerdo con la resonancia de plasmón superficial;

(b) La variante comprende un sitio de unión que se une específicamente a SA humana con una constante de velocidad de disociación (K_d) de (o de aproximadamente) 1,5 x 10^{-4} a (o de aproximadamente a) 0,1 s^{-1}, opcionalmente de (o de aproximadamente) 3 x 10^{-4} a (o de aproximadamente a) 0,1 s^{-1} determinada de acuerdo con la resonancia de plasmón superficial;

(c) La variante comprende un sitio de unión que se une específicamente a SA humana con una constante de velocidad de asociación (K_a) de (o de aproximadamente) 2 x 10^6 a (o de aproximadamente a) 1 x 10^4 $M^{-1}s^{-1}$, opcionalmente de (o de aproximadamente) 1 x 10^6 a (o de aproximadamente a) 2 x 10^4 $M^{-1}s^{-1}$ determinada de acuerdo con la resonancia de plasmón superficial;

(d) La variante comprende un sitio de unión que se une específicamente a SA de mono Cy*nomolgus* con una constante de disociación (KD) de (o de aproximadamente) 0,1 a (o a aproximadamente) 10.000 nM, opcionalmente de (o de aproximadamente) 1 a (o a aproximadamente) 6.000 nM, determinada de acuerdo con la resonancia de plasmón superficial;

(e) La variante de cualquier reivindicación anterior, en la que la variante comprende un sitio de unión que se une específicamente a SA de mono Cy*nomolgus* con una constante de velocidad de disociación (K_d) de (o de aproximadamente) 1,5 x 10^{-4} a (o a aproximadamente) 0,1 s^{-1} opcionalmente de (o de aproximadamente) 3 x 10^{-4} a (o a aproximadamente) 0,1 s^{-1}, determinada de acuerdo con la resonancia de plasmón

superficial;

(f) La variante de cualquier reivindicación anterior, en la que la variante comprende un sitio de unión que se une específicamente a SA de mono Cy*nomolgus* con una constante de velocidad de asociación (K_a) de (o de aproximadamente) 2 x 10^6 a (o a aproximadamente) 1 x 10^4 $M^{-1}s^{-1}$, opcionalmente de (o de aproximadamente) 1 x 10^6 a (o a aproximadamente) 5 x 10^3 $M^{-1}s^{-1}$, determinada de acuerdo con la resonancia de plasmón superficial;

(g) La variante comprende un sitio de unión que se une específicamente a SA de rata con una constante de disociación (KD) de (o de aproximadamente) 1 a (o a aproximadamente) 10.000 nM, opcionalmente de (o de aproximadamente) 20 a (o a aproximadamente) 6.000 nM, determinada de acuerdo con la resonancia de plasmón superficial;

(h) La variante comprende un sitio de unión que se une específicamente a SA de rata con una constante de velocidad de disociación (K_d) de (o de aproximadamente) 2 x 10^{-3} a (o a aproximadamente) 0,15 s^{-1}, opcionalmente de (o de aproximadamente) 9 x 10^{-3} a (o a aproximadamente) 0,14 s^{-1}, determinada de acuerdo con la resonancia de plasmón superficial;

(i) La variante comprende un sitio de unión que se une específicamente a SA de rata con una constante de velocidad de asociación (K_a) de (o de aproximadamente) 2 x 10^6 a (o a aproximadamente) 1 x 10^4 $M^{-1}s^{-1}$, opcionalmente de (o de aproximadamente) 1 x 10^6 a (o a aproximadamente) 3 x 10^4 $M^{-1}s^{-1}$, determinada de acuerdo con la resonancia de plasmón superficial;

(j) La variante comprende un sitio de unión que se une específicamente a SA de ratón con una constante de disociación (KD) de (o de aproximadamente) 1 a (o a aproximadamente) 10.000 nM , determinada de acuerdo con la resonancia de plasmón

superficial;

(k) La variante comprende un sitio de unión que se une específicamente a SA de ratón con una constante de velocidad de disociación (K_d) de (o de aproximadamente) 2 x 10^{-3} a (o a aproximadamente) 0,15 s^{-1}, determinada de acuerdo con la resonancia de plasmón superficial; y/o

(l) La variante comprende un sitio de unión que se une específicamente a SA de ratón con una constante de velocidad de asociación (K_a) de (o de aproximadamente) 2 x 10^6 a (o a aproximadamente) 1 x 10^4 $M^{-1}s^{-1}$, opcionalmente de (o de aproximadamente) 2 x 10^6 a (o a aproximadamente) 1,5 x 10^4 $M^{-1}s^{-1}$ determinada de acuerdo con la resonancia de plasmón superficial;

Opcionalmente la variante tiene

I: una KD de acuerdo con (a) y (b), una K_d de acuerdo con (b) y (e) y una K_a de acuerdo con (c) y (f); o

II: una KD de acuerdo con (a) y (g), una K_d de acuerdo con (b) y (h) y una K_a de acuerdo con (c) e (i); o

III: una KD de acuerdo con (a) y (j), una K_d de acuerdo con (b) y (k) y una K_a de acuerdo con (c) y (l); o

IV: cinética de acuerdo con I y II; o

V: cinética de acuerdo con I y III; o

VI: cinética de acuerdo con I, II y III.

La invención también proporciona un ligando que comprende una variante de cualquier aspecto o realización anterior de la invención. Por ejemplo, el ligando puede ser un ligando dual específico (para ejemplos de ligandos de especificidad dual, véase el documento WO04003019). En un aspecto, la invención proporciona un ligando multiespecífico que comprende una variante anti-SA de cualquier aspecto o realización

anterior de la invención y un resto de unión que se une específicamente a un antígeno diana distinto de SA. El resto de unión puede ser cualquier resto de unión que se una específicamente a una diana, por ejemplo, el resto es un anticuerpo, fragmento de anticuerpo, scFv, Fab, dAb o un resto de unión que comprende un armazón de proteína no inmunoglobulina. Dichos restos se describen con detalle en el documento WO2008/096158 (véanse los ejemplos 17 a 25, cuya descripción se incorpora en este documento como referencia). Son ejemplos de armazones de proteínas no inmunoglobulina CTLA-4, lipocalina, proteína A estafilococal (spA), Affibody™, Avimers™, adnectinas, GroEL y fibronectinas.

En una realización, se proporciona un engarce entre el resto de unión anti-diana y la variante sencilla anti-SA, comprendiendo el engarce la secuencia de aminoácidos AST, opcionalmente ASTSGPS. Engarces alternativos se describen en el documento WO200708814 (incorporado en este documento como referencia) y en el documento WO2008/096158 (véase el pasaje de la página 135, de la línea 12 a la página 140, línea 14, cuya descripción y todas las secuencias de engarces se incorporan expresamente en este documento como referencia y incluyen explícitamente en este documento y para usar con la presente invención y se contempla que cualquier parte de dicha descripción puede incorporarse en una o más de las reivindicaciones de este documento).

En una realización del ligando multiespecífico, el antígeno diana puede ser, o ser parte de, polipéptidos, proteínas o ácidos nucleicos, que pueden ser de origen natural o sintéticos. En este aspecto, el ligando de la invención puede unirse al antígeno diana y actuar como un antagonista o agonista (por ejemplo, agonista del receptor EPO). Un experto en la materia apreciará que la elección es amplia y variada. Pueden ser por ejemplo, proteínas de seres humanos o animales, citocinas, receptores de citocinas, en los que los receptores de citocinas incluyen receptores para citocinas, enzimas, co-

factores para enzimas o proteínas de unión a ADN. Las citocinas y factores de crecimiento adecuados incluyen, pero preferiblemente sin limitación: ApoE, Apo-SAA, BDNF, Cardiotropina-1, EGF, receptor de EGF, ENA-78, Eotaxina, Eotaxina-2, Exodus-2, EpoR, FGF-ácido, FGF-básico, factor 10 del crecimiento de fibroblasto, ligando FLT3, Fractalkina (CX3C), GDNF, G-CSF, GM-CSF, GF-β1, insulina, IFN-γ, IGF-I, IGF-II, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8 (72 a.a.), IL-8 (77 a.a.), IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-16, IL-17, IL-18 (IGIF), Inhibina α, Inhibina β, IP-10, factor 2 del crecimiento de queratocitos (KGF-2), KGF, Leptina, LIF, Linfotactina, sustancia inhibidora de Müllerian, factor inhibidor de colonias de monocitos, proteína atrayente de monocitos, M-CSF, MDC (67 a.a.), MDC (69 a.a.), MCP-1 (MCAF), MCP-2, MCP-3, MCP-4, MDC (67 a.a.), MDC (69 a.a.), MIG, MIP-1α, MIP-1β, MIP-3α, MIP-3β, MIP-4, factor 1 inhibidor de progenitores mieloides (MPIF-1), NAP-2, Neurturina, factor del crecimiento Nervioso, β-NGF, NT-3, NT-4, Oncostatina M, PDGF-AA, PDGF-AB, PDGF-BB, PF-4, RANTES, SDF1α, SDF1β, SCF, SCGF, factor de células madre (SCF), TARC, TGF-α, TGF-β, TGF-β2, TGF-β3, factor de necrosis tumoral (TNF), TNF-α, TNF-β, receptor I de TNF, receptor II de TNF, TNIL-1, TPO, VEGF, receptor 1 de VEGF, receptor 2 de VEGF, receptor 3 de VEGF, GCP-2, GRO/MGSA, GRO-β, GRO-γ, HCC1, 1-309, HER 1, HER 2, HER 3 y HER 4, CD4, receptores de quimioquina humana CXCR4 o CCR5, proteína no estructural de tipo 3 (NS3) del virus de la hepatitis C, TNF-alfa, IgE, IFN-gamma, MMP-12, CEA, *H. pylori*, TB, gripe, Hepatitis E, MMP-12, receptores de internalización que se sobrexpresan en determinadas células, tales como el receptor del factor del crecimiento epidérmico (EGFR), receptor de ErBb2 en células tumorales, un receptor celular internalizador, receptor de LDL, receptor de FGF2, receptor de ErbB2, receptor de transferrina, receptor de PDGF, receptor de VEGF, PsmAr, una proteína matriz extracelular, elastina, fibronectina, laminina, antitripsina-α1,

inhibidor proteasa del factor tisular, PDK1, GSK1, Bad, caspasa-9, Forkhead, un antígeno de *Helicobacter pylori*, un antígeno de *Mycobacterium tuberculosis*, y un antígeno del virus de la gripe. Deberá apreciarse de que esta enumeración no es exhaustiva.

En una realización, el ligando multiespecífico comprende una variante dAb anti-SA de la invención y un resto de unión anti-TNFR1, por ejemplo, un dAb anti-TNFR1. Opcionalmente, el ligando sólo tiene un resto de unión anti-TNFR1 (por ejemplo, dAb) para reducir la posibilidad de entrecruzamiento del receptor. Una realización, la variante dAb anti-SA es DOM7h-11-3 o DOM7h-11-15 o DOM7h-11-15^{S12P}.

En una realización, el resto de unión anti-TNFR1 es DOM1h-131-206 descrito en el documento WO2008149148 (cuya secuencia de aminoácidos y nucleótidos se describe en esta solicitud PCT, incorporada expresamente en este documento como referencia así como incluida explícitamente en este documento y para usar con la presente invención y se contempla que cualquier parte de dicha descripción pueda incorporarse en una o más de las reivindicaciones en este documento). En una realización, el ligando multiespecífico comprende o consiste en la secuencia de aminoácidos de DOM1h-131-206 y la secuencia de aminoácidos de DOM7h-11-3 o DOM7h-11-15 o DOM7h-11-15^{S12P}.

En una realización, el resto de unión anti-TNFR1 o dAb es cualquiera de dicho resto o dAb descrito en la solicitud en trámite junto con la presente USSN 61/153.746, cuya descripción se incorpora en este documento como referencia. En una realización, el resto de unión anti-TNFR1 comprende una secuencia de aminoácidos que es al menos el 95% idéntica a la secuencia de aminoácidos de DOM1h-574-156, DOM1h-574-72, DOM1h-574-109, DOM1h-574-138, DOM1h-574-162 o DOM1h-574-180 o la secuencia de aminoácidos de cualquier dAb anti-TNFR1 descrita en la Tabla 3. En una

realización, el ligando multiespecífico comprende o consiste en la secuencia de aminoácidos de DOM1h-574-156 y la secuencia de aminoácidos de DOM7h-11-3 o DOM7h-11-15 o DOM7h-11-15^{S12P}.

En una realización, el ligando de la invención es una proteína de fusión que comprende una variante de la invención fusionada directa o indirectamente a uno o más polipéptidos. Por ejemplo, la proteína de fusión puede ser una “fusión a fármaco” como se describe en el documento WO2005/118642 (cuya descripción se incorpora en este documento como referencia), que comprende una variante de la invención y un fármaco polipeptídico como se define en esa solicitud PCT.

Como se usa en este documento, “fármaco” se refiere a cualquier compuesto (por ejemplo, molécula orgánica pequeña, ácido nucleico, polipéptido) que puede administrarse a un individuo para producir un efecto benéfico, terapéutico o de diagnóstico mediante la unión a y/o modificando la función de una molécula diana biológica en el individuo. La molécula diana puede ser una molécula diana endógena codificada por el genoma del individuo (por ejemplo una enzima, receptor, factor de crecimiento, citocina codificada por el genoma del individuo) o una molécula diana exógena codificada por el genoma de un patógeno (por ejemplo una enzima codificada por el genoma de un virus, bacteria, hongo, nematodo u otro patógeno). Los fármacos adecuados para usar en las proteínas y conjugados de fusión comprenden una variante de dAb anti-SA de la invención se describe en el documento WO2005/118642 y en el documento WO2006/059106 (cuya descripción completa se incorpora en este documento como referencia e incluye la lista completa de fármacos específicos aunque también esta lista se escribe en este documento expresamente y se contempla que dicha incorporación proporciona una descripción de fármacos específicos para incluir en las reivindicaciones de este documento). Por ejemplo, el fármaco puede ser péptido 1 de

tipo glucagón (GLP-1) o una variante, alfa interferón 2b o una variante o exendina-4 o una variante.

En una realización, la invención proporciona un conjugado de fármaco como se define y se describe en el documento WO2005/118642 y en el documento WO2006/059106, en el que el conjugado comprende una variante de la invención. En un ejemplo, el fármaco está unido de manera covalente a la variante (por ejemplo, la variante y el fármaco se expresan como parte de un polipéptido sencillo).

De manera alternativa, en un ejemplo, el fármaco no está unido o asociado de manera covalente a la variante. El fármaco puede estar unido de manera covalente o no covalente a la variante de manera directa o indirecta (por ejemplo, mediante un engarce adecuado y/o mediante unión no covalente de compañeros de unión complementarios (por ejemplo, biotina y avidina)). Cuando se emplean compañeros de unión complementarios, uno de los compañeros de unión puede unirse de manera covalente al fármaco directamente o mediante un resto de engarce adecuado y el compañero de unión complementario puede unirse de manera covalente a la variante directamente o mediante un resto de engarce adecuado. Cuando el fármaco es un polipéptido o péptido, la composición del fármaco puede ser una proteína de fusión, en la que el polipéptido o péptido, fármaco y el resto de unión a polipéptido son partes específicas (restos) de una cadena polipeptídica continua. Como se describe en este documento, los restos de unión al polipéptido y los restos de fármaco polipeptídicos pueden unirse directamente entre sí mediante un enlace peptídico, o unirse mediante un aminoácido, péptido o engarce polipeptídico adecuado.

Un ligando que contiene una variante (monómero) de dominio variable sencillo de la invención o más de un dominio variable sencillo (multímero, proteína de fusión, conjugado y ligando de especificidad dual como se define este documento) que se une

específicamente a la albúmina de suero, puede comprender adicionalmente una o más entidades seleccionadas de, pero preferiblemente no limitadas, un marcador, una etiqueta, un dominio variable sencillo adicional, un dAb, un anticuerpo, un fragmento de anticuerpo, un marcador y un fármaco. Una o más de estas entidades puede localizarse en el extremo COOH o en el extremo N o en ambos extremos N y COOH del ligando que comprende el dominio variable sencillo, (de dominio variable sencillo de inmunoglobulina o no inmunoglobulina). Una o más de estas entidades puede localizarse en el extremo COOH, o en el extremo N, o en ambos extremos N y COOH del dominio variable sencillo que se une específicamente a la albúmina de suero del ligando que contiene un dominio variable sencillo (monómero) o más de un dominio variable sencillo (multímero, proteína de fusión, conjugado y ligando de especificidad dual como se define en este documento). Los ejemplos no limitantes de etiquetas que pueden posicionarse en uno o ambos de estos extremos incluyen una etiqueta HA, his o una myc. Las entidades, que incluyen una o más etiquetas, marcadores y fármacos, pueden unirse al ligando que contiene un dominio variable sencillo (monómero) o más de un dominio variable sencillo (multímero, proteína de fusión, conjugado y ligando de especificidad dual como se define en este documento) que se une a la albúmina de suero, de manera directa o mediante engarces como se describe anteriormente.

Un aspecto de la invención proporciona un producto de fusión, por ejemplo, una proteína de fusión o fusión con un péptido o conjugado con un fármaco NCE (nueva entidad química) que comprende un fármaco polipeptídico fusionado o conjugado (para un NCE) a cualquier variante como se describe anteriormente, en la que la variante es opcionalmente DOM7h-11-15 o DOM7h-11-15^{S12P} (o una variante que tiene una identidad de secuencia de aminoácidos de al menos el 95, 96, 97, 98 ó 99% con la secuencia de aminoácidos de DOM7h-11-15 o DOM7h-11-15^{S12P}) o DOM7h-11-12 (o

una variante que tiene una identidad de secuencia de al menos el 95, 96, 97, 98 ó 99% con la secuencia de aminoácidos de DOM7h-11-15 o DOM7h-11-15^{S12P}). DOM7h-11-15, DOM7h-11-15^{S12P} y DOM7h-11-12 producen únicamente una modesta disminución de afinidad cuando se fusionan o se conjugan con el compañero haciéndoles útiles en los productos de fusión.

La invención proporciona una composición que comprende una variante, proteína de fusión, conjugado o ligando de cualquier aspecto de la invención y un diluyente, transportador, excipiente o vehículo farmacéuticamente aceptable.

También se incluye en este documento un ácido nucleico aislado que codifica cualquiera de las variantes, proteínas de fusión, conjugados o ligandos descritos en este documento, por tanto, un ligando que contiene una variante de dominio variable sencillo (monómero) de la invención o más de una variante de dominio variable sencillo (por ejemplo, multimérico, proteína de fusión, conjugado, y ligando de especificidad dual como se define en este documento) que se une específicamente a la albúmina de suero o que se une específicamente a la albúmina de suero humana y al menos a una albúmina de suero no humana o fragmentos funcionalmente activos de los mismos. También se incluye en este documento un vector y/o un vector de expresión, una célula huésped que comprende el vector, por ejemplo, una célula vegetal o animal y/o una línea celular transformada con un vector, un método de expresión y/o de producción de una o más variantes, proteínas de fusión o ligandos que contienen una variante de dominio variable sencillo (monómero) o más de una variante de dominio variable sencillo (por ejemplo, multimérico, proteína de fusión, conjugado, y ligando específico dual como se define en este documento) que se une específicamente a la albúmina de suero, o fragmento (o fragmentos) de la misma codificada por dichos vectores, que incluye en algunos casos cultivar la célula huésped de manera que la una o más variantes,

proteínas de fusión, ligandos o fragmentos de los mismos se expresen y opcionalmente recuperen el ligando que contiene un dominio variable sencillo (monómero) o más de un dominio de variable sencillo (por ejemplo, multimérico, proteína de fusión, conjugado, y ligando específico dual como se define en este documento) que se une específicamente a la albúmina de suero, del medio de cultivo de la célula huésped. También se incluyen métodos para poner en contacto un ligando descrito en este documento con albúmina de suero, que incluye albúmina de suero y/o albúmina (o albúminas) de suero no humanas, y/o una o más dianas distintas de la albúmina de suero, en la que las dianas incluyen moléculas biológicamente activas e incluyen proteínas de animales, citocinas como las enumeradas anteriormente e incluyen métodos en los que el poner en contacto se realiza *in vitro* así como la administración de cualquiera de las variantes, proteínas de fusión o ligandos descritos en este documento a un animal huésped individual o célula *in vitro* y/o *ex vivo*. Preferiblemente, la administración de ligandos descritos en este documento que comprenden un dominio de variable sencillo (inmunoglobulina o no inmunoglobulina) dirigidos a la albúmina de suero y/o albúmina (o albúminas) de suero no humanas, y uno o más dominios dirigidos a una o más dianas distintas a la albúmina de suero, aumentarán la semivida, incluyendo la semivida T beta y/o terminal del ligando anti-diana. Las moléculas de ácido nucleico que codifican las variantes, proteínas de fusión o dominios sencillos que contienen ligandos o fragmentos de los mismos, incluyendo fragmentos funcionales de los mismos, se contemplan en este documento. Los vectores que codifican las moléculas de ácido nucleico que incluyen pero preferiblemente no limitan vectores de expresión, se contemplan en este documento, como también células huésped de una línea celular u organismo que contiene uno o más de estos vectores de expresión. También se contemplan métodos para producir cualquier variante, proteína de fusión o ligando, incluyendo, pero preferiblemente sin

limitación, cualquiera de los ácidos nucleicos, vectores y células huésped mencionadas anteriormente.

Un aspecto de la invención proporciona un ácido nucleico que comprende una secuencia de nucleótidos que codifica una variante de acuerdo con la invención o un ligando multiespecífico de la invención o una proteína de fusión de la invención.

Un aspecto de la invención proporciona un ácido nucleico que comprende la secuencia de nucleótidos de una variante de DOM7h-11 seleccionada de DOM7h-11-3, DOM7h-11-15, DOM7h-11-15^{S12P}, DOM7h-11-12, DOM7h-11-18 y DOM7h-11-19 o una secuencia de nucleótidos que es al menos 70, 75, 80, 85, 90, 95, 96, 97, 98 ó 99% idéntica a dicha secuencia seleccionada.

Un aspecto de la invención proporciona un vector que comprende el ácido nucleico de la invención. Un aspecto de la invención proporciona una célula huésped aislada que comprende el vector.

Se hace referencia al documento WO2008/096158 para detalles de sistemas de vectores de bibliotecas, combinación de dominios variables sencillos, caracterización de ligandos específicos duales, estructura de ligandos específicos duales, armazones para usar en la construcción de ligandos específicos duales, usos de dAb anti-albúmina de suero y ligandos multiespecíficos y ligandos que mejoran la semivida y composiciones y formulaciones que comprenden dAb anti-albúmina de suero. Estas descripciones se incorporan en este documento como referencia para proporcionar una guía de uso con la presente invención, que incluyen variantes, ligandos, proteínas de fusión, conjugados, ácidos nucleicos, vectores, huéspedes y composiciones de la presente invención.

Las secuencias de la variante DOM7h-14, que no son de acuerdo con la invención, se describen en una Solicitud de Patente provisional de Estados Unidos en trámite junto con la presente titulada VARIANTES DE UNIÓN ANTI-ALBÚMINA DE

SUERO MEJORADAS, presentada el mismo día que la presente solicitud. Estas secuencias de las variantes de DOM7h-14 (SEC ID Nº: 1-10 en la solicitud en trámite junto con la presente) se incorporan en este documento como referencia como se ha descrito de forma explícita.

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SECUENCIAS

Tabla 1: Secuencias de Aminoácidos de dAbs Variante DOM7h-11

DOM7h-11-12 (SEC ID Nº: 1)

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILFGSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

DOM7h-11-15 (SEC ID Nº: 2)

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

DOM7h-11-18 (SEC ID Nº: 3)

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLIWFGSRLQSGV
P
SRFSGSGSGTDFTLTISSLQPEDFATYHCAQAGTHPTTFGQGTKVEIKR

DOM7h-11-19 (SEC ID Nº: 4)

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILFGSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQTGTHPTTFGQGTKVEIKR

DOM7h-11-3 (SEC ID Nº: 5)

DIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPKLLILWNSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Tabla 2: Secuencias de Nucleótidos de dAbs Variante DOM7h-11

DOM7h-11-12 (SEC ID Nº: 6)

GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGTACCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTTGTTT GGTTCCCGGT TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCGCAG GCTGGGACGC ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-11-15 (SEC ID Nº: 7)

GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGTACCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCCTTGCT TTTTCCCGTT TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGCGCGCAG GCTGGGACGC ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-11-18 (SEC ID Nº: 8)

GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGTACCA GCAGAAACCA GGGAAAGCCC CAAAGCTCCT GATCTGGTTT GGTTCCCGGT TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC

TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG CTACGTACCA CTGTGCGCAG GCGGGGACGC ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-11-19 (SEC ID Nº: 9)

GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGTACCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTTGTTT GGTTCCCGGT TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACGGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCGCAG ACTGGGACGC ATCCCACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

DOM7h-11-3 (SEC ID Nº: 10)

GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCGTGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGACGTTAA GTTGGTACCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCCTTTGG AATTCCCGTT TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGTGCGCAG GCTGGGACGC ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAATCAA ACGG

Tabla 3: Secuencias de Aminoácidos de dAbs anti-TNFR1

>DOM1h-509 (SEC ID Nº: 11)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSQYRMHWVRQAPGKSLEWVSSIDTRGS
STYYADPVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKAVTMFSPFFDYWGQGT
LVTVSS

>DOM1h-510 (SEC ID Nº: 12)

EVQLLESGGGLVQPGGSLRLSCAASGFTFADYGMRWVRQAPGKGLEWVSSITRTGR
VTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWRNRHGEYLADFDYW
GQGTLVTVSS

>DOM1h-543 (SEC ID Nº: 13)

EVQLLESGGGLVQPGGSLRLSCAASGFTFMRYRMHWVRQAPGKGLEWVSSIDSNGS
STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRTERSPVFDYWGQG
TLVTVSS

>DOM1h-549 (SEC ID Nº: 14)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVDYEMHWVRQAPGKGLEWVSSISESGTT
TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKRRFSASTFDYWGQGTLV
TVSS

>DOM1h-574 (SEC ID Nº: 15)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGHWEPFDYWGQGT
LVTVSS

>DOM1h-574-1 (SEC ID Nº: 16)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPYDYWGQGT
LVTVSS

>DOM1h-574-2 (SEC ID Nº: 17)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDYWGQGT
LVTVSS

>DOM1h-574-7 (SEC ID Nº: 18)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-8 (SEC ID Nº: 19)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-9 (SEC ID Nº: 20)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYMQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGT
LVTVSS

>DOM1h-574-10 (SEC ID Nº: 21)

EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKDLEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-11 (SEC ID Nº: 22)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGG
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDHWGQGT
LVTVSS

>DOM1h-574-12 (SEC ID Nº: 23)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDYWGQGT
LVTVSS

>DOM1h-574-13 (SEC ID Nº: 24)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDYWGQGT
LVTVSS

>DOM1h-574-14 (SEC ID Nº: 25)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-15 (SEC ID Nº: 26)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-16 (SEC ID Nº: 27)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-17 (SEC ID Nº: 28)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTGD
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-18 (SEC ID Nº: 29)

EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKDLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-19 (SEC ID Nº: 30)

EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKDLEWVSQISNTGD
HTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-25 (SEC ID Nº: 31)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTL
VTVSS

>DOM1h-574-26 (SEC ID Nº: 32)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFEYWGQGTL
VTVSS

>DOM1h-574-27 (SEC ID Nº: 33)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTL
VTVSS

>DOM1h-574-28 (SEC ID Nº: 34)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-29 (SEC ID Nº: 35)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTL
VTVSS

>DOM1h-574-30 (SEC ID Nº: 36)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAAYYCAIYTGRWEPFDYWGQGT
LVTVSS

>DOM1h-574-31 (SEC ID Nº: 37)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFNYWGQGTL
VTVSS

>DOM1h-574-32 (SEC ID Nº: 38)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-33 (SEC ID Nº: 39)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNSLYLQMNSLRAEDTAVYYCAIYTGRWVPFDNWGQGT
LVTVSS

>DOM1h-574-35 (SEC ID Nº: 40)

EVQLLESGGGLVQPGGSLRLSCAASGFTFITYSMGWVRQAPGKGLEWVSQISNTGDR
TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFQYWGQGTLV
TVSS

>DOM1h-574-36 (SEC ID Nº: 41)

EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-37 (SEC ID Nº: 42)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-38 (SEC ID Nº: 43)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGT
LVTVSS

>DOM1h-574-39 (SEC ID Nº: 44)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGT
LVTVSS

>DOM1h-574-40 (SEC ID Nº: 45)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFKYWGQGTL
VTVSS

>DOM1h-574-53 (SEC ID Nº: 46)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSKYSMGWVRQAPGKGLEWVSQISNTGE
RRYYADSVKGRFTISRDNPKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFEYWGQGT
LVTVSS

>DOM1h-574-54 (SEC ID Nº: 47)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVNYSMGWVRQAPGKGLEWVSQISNTGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPYEYWGQGTL
VTVTS

>DOM1h-574-65 (SEC ID Nº: 48)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-66 (SEC ID Nº: 49)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGT
LVTVSS

>DOM1h-574-67 (SEC ID Nº: 50)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGT
LVTVSS

>DOM1h-574-68 (SEC ID Nº: 51)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGT
LVTVSS

>DOM1h-574-69 (SEC ID Nº: 52)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-70 (SEC ID Nº: 53)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAVYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-71 (SEC ID Nº: 54)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTL
VTVSS

>DOM1h-574-72 (SEC ID Nº: 55)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-73 (SEC ID Nº: 56)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTL
VTVSS

>DOM1h-574-74 (SEC ID Nº: 57)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-75 (SEC ID Nº: 58)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-76 (SEC ID Nº: 59)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGT
LVTVSS

>DOM1h-574-77 (SEC ID Nº: 60)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGT
LVTVSS

>DOM1h-574-78 (SEC ID Nº: 61)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGT
LVTVSS

>DOM1h-574-79 (SEC ID Nº: 62)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-84 (SEC ID Nº: 63)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-85 (SEC ID Nº: 64)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGT
LVTVSS

>DOM1h-574-86 (SEC ID Nº: 65)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGT
LVTVSS

>DOM1h-574-87 (SEC ID Nº: 66)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGT
LVTVSS

>DOM1h-574-88 (SEC ID Nº: 67)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-90 (SEC ID Nº: 68)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKFSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-91 (SEC ID Nº: 69)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-92 (SEC ID Nº: 70)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-93 (SEC ID Nº: 71)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-94 (SEC ID Nº: 72)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAAYYCAIYTGRWPDFDYWGQGT
LVTVSS

>DOM1h-574-95 (SEC ID Nº: 73)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAAYYCAIYTGRWPDFEYWGQGT
LVTVSS

>DOM1h-574-96 (SEC ID Nº: 74)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFDYWGQGT
LVTVSS

>DOM1h-574-97 (SEC ID Nº: 75)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFEYWGQGTL
VTVSS

>DOM1h-574-98 (SEC ID Nº: 76)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFDYWGQGT
LVTVSS

>DOM1h-574-99 (SEC ID Nº: 77)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFEYWGQGT
LVTVSS

>DOM1h-574-100 (SEC ID Nº: 78)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISAWGD
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-101 (SEC ID Nº: 79)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDGGQ
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-102 (SEC ID Nº: 80)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDSGY
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-103 (SEC ID Nº: 81)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDGGT
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-104 (SEC ID Nº: 82)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDKGT
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-105 (SEC ID Nº: 83)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISETGR
RTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-106 (SEC ID Nº: 84)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQINNTGS
TTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTL
VTVSS

>DOM1h-574-107 (SEC ID Nº: 85)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL

VTVSS

>DOM1h-574-108 (SEC ID Nº: 86)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-109 (SEC ID Nº: 87)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-110 (SEC ID Nº: 88)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-111 (SEC ID Nº: 89)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGT
LVTVSS

>DOM1h-574-112 (SEC ID Nº: 90)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL

VTVSS

>DOM1h-574-113 (SEC ID Nº: 91)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RRYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-114 (SEC ID Nº: 92)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQILNTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-115 (SEC ID Nº: 93)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-116 (SEC ID Nº: 94)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RRYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-117 (SEC ID Nº: 95)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RRYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT

LVTVSS

>DOM1h-574-118 (SEC ID Nº: 96)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAVYTGRWVSFEYWGQGT
LVTVSS

>DOM1h-574-119 (SEC ID Nº: 97)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCALYTGRWVSFEYWGQGT
LVTVSS

>DOM1h-574-120 (SEC ID Nº: 98)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAVYTGRWVPFEYWGQGT
LVTVSS

>DOM1h-574-121 (SEC ID Nº: 99)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCALYTGRWVPFEYWGQGT
LVTVSS

>DOM1h-574-122 (SEC ID Nº: 100)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTAD
RRYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT

LVTVSS

>DOM1h-574-123 (SEC ID Nº: 101)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-124 (SEC ID Nº: 102)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGD
RRYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-125 (SEC ID Nº: 103)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTAD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-126 (SEC ID Nº: 104)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-127 (SEC ID Nº: 105)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTAD
RRYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT

LVTVSS

>DOM1h-574-128 (SEC ID Nº: 106)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTAD
RRYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-129 (SEC ID Nº: 107)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIVNTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-130 (SEC ID Nº: 108)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGD
RRYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-131 (SEC ID Nº: 109)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-132 (SEC ID Nº: 110)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGT

LVTVSS

>DOM1h-574-133 (SEC ID Nº: 111)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTL
VTVSS

>DOM1h-574-134 (SEC ID Nº: 112)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYSHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-135 (SEC ID Nº: 113)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-137 (SEC ID Nº: 114)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYTDAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTL
VTVSS

>DOM1h-574-138 (SEC ID Nº: 115)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL

VTVSS

>DOM1h-574-139 (SEC ID Nº: 116)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-140 (SEC ID Nº: 117)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTGD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-141 (SEC ID Nº: 118)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-142 (SEC ID Nº: 119)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-143 (SEC ID Nº: 120)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDDAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT

LVTVSS

>DOM1h-574-144 (SEC ID Nº: 121)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTAD
RRYYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-145 (SEC ID Nº: 122)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTGD
RRYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-146 (SEC ID Nº: 123)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTGD
RRYYDDAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-147 (SEC ID Nº: 124)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWGPFVYWGQGT
LVTVSS

>DOM1h-574-148 (SEC ID Nº: 125)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFAYWGQGTL

VTVSS

>DOM1h-574-149 (SEC ID Nº: 126)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWGPFQYWGQGT
LVTVSS

>DOM1h-574-150 (SEC ID Nº: 127)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFQYWGQGT
LVTVSS

>DOM1h-574-151 (SEC ID Nº: 128)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-152 (SEC ID Nº: 129)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFQYWGQGT
LVTVSS

>DOM1h-574-153 (SEC ID Nº: 130)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFQYWGQGT

LVTVSS

>DOM1h-574-154 (SEC ID Nº: 131)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-155 (SEC ID Nº: 132)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-156 (SEC ID Nº: 133)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-157 (SEC ID Nº: 134)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGT
LVTVSS

>DOM1h-574-158 (SEC ID Nº: 135)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGT
LVTVSS

>DOM1h-574-159 (SEC ID Nº: 136)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTL
VTVSS

>DOM1h-574-160 (SEC ID Nº: 137)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTL
VTVSS

>DOM1h-574-161 (SEC ID Nº: 138)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYSHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-162 (SEC ID Nº: 139)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYSHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-163 (SEC ID Nº: 140)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-164 (SEC ID Nº: 141)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-165 (SEC ID Nº: 142)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-166 (SEC ID Nº: 143)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTL
VTVSS

>DOM1h-574-167 (SEC ID Nº: 144)

EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTGD
RRYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-169 (SEC ID Nº: 145)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTAD
RTYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-170 (SEC ID Nº: 146)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-171 (SEC ID Nº: 147)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTAD
RTYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-172 (SEC ID Nº: 148)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTAD
RTYYDHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

>DOM1h-574-173 (SEC ID Nº: 149)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTAD
RRYYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-174 (SEC ID Nº: 150)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RRYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-175 (SEC ID Nº: 151)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTAD
RRYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-176 (SEC ID Nº: 152)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RRYYDHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-177 (SEC ID Nº: 153)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTAD
RRYYDHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-178 (SEC ID Nº: 154)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTAD
RRYYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGT
LVTVSS

>DOM1h-574-179 (SEC ID Nº: 155)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTAD
RRYYDDAVKGRFTITRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGT
LVTVSS

>DOM1h-574-180 (SEC ID Nº: 156)

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTAD
RTYYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTL
VTVSS

Tabla 4: Secuencias de Nucleótidos de dAbs anti-TNFR1

>DOM1h-509 (SEC ID Nº: 157)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAGTCAGTATAGGATGCATTGGGT
CCGCCAGGCTCCAGGGAAGAGTCTAGAGTGGGTCTCAAGTATTGATACTAGGGGT
TCGTCTACATACTACGCAGACCCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAAGCTGTGACGATGTTTTCTCCTTTTTTTGACTACTGGGG
TCAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-510 (SEC ID Nº: 158)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGCTGATTATGGGATGCGTTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTACGCGGACTGGT

CGTGTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATGGCGGAATCGGCATGGTGAGTATCTTGCTGATTTTG
ACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-543 (SEC ID Nº: 159)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTATGAGGTATAGGATGCATTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCGATTGATTCTAATGGT
TCTAGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
GTATATTACTGTGCGAAAGATCGTACGGAGCGTTCGCCGGTTTTTGACTACTGGGG
TCAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-549 (SEC ID Nº: 160)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTGATTATGAGATGCATTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTAGTGAGAGTGGT
ACGACGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAACGTCGTTTTTCTGCTTCTACGTTTGACTACTGGGGTCA
GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574 (SEC ID Nº: 161)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG

CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATATACGGGTCATTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-1 (SEC ID Nº: 162)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATATACGGGTCGTTGGGAGCCTTATGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-2 (SEC ID Nº: 163)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-4 (SEC ID Nº: 164)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATATACGGGTCGTTGGGAGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-180 (SEC ID Nº: 165)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCT
GATCGTACATACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-7 (SEC ID Nº: 166)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC

AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-8 (SEC ID Nº: 167)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGATGGGT
CCGCCAGGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACAGTCTCGAGC

>DOM1h-574-9 (SEC ID Nº: 168)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATATCCCGCGACA
ATTCCAAGAACACGCTGTATATGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-10 (SEC ID Nº: 169)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGGTAAGTATTCGATGGGGTGGG
TCCGCCAGGCTCCAGGGAAGGATCTAGAGTGGGTCTCACAGATTTCGAATACGGG
TGGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGAC

AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-11 (SEC ID Nº: 170)

GAGGTGCAGCTGTTGGAGTCAGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATATACGGGTCGTTGGGAGCCTTTTGACCACTGGGGTC
AGGGGACCCTGGTCACCGTCTCGAGC

>DOM1h-574-12 (SEC ID Nº: 171)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-13 (SEC ID Nº: 172)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT

CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGAAATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-14 (SEC ID Nº: 173)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-15 (SEC ID Nº: 174)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-16 (SEC ID Nº: 175)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGATGGGT
CCGCCAGGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACAGTCTCGAGC

>DOM1h-574-17 (SEC ID Nº: 176)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGATGGGT
CCGCCAGGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACAGTCTCGAGC

>DOM1h-574-18 (SEC ID Nº: 177)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGGTAAGTATTCGATGGGGTGGG
TCCGCCAGGCTCCAGGGAAGGATCTAGAGTGGGTCTCACAGATTTCGAATACGGG
TGATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-19 (SEC ID Nº: 178)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGGTAAGTATTCGATGGGGTGGG
TCCGCCAGGCTCCAGGGAAGGATCTAGAGTGGGTCTCACAGATTTCGAATACGGG
TGATCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-25 (SEC ID Nº: 179)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-26 (SEC ID Nº: 180)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC

GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-27 (SEC ID Nº: 181)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCGGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGAAGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-28 (SEC ID Nº: 182)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-29 (SEC ID Nº: 183)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT

GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-30 (SEC ID Nº: 184)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGCATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-31 (SEC ID Nº: 185)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTAACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-32 (SEC ID Nº: 186)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG

CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-33 (SEC ID Nº: 187)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACTCGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGTGCCTTTTGACAACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-35 (SEC ID Nº: 188)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTATTACGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTCAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-36 (SEC ID Nº: 189)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGGTAAGTATTCGATGGGGTGGG
TCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGG
TGATCGTACATACTACGCGGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-37 (SEC ID Nº: 190)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTTTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAAGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-38 (SEC ID Nº: 191)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGT
GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC

AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-39 (SEC ID Nº: 192)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-40 (SEC ID Nº: 193)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTAAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-53 (SEC ID Nº: 194)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAGTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GAGCGTAGATACTACGCAGACTCAGTGAAGGGCCGGTTCACCATCTCCCGCGACA

ATCCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGAGCCTTTTGAATACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-54 (SEC ID Nº: 195)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAACTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTACATACTACGCGGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTATGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCACGAGC

>DOM1h-574-65 (SEC ID Nº: 196)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGATA
ATTCCAAGAACACACTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-66 (SEC ID Nº: 197)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT

CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGTATATTACTGTGCGATATATACGGGTCGTTGGAAGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-67 (SEC ID Nº: 198)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-68 (SEC ID Nº: 199)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
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CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-69 (SEC ID Nº: 200)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGG
TCAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-70 (SEC ID Nº: 201)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGGTATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-71 (SEC ID Nº: 202)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGAAGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-72 (SEC ID Nº: 203)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-73 (SEC ID Nº: 204)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-74 (SEC ID Nº: 205)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC

GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-75 (SEC ID Nº: 206)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGT
GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-76 (SEC ID Nº: 207)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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CCGCCAGGCCCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGG
TGATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGAAGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-77 (SEC ID Nº: 208)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGT

GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-78 (SEC ID Nº: 209)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGT
GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-79 (SEC ID Nº: 210)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGT
GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-84 (SEC ID Nº: 211)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG

CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-85 (SEC ID Nº: 212)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGAAGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-86 (SEC ID Nº: 213)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCCCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAAGACACCGC
GGTATATTACTGTGCGATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-87 (SEC ID Nº: 214)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-88 (SEC ID Nº: 215)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGT
GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-90 (SEC ID Nº: 216)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTTTTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGG

TCAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-91 (SEC ID Nº: 217)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-92 (SEC ID Nº: 218)

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GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-93 (SEC ID Nº: 219)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACGGGT
GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA

ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-94 (SEC ID Nº: 220)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGCATATTACTGTGCGATATATACGGGTCGGTGGCCCGACTTTGACTACTGGGG
TCAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-95 (SEC ID Nº: 221)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGG
TGATCGTAGATACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
CGGCATATTACTGTGCGATATATACGGGTCGGTGGCCCGACTTTGAGTACTGGGG
TCAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-96 (SEC ID Nº: 222)
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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-97 (SEC ID Nº: 223)

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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-98 (SEC ID Nº: 224)

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>DOM1h-574-99 (SEC ID Nº: 225)

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GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGCCCGACTTTGAGTACTGGGGT
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>DOM1h-574-100 (SEC ID Nº: 226)

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AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
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CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-101 (SEC ID Nº: 227)

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AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
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CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-102 (SEC ID Nº: 228)

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>DOM1h-574-103 (SEC ID Nº: 229)

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TACGCGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
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>DOM1h-574-104 (SEC ID Nº: 230)

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>DOM1h-574-105 (SEC ID Nº: 231)

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>DOM1h-574-106 (SEC ID Nº: 232)

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>DOM1h-574-107 (SEC ID Nº: 233)

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>DOM1h-574-108 (SEC ID Nº: 234)

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>DOM1h-574-109 (SEC ID Nº: 235)

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>DOM1h-574-110 (SEC ID Nº: 236)

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>DOM1h-574-111 (SEC ID Nº: 237)

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>DOM1h-574-112 (SEC ID Nº: 238)

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>DOM1h-574-113 (SEC ID Nº: 239)

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>DOM1h-574-114 (SEC ID Nº: 240)

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>DOM1h-574-115 (SEC ID Nº: 241)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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GATCGTACATACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-116 (SEC ID Nº: 242)

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GATCGTAGATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-117 (SEC ID Nº: 243)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-118 (SEC ID Nº: 244)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA

ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-119 (SEC ID Nº: 245)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-120 (SEC ID Nº: 246)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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>DOM1h-574-121 (SEC ID Nº: 247)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-122 (SEC ID Nº: 248)

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GATCGTAGATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-123 (SEC ID Nº: 249)

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GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-124 (SEC ID Nº: 250)

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GATCGTAGATACTACGCACACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-125 (SEC ID Nº: 251)

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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACTGCT
GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-126 (SEC ID Nº: 252)

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TGATCGTAGATACTACGCACACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
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CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-127 (SEC ID Nº: 253)

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GATCGTAGATACTACGCACACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-128 (SEC ID Nº: 254)

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GATCGTAGATACTACGCACACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-129 (SEC ID Nº: 255)

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GATCGTAGATACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC

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>DOM1h-574-130 (SEC ID Nº: 256)

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AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
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>DOM1h-574-131 (SEC ID Nº: 257)

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GATCGTACATACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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>DOM1h-574-132 (SEC ID Nº: 258)

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TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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>DOM1h-574-133 (SEC ID Nº: 259)

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GATCGTACATACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
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>DOM1h-574-134 (SEC ID Nº: 260)

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GATCGTACATACTACTCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-135 (SEC ID Nº: 261)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG

CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCT
GATCGTACATACTACACACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-137 (SEC ID Nº: 262)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
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GATCGTACATACTACACAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-138 (SEC ID Nº: 263)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGT
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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-139 (SEC ID Nº: 264)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGT
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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-140 (SEC ID Nº: 265)

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TGATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-141 (SEC ID Nº: 266)

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GATCGTAGATACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-142 (SEC ID Nº: 267)

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TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-143 (SEC ID Nº: 268)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-144 (SEC ID Nº: 269)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-145 (SEC ID Nº: 270)

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TGATCGTAGATACTACGATCACTCTGTGAAGGGCCGGTTCACTATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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>DOM1h-574-146 (SEC ID Nº: 271)

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TGATCGTAGATACTACGATGACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGAC
AATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCG
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CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-147 (SEC ID Nº: 272)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-148 (SEC ID Nº: 273)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-149 (SEC ID Nº: 274)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-150 (SEC ID Nº: 275)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACTCTGGTCACCGTCTCGAGC

>DOM1h-574-151 (SEC ID Nº: 276)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-152 (SEC ID Nº: 277)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACTCTGGTCACCGTCTCGAGC

>DOM1h-574-153 (SEC ID Nº: 278)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGCACCCTGGTCACCGTCTCGAGC

>DOM1h-574-154 (SEC ID Nº: 279)

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GATCGTAGATACTACGATCACTCTGTGAAGGGCCGGTTCACTATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-155 (SEC ID Nº: 280)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC

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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-156 (SEC ID Nº: 281)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-157 (SEC ID Nº: 282)

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GATCGTACATACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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>DOM1h-574-158 (SEC ID Nº: 283)

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GATCGTACATACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
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>DOM1h-574-159 (SEC ID Nº: 284)

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GATCGTACATACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-160 (SEC ID Nº: 285)

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TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-161 (SEC ID Nº: 286)

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GATCGTACATACTACTCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-162 (SEC ID Nº: 287)

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GATCGTACATACTACTCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-163 (SEC ID Nº: 288)

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GATCGTACATACTACACACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-164 (SEC ID Nº: 289)

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GATCGTACATACTACACACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-165 (SEC ID Nº: 290)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-166 (SEC ID Nº: 291)

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GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-167 (SEC ID Nº: 292)

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GATCGTAGATACTACGATCACTCTGTGAAGGGCCGGTTCACTATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-168 (SEC ID Nº: 293)

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GATCGTAGATACTACGATCACTCTGTGAAGGGCCGGTTCACTATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-169 (SEC ID Nº: 294)

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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCT
GATCGTACATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA

ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-170 (SEC ID Nº: 295)

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GATCGTACATACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-171 (SEC ID Nº: 296)

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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCT
GATCGTACATACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAA
TTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCG
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GGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-172 (SEC ID Nº: 297)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
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CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCT
GATCGTACATACTACGATCACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGC
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AGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-173 (SEC ID Nº: 298)

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GATCGTAGATACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-174 (SEC ID Nº: 299)

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ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-175 (SEC ID Nº: 300)

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GATCGTAGATACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACA
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GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-176 (SEC ID Nº: 301)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCT
GATCGTAGATACTACGATCACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-177 (SEC ID Nº: 302)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCT
GATCGTAGATACTACGATCACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGGACCCTGGTCACCGTCTCGAGC

>DOM1h-574-178 (SEC ID Nº: 303)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCT
GATCGTAGATACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGT
CAGGGAACCCTGGTCACCGTCTCGAGC

>DOM1h-574-179 (SEC ID Nº: 304)

GAGGTGCAGCTGCTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCT
GATCGTAGATACTACGATGACGCGGTGAAGGGCCGGTTCACCATCACCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
GGTATATTACTGTGCGATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTC
AGGGAACCCTGGTCACCGTCTCGAGC

Tabla 5: Fusiones dAb anti-albúmina de suero (DOM7h)

(usados en estudios de Rata):

Fusión DOM7h-14/Exendina-4 número DMS 7138

Secuencia de aminoácidos (SEC ID Nº: 305)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGGGS

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSG

VPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGAALPRTFGQGTKVEIKR

Secuencia de nucleótidos (SEC ID Nº: 306)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGT

GCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGCACCTCCG

CCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGCGGTGGCGGGTC

GGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGT

GTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTGGTACCA

GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTCCTCGTTGCAA

AGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA

CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCTCAGGGTGCG

GCGTTGCCTAGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Fusión DOM7h-14-10/Exendina-4 número DMS 7139

Secuencia de aminoácidos (SEC ID Nº: 307)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGGGS

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSG

VPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKR

Secuencia de nucleótidos (SEC ID Nº: 308)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGT
GCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGCACCTCCG
CCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGCGGTGGCGGGTC
GGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGT
GTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTGGTACCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTCCTCGTTGCAA
AGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA
CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCTCAGGGTTTG
AGGCATCCTAAGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Fusión DOM7h-14-18/Exendina-4 número DMS 7140

Secuencia de aminoácidos (SEC ID Nº: 309)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGGGS
DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLMKPMTFGQGTKVEIKR

Secuencia de nucleótidos (SEC ID Nº: 310)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGT
GCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGCACCTCCG
CCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGCGGTGGCGGGTC
GGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGT
GTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTGGTACCA
GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTCCTCGTTGCAA

AGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA
CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCTCAGGGTCTT
ATGAAGCCTATGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Fusión DOM7h-14-19/Exendina-4 número DMS 7141

Secuencia de aminoácidos (SEC ID Nº: 311)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGGGS
DIQMTQSPSSLSASVGDRVTISCRASQWIGSQLSWYQQKPGEAPKLLIMWRSSLQSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGAALPRTFGQGTKVEIKR

Secuencia de nucleótidos (SEC ID Nº: 312)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGT
GCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGCACCTCCG
CCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGCGGTGGCGGGTC
GGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGT
GTCACCATCTCTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTGGTACCA
GCAGAAACCAGGGGAAGCCCCTAAGCTCCTGATCATGTGGCGTTCCTCGTTGCAA
AGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA
CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCTCAGGGTGCG
GCGTTGCCTAGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Fusión DOM7h-11/Exendina-4 número DMS 7142

Secuencia de aminoácidos (SEC ID Nº: 313)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGGGS
DIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPKLLIWFGSRLQSGV
PSRFSSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Secuencia de nucleótidos (SEC ID Nº: 314)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGT
GCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGCACCTCCG
CCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGCGGTGGCGGGTC
GGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGT
GTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGACGTTAAGTTGGTACC
AGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTGGTTTGGTTCCCGGTTGCA
AAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA
CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGG
GACGCATCCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Fusión DOM7h-11-12/Exendina-4 número DMS 7147

Secuencia de aminoácidos (SEC ID Nº: 315)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGGGS
DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILFGSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Secuencia de nucleótidos (SEC ID Nº: 316)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGT
GCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGCACCTCCG
CCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGCGGTGGCGGGTC
GGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGT
GTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACC
AGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTTGTTTGGTTCCCGGTTGCAA
AGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA
CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGG
GACGCATCCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Fusión DOM7h-11-15/Exendina-4 número DMS 7143

Secuencia de aminoácidos (SEC ID Nº: 317)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGGGS
DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Secuencia de nucleótidos (SEC ID Nº: 318)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAGGCAGT
GCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGGGCACCTCCG
CCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGCGGTGGCGGGTC
GGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGT

GTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACC
AGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCCCGTTTGCAA
AGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA
CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGCGCGCAGGCTGG
GACGCATCCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Fusión DOM7h-14-10/G4SC - NCE

Secuencia de aminoácidos (SEC ID Nº: 319) que codifica DOM7h14-10/G4SC

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKRGGGGSC

La cisteína C-terminal puede unirse a una nueva entidad química (compuesto químico farmacéutico NCE), por ejemplo usando enlace maleimida.

Secuencia de nucleótidos (SEC ID Nº: 320) que codifica DOM7h14-10/G4SC

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGT
CACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTGGTACCAGC
AGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTCCTCGTTGCAAAGT
GGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCAT
CAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCTCAGGGTTTGAGGC
ATCCTAAGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGGGTGGCGGAG
GGGGTTCCTGT

Fusión DOM7h14-10/TVAAPSC

Secuencia de aminoácidos (SEC ID Nº: 321)

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKRTVAAPSC

La cisteína C-terminal puede unirse a una nueva entidad química (compuesto químico farmacéutico NCE), por ejemplo usando enlace maleimida.

Secuencia de nucleótidos (SEC ID Nº: 322)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGT
CACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTGGTACCAGC
AGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTCCTCGTTGCAAAGT
GGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCAT
CAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCTCAGGGTTTGAGGC
ATCCTAAGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGACCGTCGCTGC
TCCATCTTGT

(usada en estudios de ratón):-

Fusión DOM7h-11/DOM1m-21-23 número DMS 5515

Secuencia de aminoácidos (SEC ID Nº: 323)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDSYGR
GTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNAFDYWGQGT

QVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPK
LLIWFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTK
VEIKR

Secuencia de aminoácidos más secuencia de nucleótidos más etiqueta myc (SEC ID Nº: 324)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDSYGR
GTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNAFDYWGQGT
QVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPK
LLIWFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTK
VEIKRAAAEQKLISEEDLN

Secuencia de nucleótidos (SEC ID Nº: 325)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGGGGTGGCT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTGATTCTTATGGT
CGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCAGCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
CGTATATTACTGTGCGAAAATTTCTCAGTTTGGGTCAAATGCGTTTGACTACTGGG
GTCAGGGAACCCAGGTCACCGTCTCGAGCGCTAGCACCAGTGGTCCATCGGACAT
CCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCACCA
TCACTTGCCGGGCAAGTCGTCCGATTGGGACGACGTTAAGTTGGTACCAGCAGAA
ACCAGGGAAAGCCCCTAAGCTCCTGATCTGGTTTGGTTCCCGGTTGCAAAGTGGG

GTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAG
CAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCAT
CCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Secuencia de nucleótidos más etiqueta myc (SEC ID Nº: 326)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGGGGTGGCT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTGATTCTTATGGT
CGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCAGCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
CGTATATTACTGTGCGAAAATTTCTCAGTTTGGGTCAAATGCGTTTGACTACTGGG
GTCAGGGAACCCAGGTCACCGTCTCGAGCGCTAGCACCAGTGGTCCATCGGACAT
CCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCACCA
TCACTTGCCGGGCAAGTCGTCCGATTGGGACGACGTTAAGTTGGTACCAGCAGAA
ACCAGGGAAAGCCCCTAAGCTCCTGATCTGGTTTGGTTCCCGGTTGCAAAGTGGG
GTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAG
CAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCAT
CCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAA
CAAAAACTCATCTCAGAAGAGGATCTGAATTAA

Fusión DOM7h-11-12/DOM1m-21-23 número DMS 5516

Secuencia de aminoácidos (SEC ID Nº: 327)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDSYGR

GTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNAFDYWGQGT
QVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPK
LLILFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKV
EIKR

Secuencia de aminoácidos más secuencia de nucleótidos más etiqueta myc (SEC ID Nº: 328)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDSYGR
GTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNAFDYWGQGT
QVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPK
LLILFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKV
EIKRAAAEQKLISEEDLN

Secuencia de nucleótidos (SEC ID Nº: 329)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGGGGTGGCT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTGATTCTTATGGT
CGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCAGCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
CGTATATTACTGTGCGAAAATTTCTCAGTTTGGGTCAAATGCGTTTGACTACTGGG
GTCAGGGAACCCAGGTCACCGTCTCGAGCGCTAGCACCAGTGGTCCATCGGACAT
CCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCACCA
TCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACCAGCAGAA

ACCAGGGAAAGCCCCTAAGCTCCTGATCTTGTTTGGTTCCCGGTTGCAAAGTGGG
GTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAG
CAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCAT
CCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Secuencia de nucleótidos más etiqueta myc (SEC ID Nº: 330)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGGGGTGGCT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTGATTCTTATGGT
CGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCAGCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
CGTATATTACTGTGCGAAAATTTCTCAGTTTGGGTCAAATGCGTTTGACTACTGGG
GTCAGGGAACCCAGGTCACCGTCTCGAGCGCTAGCACCAGTGGTCCATCGGACAT
CCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCACCA
TCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACCAGCAGAA
ACCAGGGAAAGCCCCTAAGCTCCTGATCTTGTTTGGTTCCCGGTTGCAAAGTGGG
GTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAG
CAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCAT
CCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAA
CAAAAACTCATCTCAGAAGAGGATCTGAATTAA

Fusión DOM7h-11-15/DOM1m-21-23 número DMS 5517

Secuencia de aminoácidos (SEC ID Nº: 331)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDSYGR
GTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNAFDYWGQGT
QVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPK
LLILAFSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKV
EIKR

Secuencia de aminoácidos más secuencia de nucleótidos más etiqueta myc (SEC ID Nº: 332)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDSYGR
GTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNAFDYWGQGT
QVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPK
LLILAFSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKV
EIKRAAAEQKLISEEDLN

Secuencia de nucleótidos (SEC ID Nº: 333)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGGGGTGGCT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTGATTCTTATGGT
CGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCAGCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
CGTATATTACTGTGCGAAAATTTCTCAGTTTGGGTCAAATGCGTTTGACTACTGGG
GTCAGGGAACCCAGGTCACCGTCTCGAGCGCTAGCACCAGTGGTCCATCGGACAT
CCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCACCA

TCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACCAGCAGAA
ACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCCCGTTTGCAAAGTGGGG
TCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGTCTGCAACCTGAAGATTTTGCTACGTACTACTGCGCGCAGGCTGGGACGCATC
CTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Secuencia de nucleótidos más etiqueta myc (SEC ID Nº: 334)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTG
CGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGGGGTGGCT
CCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTGATTCTTATGGT
CGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCAGCATCTCCCGCGACA
ATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGC
CGTATATTACTGTGCGAAAATTTCTCAGTTTGGGTCAAATGCGTTTGACTACTGGG
GTCAGGGAACCCAGGTCACCGTCTCGAGCGCTAGCACCAGTGGTCCATCGGACAT
CCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCACCA
TCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACCAGCAGAA
ACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCCCGTTTGCAAAGTGGGG
TCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGTCTGCAACCTGAAGATTTTGCTACGTACTACTGCGCGCAGGCTGGGACGCATC
CTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAAC
AAAAACTCATCTCAGAAGAGGATCTGAATTAA

Cuando en esta tabla se indica una molécula etiquetada con myc, ésta era la versión usada en estudios PK en los ejemplos. Cuando no se proporcionan secuencias

etiquetadas con myc, los estudios PK en los ejemplos no se realizaron con material etiquetado con myc, es decir, los estudios se realizaron con las construcciones mostradas no etiquetados.

EJEMPLIFICACIÓN

En el apartado experimental toda la numeración se realiza de acuerdo con Kabat (Kabat, E.A. National Institutes of Health (US) & Columbia University. Sequences of proteins of immunological interst, 5 ed. (US Dept. Of Health and Human Services Public Health Service, National Institues of Health, Bethesda, MD, 1991)).

Se describen variantes derivadas de DOM7h-11 y DOM7h-14. Las variantes DOM7h-14 no son de acuerdo con la invención.

EJEMPLO 1: Maduración de Afinidad Vk

Selecciones:

Se obtuvieron antígenos de HSA (Albúmina de Suero Humana) y RSA (Albúmina de Suero de Rata) de Sigma (esencialmente sin ácidos grasos, ~99% (electroforesis en gel de agarosa), polvo liofilizado Cat. Nº A3782 y A6414 respectivamente).

Se prepararon productos biotinilados de los dos antígenos anteriores usando Sulfo-NHS-SS-Biotina unida a Ez (Pierce, Cat. Nº 21331). El reactivo sin biotina se eliminó pasando las muestras dos veces a través de una columna de desalinización PD10 seguido de diálisis durante una noche frente un volumen sobrante1000x de PBS a 4 ºC. El producto resultante se ensayó por espectrofotometría de masas y se observaron 1-2 biotinas por molécula.

Bibliotecas de maduración de afinidad:

Se crearon bibliotecas propensas a errores y CDR usando los dAb parentales DOM7h-11 y DOM7h-14 (véase el documento WO208/096158 para las secuencias de DOM7h-11 y DOM7h-14). Las bibliotecas de CDR se crearon en el vector pDOM4 y las bibliotecas propensas a errores se generaron en el vector pDOM33 (para permitir la selección con o sin tratamiento con proteasa). El vector pDOM4, es un derivado del vector del fago Fd en el que la secuencia peptídica de señal del *gen III* se reemplazó con el péptido de señal de la proteína de superficie glicolipídica anclada (GAS) de levadura. Éste también contiene una etiqueta *c-myc* entre la secuencia líder y el *gen III,* que restablece al *gen III* en fase de lectura. Esta secuencia líder actúa bien en vectores de presentación de fagos pero también en otros vectores de expresión procariotas y puede usarse universalmente. pDOM33 es una versión modificada del vector pDOM4 en el que se ha eliminado la etiqueta c-myc lo que hace que la fusión fago-dAb sea resistente a la tripsina proteasa. Esto permite el uso de tripsina en la selección del fago para seleccionar los dAbs que son más estables a proteasa (véase el documento WO2008149143).

Para las bibliotecas de maduración propensas a errores, el ADN plasmídico que codifica el dAb a madurar se amplificó por PCR, usando el KIT DE MUTAGÉNESIS ALEATORIA GENEMORPH® II (kit de mutagénesis único, aleatorio Stratagene). Se realizó la digestión del producto con *Sal* I y *Not* I en una reacción de ligación con el vector del fago de corte pDOM33.

Para las bibliotecas CDR, se realizaron reacciones PCR usando oligonucleótidos degenerados que contenían codones NNK o NNS para diversificar las posiciones necesarias en el dAb a madurar afinidad. A continuación se usó PCR de ensamblaje para generar un inserto diversificado de longitud completa. La digestión del inserto se realizó con *Sal* I y *Not* I y se usó en una reacción de ligación con pDOM4 para

mutagénesis de restos múltiples y pDOM5 para mutagénesis de restos sencillos. El vector pDOM5 es un vector de expresión basado en pUC119 en el que la expresión de la proteína se realiza mediante el promotor LacZ. Una secuencia líder GAS1 (véase el documento WO 2005/093074) garantiza la secreción del dAbs soluble, aislado en el periplasma y sobrenadante de cultivo de *E. coli.* Los dAbs se clonaron usando SalI/NotI en este vector, que añade una etiqueta myc en el extremo C del dAb. Este protocolo usando *SalI* y *Not I* da como resultado la inclusión de una secuencia de aminoácidos ST en el extremo N.

La ligación producida por cualquier método se usó después para transformar la cepa *E. coli* TB1 por electroporación y las células transformadas se cultivaron en placas en agar TY 2x que contenía tetraciclina 15 μg/ml, produciendo tamaños de bibliotecas de $>5\times10^7$ clones.

Las bibliotecas propensas a errores tenían la siguiente tasa de mutación promedio y tamaño: DOM7h-11 (2,5 mutaciones por dAb), tamaño: $6,1 \times 10^8$, DOM7h-14 (2,9 mutaciones por dAb), tamaño: $5,4 \times 10^8$.

Cada biblioteca CDR tiene una diversidad de cuatro aminoácidos. Se generaron dos bibliotecas para cada una de las CDR 1 y 3 y una biblioteca para CDR2. Las posiciones diversificadas en cada biblioteca son las siguientes (aminoácidos en base a la secuencia DPK9 ficticia para VK):

	Tamaño de la biblioteca	
	DOM7h-11	DOM7h-11
1 – Q27, S28, S30, S31 (CDR1)	$8,8 \times 10^7$	$5,8 \times 10^7$
2 – S30, S31, Y32, N34 (CDR1)	$4,6 \times 10^8$	$4,2 \times 10^8$
3 – Y49, A50, A51, S53 (CDR2)	$3,9 \times 10^8$	$2,4 \times 10^8$

4 – Q89, S91, Y92, S93 (CDR3	$1,8 \times 10^8$	$2,5 \times 10^8$
5 – Y92, Y93, T94, N96 (CDR3)	$4,0 \times 10^8$	$3,3 \times 10^8$

Ejemplo 2: Estrategias de selección:

Se adoptaron tres estrategias de selección de fagos para maduración de afinidad Vκ AlbudAb™ (dAB anti-albúmina de suero):

1) Selecciones frente HSA únicamente:

Se realizaron tres rondas de selección frente a HSA. Las bibliotecas propensas a errores y cada biblioteca de CDR se seleccionaron como un grupo individual en todas las rondas. La primera ronda de selección se realizó frente HSA revestida de modo pasivo sobre un inmunotubo a 1 mg/ml. La segunda ronda se realizó frente HSA 100 nM y la tercera ronda frente HSA 10 nM (selecciones para CDR) o 20 ó 100 nM (selecciones para propensas a Error), ambas como selecciones solubles seguido de una cuarta ronda de selección con las bibliotecas propensas a errores frente HSA 1,5 nM como una selección soluble. Las bibliotecas propensas a errores se eluyeron con glicina 0,1 M pH 2,0 antes de la neutralización con Tris 1 M pH 8,0 y las bibliotecas CDR se eluyeron con tripsina 1 mg/ml antes de la infección en células TG1 en fase logarítmica. La tercera ronda de cada selección se subclonó en pDOM5 para la exploración. Las selecciones solubles usaron HSA biotinilado.

2) Selecciones de tripsina frente HSA:

Para seleccionar los dAb con resistencia a proteasa aumentada en comparación con el clon parenteral y con las propiedad biofísicas potencialmente mejoradas, se usó tripsina en selecciones de fagos (véase el documento WO2008149143). Se realizaron cuatro

rondas de selección frente a HSA. La primera ronda de selección de bibliotecas propensas a errores se realizó frente a HSA revestida de modo pasivo a 1 mg/ml sin tripsina; la segunda ronda frente HSA revestida de modo pasivo a 1 mg/ml con tripsina 20 μg/ml durante 1 hora a 37ºC; la tercera ronda de selección se realizó por selección soluble usando HSA biotinilado frente a HSA 100 nM con 20 μg/ml o 100 μg/ml de tripsina durante 1 hora a 37ºC. La ronda de selección final se realizó por selección soluble usando HSA biotinilada frente a HSA 100 nM con tripsina 100 μg/ml durante una noche a 37ºC.

3) Selecciones de entrecruzamiento frente HSA (ronda 1) y RSA (rondas 2-4):

La primera ronda de selección se realizó frente HSA revestida de modo pasivo 1mg/ml o HSA 1 μM (selección soluble), seguido de tres rondas adicionales de selecciones solubles frente RSA biotinilada a concentraciones de 1 μM para la ronda 1, 100 nm para la ronda 2 y 20 nM, 10 nM o 1 nM para la ronda 3.

Estrategia de exploración y determinación de afinidad:

Después de la selección en cada caso se preparó un conjunto de ADN de fagos de la ronda de selección apropiada usando un kit QIAfilter midiprep (Qiagen), la digestión del ADN se realizó usando las enzimas de restricción Sal1 y Not1 y los genes V enriquecidos se ligaron en los sitios correspondientes en pDOM5 el vector de expresión soluble que expresa el dAb con una etiqueta myc (véase el documento PCT/EP2008/067789). El ADN ligado se usó para electro transformar células HB 2151 de *E. coli* que después se cultivaron durante una noche en placas de agar que contenían el antibiótico carbenicilina. Las colonias resultantes se evaluaron individualmente para la unión al antígeno. En cada caso se ensayaron al menos 96

clones para la unión a HSA, CSA, (Albúmina de Suero de mono *Cynomolgus*), MSA (albúmina de suero de ratón) y RSA por BIAcore™ (resonancia de plasmón superficial). El antígeno MSA se obtuvo de Sigma (esencialmente sin ácidos grasos, ~99% (electroforesis en gel de agarosa), polvo liofilizado Cat. Nº A3559) y CSA se purificó de la albúmina de suero de *Cynomolgus* usando resina azul prometic (Amersham). Se produjeron fragmentos solubles de dAb en cultivos de bacterias en medios de cultivo ONEX (Novagen) durante una noche a 37ºC en placas de 96 pocillos. El sobrenadante de cultivo conteniendo dAb soluble se centrifugó y se analizó por BIAcore para la unión a microplacas CM5 con HSA, CSA, MSA y RS de elevada densidad. Se descubrió que los clones se unían a todas estas especies de albúmina de suero mediante exploración de velocidad de disociación. Los clones se secuenciaron revelando secuencias dAb únicas.

La identidad mínima de los clones seleccionados con respecto al parental (a nivel de aminoácidos) eral del 97,2% (DOM7h-11-3: 97,2%, DOM7h-11-12: 98,2%, DOM7h11-15: 96,3%, DOM7h-11-18: 98,2%, DOM7h-11-19: 97,2%).

La identidad mínima de los clones seleccionados con respecto al parental (a nivel de aminoácidos) era del 96,3% (DOM7h-14-10: 96,3%, DOM7h-14-18: 96,3%, DOM7h-14-19: 98,2%, DOM7h-14-28: 99,1%, DOM7h-14-36: 97,2%).

Los dAb únicos se expresaron como sobrenadantes bacterianos en un matraz agitador de 2,5 l en medio Onex a 30ºC durante 48 h a 250 rpm. Los dAb se purificaron del medio de cultivo mediante absorción por proteína L agarosa seguido de elución con glicina 10 mM pH 2,0. La unión a HSA, CSA, MSA y RSA por BIAcore se confirmó usando proteína purificada a 3 concentraciones 1 μM, 500 nM y 50 nM. Para determinar la afinidad de unión (K_D) de los AlbudAbs para cada albúmina de suero; los dAb purificados se analizaron por BIAcore sobre un intervalo de concentración de albúmina de 5000 nM a 39 nM (5000 nM, 2500 nM, 1250 nM, 625 nM, 312 nM, 156 nM, 78 nM, 39

nM).

Tabla 6

AlbudAb	Afinidad (K_D) para SA (nM)	Kd	Ka
	Rata		
DOM7h-14	60	2,095E-01	4,00E+06
DOM7h-14-10	4	9,640E-03	4,57E+06
DOM7h-14-18	410	2,275E-01	5,60E+05
DOM7h-14-19	890	2,870E-01	3,20E+05
DOM7h-14-28	45 (140)	7,0E-02 (1,141e-1)	2,10E+06 (8,3e5)
DOM7h-14-36	30 (6120)	2,9E-02 (5,54e-2)	1,55E+06 (9e3)
DOM 7h-11	2100	1,00E-01	4,80E+04
DOM 7h-11-3	10000 (88000)	(7,18e-1)	(8,11e3)
DOM7h-11-12	200	5,22E-01	2,76E+06
DOM7h-11-15	20	2,10E-02	1,10E+06
DOM7h-11-18	80 (29000)	6,0E-02 (3,7e-1)	1,64E+06 (1,3e4)
DOM7h-11-19	28 (17000)	9,1e-02 (1,4e-1)	9,80E+05 (8,1e3)
	Cyno		
DOM 7h-14	66	9,65E-02	1,50E+06
DOM7h-14-10	9	1,15E-02	1,60E+06
DOM7h-14-18	180	1,05E-01	6,30E+5
DOM7h-14-19	225	1,56E-01	7,00E+05
DOM7h-14-28	66 (136)	1,3E-01 (1,34e-1)	2,50E+06 (9,8e5)
DOM7h-14-36	35 (7830)	1,9E-02 (1,1e-1)	9,80E+06 (1,43e4)
DOM 7h-11	1000	6,82E-01	8,00E+05
DOM 7h-11-3	670 (200)	9,6E-02 (1,5e-1)	2,90E+05 (7,26e5)
DOM7h-11-12	≥6000		

AlbudAb	Afinidad (K_D) para SA (nM)	Kd	Ka
DOM7h-11-15	3	5,57E-03	5,80E+06
DOM7h-11-18	10000 (65000)	1,36 (4,8e-1)	2,25E+05 (7,3e3)
DOM7h-11-19	≥10000 (375000)	(6,2e-1)	(1,7e3)
	Ratón		
DOM 7h-14	12	4,82E-02	4,10E+06
DOM7h-14-10	30	3,41E-02	1,29E+06
DOM7h-14-18	65	9,24E-02	2,28E+06
DOM7h-14-19	60	5,76E-02	1,16E+06
DOM7h-14-28	26 (31)	3,4E-02 (7,15e-2)	1,60E+06 (2,28e6)
DOM7h-14-36	35 (33)	2,3E-02 (7,06e-2)	8,70E+05 (2,11e6)
DOM 7h-11	5000	9,00E-01	
DOM 7h-11-3	≥10000 (36000)	(6,12e-1)	(1,67e4)
DOM7h-11-12	130	1,89E-01	1,53E+06
DOM7h-11-15	10	9,40E-03	1,10E+06
DOM7h-11-18	150 (1600)	2,4E-02 (6,23e-2)	4,40E+05 (4e4)
DOM7h-11-19	100 (18000)	3,7E-02 (8,8e-2)	1,40E+06 (4,9e3)
	Humana		
DOM 7h-14	33	4,17E-02	1,43E+06
DOM 7h-14-10	12	1,39E-02	1,50E+06
DOM 7h-14-18	280	3,39E-02	1,89E+05
DOM 7h-14-19	70	5,25E-02	8,26E+05

AlbudAb	Afinidad (K_D) para SA (nM)	Kd	Ka
DOM 7h-14-28	30 (8260)	3,3E-02 (5,6e-2)	1,24E+06 (6,78e3)
DOM 7h-14-36	28 (1260)	2,4E-02 (6,7e-2)	1,23E+06 (5,4e4)
DOM 7h-11	2800	6,41E-01	7,00E+05
DOM 7h-11-3	32 (130)	1,6E-02 (2,35e-2)	6,50E+05 (1,86e5)
DOM7h-11-12	350	4,13E-01	1,26E+06
DOM7h-11-15	1	1,84E-03	2,00E+06
DOM7h-11-18	36 (32000)	5,1E-02 (2,7e-1)	3,40E+06 (8,39e3)
DOM7h-11-19	65 (38000)	1,1E-01 (2,09e-1)	1,80E+06 (5,4e3)

*: los valores entre paréntesis proceden de un segundo experimento SPR independiente.

Todas las variantes derivadas de DOM7h-14 tienen reactividad cruzada para la albúmina de suero, rata, ser humano y cyno. DOM7h-14-10 tenía afinidad mejorada para la albúmina de suero de rata, cyno y ser humano en comparación con la parental. DOM7h-14-28 tenía afinidad mejorada para RSA. DOM7h-14-36 tenía afinidad mejorada para RSA, CSA y MSA.

DOM7h-11-3 tenía afinidad mejorada para CSA y HSA. DOM7h-14-12 tenía afinidad mejorada para RSA, MSA y HSA. DOM7h-11-15 tenía afinidad mejorada para RSA, MSA, CSA y HSA. DOM7h-11-18 y DOM7h-11-19 tenía la afinidad mejorada para RSA, MSA y HSA.

Ejemplo 3: Orígenes de clones clave del linaje DOM7h-11:

DOM7h-11-3: A partir de la maduración de afinidad realizada frente a HSA usando la biblioteca CDR2 (Y49, A50, A51, S53), producción de la ronda 3 HSA 10 nM.

DOM7h-11-12: A partir de la maduración de afinidad realizada frente HSA usando la biblioteca propensa a error, producción de la ronda 3 (HSA, 100 nM) con tripsina 100 µg/ml.

DOM7h-11-15: A partir de selecciones de entrecruzamiento realizadas frente HSA como 1 ronda seguido 3 rondas adicionales de selección frente RSA usando la biblioteca CDR2 (Y49, A50, A51, S53) a selección de 3 rondas con 1 nM de RSA.

DOM7h-11-18: A partir de selecciones de entrecruzamiento realizadas frente HSA como 1 ronda seguido 3 rondas adicionales de selección frente RSA usando la biblioteca propensa a error, producción de la ronda 3 con 20 nM de RSA.

DOM7h-11-19: A partir de selecciones de entrecruzamiento realizadas frente HSA como 1 ronda seguido 3 rondas de selección adicionales frente RSA usando la biblioteca propensa a error, producción de la ronda 3 con 5 nM de RSA.

Tabla 7: Secuencias CDR (de acuerdo con Kabat; ref. como se ha indicado anteriormente)

AlbudAb	CDR		
	CDR1	CDR2	CDR3
DPK9 Vk ficticia	SQSISSYLN (SEC ID Nº: 335)	YAASSLQS (SEC ID Nº: 336)	QQSYSTPNT (SEC ID Nº: 337)
DOM7h-11	SRPIGTTLS (SEC ID Nº: 338)	WFGSRLQS (SEC ID Nº: 339)	AQAGTHPTT (SEC ID Nº: 340)
DOM7h-11-12	SRPIGTMLS (SEC ID Nº: 341)	LFGSRLQS (SEC ID Nº: 342)	AQAGTHPTT (SEC ID Nº: 343)

AlbudAb	CDR		
	CDR1	CDR2	CDR3
DOM 7h-11-15	SRPIGTMLS (SEC ID Nº: 344)	LAFSRLQS (SEC ID Nº: 345)	AQAGTHPTT (SEC ID Nº: 346)
DOM 7h-11-18	SRPIGTMLS (SEC ID Nº: 347)	WFGSRLQS (SEC ID Nº: 348)	AQAGTHPTT (SEC ID Nº: 349)
DOM 7h-11-19	SRPIGTMLS (SEC ID Nº: 350)	LFGSRLQS (SEC ID Nº: 351)	AQTGTHPTT (SEC ID Nº: 352)
DOM 7h-11-3	SRPIGTTLS (SEC ID Nº: 353)	LWFSRLQS (SEC ID Nº: 354)	AQAGTHPTT (SEC ID Nº: 355)

Ejemplo 4: Orígenes de clones clave del linaje DOM7h-14:

DOM7h-14-19: A partir de la maduración de afinidad realizada frente a HSA usando la biblioteca propensa a error, producción ronda 3 (HSA, 100 nM) con tripsina 100 µg/ml.

DOM7h-14-10, DOM7h-14-18, DOM7h-14-28, DOM7h-14-36: A partir de la maduración de afinidad realizada frente a HSA usando la biblioteca de CDR3 (Y92, Y93, T94, N96), producción ronda 3.

Tabla 8: Secuencias CDR (de acuerdo con Kabat); ref. como se ha indicado anteriormente)

AlbudAb	CDR		
	CDR1	CDR2	CDR3
DPK9 Vk ficticia	SQSISSYLN (SEC ID Nº: 335)	YAASSLQS (SEC ID Nº: 336)	QQSYSTPNT (SEC ID Nº: 337)
DOM 7h-14	SQWIGSQLS (SEC ID Nº: 356)	MWRSSLQS (SEC ID Nº: 357)	AQGAALPRT (SEC ID Nº: 358)
DOM 7h-14-10	SQWIGSQLS (SEC ID Nº: 359)	MWRSSLQS (SEC ID Nº: 360)	AQGLRHPKT (SEC ID Nº: 361)

AlbudAb	CDR		
	CDR1	CDR2	CDR3
DOM 7h-14-18	SQWIGSQLS (SEC ID Nº: 362)	MWRSSLQS (SEC ID Nº: 363)	AQGLMKPMT (SEC ID Nº: 364)
DOM 7h-14-19	SQWIGSQLS (SEC ID Nº: 365)	MWRSSLQS (SEC ID Nº: 366)	AQGAALPRT (SEC ID Nº: 367)
DOM 7h-14-28	SQWIGSQLS (SEC ID Nº: 368)	MWRSSLQS (SEC ID Nº: 369)	AQGAALPKT (SEC ID Nº: 370)
DOM 7h-14-36	SQWIGSQLS (SEC ID Nº: 371)	MWRSSLQS (SEC ID Nº: 372)	AQGFKKPRT (SEC ID Nº: 373)

Ejemplo 5: Expresión y Caracterización Biofísica:

El nivel de expresión bacteriano se determinó de la manera habitual en matraces de agitación de 2,5 l seguido del cultivo en medio Onex a 30ºC durante 48 horas a 250 rpm. Las características biofísicas se determinaron por SEC MALLS y DSC.

SEC MALLS (cromatografía de exclusión por tamaño con dispersión de luz LÁSER multiángulo) es una técnica no invasiva para la caracterización de macromoléculas en solución. En resumen, las proteínas (a una concentración de 1 mg/ml en tampón PBS de Dubelcco a 0,5 ml/min) se separaron de acuerdo con sus propiedades hidrodinámicas por cromatografía de exclusión por tamaño (columna: TSK3000 de TOSOH Biosciences; S200 de Phamarcia). Después de la separación, se midió la propensión de la proteína a la dispersión lumínica usando un detector de dispersión de luz LÁSER multiángulo (MALLS). La intensidad de la luz dispersa cuando la proteína pasa a través del detector se mide como una función de ángulo. Esta medida tomada junto con la concentración de la proteína determinada usando el detector de índice refractivo (RI) permite calcular la masa molar usando ecuaciones apropiadas (parte integral del análisis informático Astra v.5.3.4.12).

DSC (Calorimetría de Escáner Diferencial): en resumen, la proteína se calentó a

una velocidad constante de 180 ºC/h (PBS 1 mg/ml) y se midió un cambio térmico detectable asociado a la desnaturalización térmica. Se determinó el punto medio de transición ($_{app}T_m$), que se describe como la temperatura en la cual el 50% de la proteína se encuentra en su conformación nativa y el otro 50% desnaturalizada. En este caso, el valor DSC determinó el punto medio de transición aparente ($_{app}T_m$) ya que la mayoría de las proteínas examinadas no estaban completamente replegadas. A mayor Tm, más estable la molécula. Las curvas desdobladas se analizaron mediante ecuaciones que no eran de 2 estados. El paquete informático usado era Origin^R v7.0383.

Tabla 9

AlbudAb	Parámetros Biofísicos	
	SEC MALLS	DSC Tm (ºC)
DOM7h-14	M	60
DOM 7h-14-10	M	59
DOM 7h-14-18	M	58
DOM 7h-14-19	M	59
DOM 7h-14-28	M	58,3/60,2
DOM 7h-14-36	M	59,2
DOM 7h-11	M	66,9-72,2
DOM 7h-11-3	M (95%)*	66,6/70,5
DOM 7h-11-12	M (<2% D)	71,7
DOM 7h-11-15	M (<5% D)	58,5-60,5
DOM 7h-11-18	M (98%)	58,9/65,8

AlbudAb	Parámetros Biofísicos	
	SEC MALLS	DSC Tm (ºC)
DOM 7h-11-19	M	71,8/76,6

*en otro ensayo, se observó principalmente monomérico mediante SEC MALLS, aunque inferior al 95%.

En la Tabla 9 se observan los niveles de expresión para todos los clones en el intervalo de 15 a 119 mg/l en *E. coli.*

En las variantes DOM7h-14 y DOM7h-11, durante la maduración de afinidad se mantuvieron los parámetros biofísicos favorables (monoméricos en solución según se determina por SEC MALL y appTm >55 ºC según se determina por DSC) y los niveles de expresión. El estado monomérico es ventajoso porque evita la dimerización y el riesgo de productos que puedan entrecruzarse con las dianas tales como receptores de la superficie celular.

Ejemplo 6: Determinación de semivida en suero en rata, ratón y mono *Cynomolgus* Se clonaron AlbudAbs DOM7h-14-10, DOM7h-14-18, DOM7h-14-19, DOM7h-11, DOM7h11-12 y DOM7h-11-15 en el vector pDOM5. Para cada AlbudAb™, se expresaron cantidades de 20-50 mg en *E. coli* y se purificaron del sobrenadante de cultivo bacteriano usando la resina de afinidad para proteína L y se eluyó con glicina 100 mM pH 2. Las proteínas se llevaron a una concentración superior a 1 mg/ml, el tampón se intercambió a PBS y la endotoxina se agotó usando columnas de giro Q (Vivascience). Para realizar el análisis farmacocinético (PK) de Rata, se dosificaron AlbudAbs como inyecciones i.v. únicas de 2,5 mg/kg usando 3 ratas por compuesto. Las muestras de suero se tomaron a 0,16, 1, 4, 12, 24, 48, 72, 120, 168 h. El análisis de los niveles en suero se realizó mediante ELISA anti-myc según el método descrito a

continuación.

Para el PK de Ratón, se dosificaron DOM7h-11, DOM7h11-12 y DOM7h-11-15 como inyecciones i.v. únicas de 2,5 mg/kg por dosis a un grupo de 3 sujetos y las muestras de suero se tomaron a 10 min; 1 h; 8 h; 24 h; 48 h; 72 h; 96 h. El análisis de los niveles en suero se realizó mediante ELISA anti-myc según el método descrito a continuación.

Para el PK del mono *Cynomolgus* se dosificaron DOM7h-14-10 y DOM7h11-15 como inyecciones i.v. únicas de 2,5 mg/kg por dosis a un grupo de tres hembras de mono *Cynomolgus* y las muestras de suero se tomaron a 0,083, 0,25, 0,5, 1, 2, 4, 8, 24, 48, 96, 144, 192, 288, 336, 504 h. El análisis de los niveles en suero se realizó mediante ELISA anti-myc según el método descrito a continuación.

Método de ELISA anti-myc

La concentración de AlbudAb en suero se midió por ELISA anti-myc. En resumen, en placas NuncMaxisorp de 96 pocillos, se revistió durante una noche anticuerpo policlonal de cabra anti-myc (1:500; Abcam, catálogo número ab9132) y se bloqueó con BSA/PBS al 5% + tween al 1%. Se añadieron muestras de suero a un intervalo de diluciones junto a concentraciones conocidas convencionales. La unión de AlbudAb marcado con myc se detectó a continuación usando un anti-Vk policlonal de conejo (1:1000; reactivo casero, las extracciones se agruparon y la proteína A se purificó antes del uso) seguido de un anticuerpo HRP anti-IgG de conejo (1:10.000; Sigma, catálogo número A2074). Las placas se lavaron entre cada etapa del ensayo con PBS 3 x + Tween 20 al 0,1% seguido de PBS 3 x. Después del último lavado se añadió TMB (Sustrato de Peroxidasa para Micropocillo de Componente SureBlue TMB1, KPL, catálogo número 52-00-00) y se dejó desarrollar. El proceso se detuvo con HCl 1 M y

después se midió la señal usando una absorbancia a 450 nm.

A partir de datos ELISA sin procesar, la concentración de muestras desconocidas se estabilizó por interpolación frente a la curva convencional teniendo en cuenta los factores de dilución. La concentración media que resulta de cada momento se determinó a partir de valores de repetición y se introdujeron en un paquete de análisis WinNonLin (por ejemplo, versión 5.1 (disponible de Pharsight Corp., Mountain View, CA94040, USA). Los datos se ajustaron usando un modelo no-compartimental, en el que los parámetros PK se estimaron mediante el programa informático para proporcionar las semividas terminales. La información de la dosificación y los momentos se seleccionaron para reflejar la fase terminal de cada perfil PK.

Tabla 10: PK de AlbudAb™ Sencillo

Especie	AlbudAb	Albúmina K_D (nM)	Parámetros PK			
			AUC h x µg/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
Rata	**DOM7h-14***	60				
	DOM7h-14-10	4	2134,6	1,2	42,1	71,2
	DOM7h-14-18	410	617,3	4,1	38,4	228,1
	DOM7h-14-19	890	632,6	4,1	36,3	213,3
	DOM7h-11	2100	320,1	7,8	23,3	263,9
	DOM7h-11-12	200	398,7	6,4	35,5	321,2

Especie	AlbudAb	Albúmina K_D (nM)	Parámetros PK			
			AUC h x µg/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
	DOM7h-11-15	20	843,4	3,0	30,3	130,7
Ratón	**DOM7h-11**	5000	304,7	8,2	18,3	216,8
	DOM7h-11-12	130	646,6	3,9	43,9	244,8
	DOM7h-11-15	10	499,2	5,0	33,7	243,4
Cyno	**DOM7h-14***	66			217,5	
	DOM7h-14-10	9	6174,6	0,4	200,8	117,8
	DOM7h-11*	3300			135,1	
	DOM7h-11-15	3	4195	0,6	198,1	170,3

* Datos históricos

Los parámetros farmacocinéticos obtenidos de estudios de rata, ratón y mono *Cynimolgus* se ajustaron usando un modelo no - compartimental. Clave: AUC: Área bajo la curva del tiempo de dosificación extrapolado al infinito; CL: eliminación; t1/2: es el tiempo durante el cual la concentración en sangre se divide en dos; Vz: volumen de distribución en base a la fase terminal.

DOM7h-11 12 y DOM7h-11-15 tienen una AUC y un t1/2 mejorados en rata y ratón en comparación con el parental. DOM7h-11-15 también tiene una AUC y un t1/2 mejorados en C*yno* en comparación con el parental. Esta mejora del AUC/t1/2 equivale a una KD mejorada *in vitro* para la albúmina de suero.

Ejemplo 7: Fusiones AlbudAb™ IFN

Clonación y expresión

Al igual que en los AlbudAbs sencillos, los Albudabs Vk madurados por afinidad se unieron al Interferón alfa 2b (IFNα2b) para determinar si se mantenía un PK útil del AlbudAb como una proteína de fusión.

Secuencia de aminoácidos del Interferón alfa 2b:

CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHE MIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTETPLMKEDSILA VRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRSKE (SEC ID Nº: 374)

Secuencia de nucleótidos del Interferón alfa 2b:

TGTGATCTGCCTCAAACCCACAGCCTGGGTAGCAGGAGGACCTTGATGCTCCTGG CACAGATGAGGAGAATCTCTCTTTTCTCCTGCTTGAAGGACAGACATGACTTTGGA TTTCCCCAGGAGGAGTTTGGCAACCAGTTCCAAAAGGCTGAAACCATCCCTGTCCT CCATGAGATGATCCAGCAGATCTTCAATCTCTTCAGCACAAAGGACTCATCTGCTG CTTGGGATGAGACCCTCCTAGACAAATTCTACACTGAACTCTACCAGCAGCTGAAT GACCTGGAAGCCTGTGTGATACAGGGGGTGGGGGTGACAGAGACTCCCCTGATG AAGGAGGACTCCATTCTGGCTGTGAGGAAATACTTCCAAAGAATCACTCTCTATCT GAAAGAGAAGAAATACAGCCCTTGTGCCTGGGAGGTTGTCAGAGCAGAAATCATG AGATCTTTTTCTTTGTCAACAAACTTGCAAGAAAGTTTAAGAAGTAAGGAA (SEC ID Nº: 375)

Mediante una región engarzadora TVAAPS (véase el documento WO2007085814) se realizó la unión del IFNa2b con AlbudAb. Las construcciones se clonaron por SOE-PCR (extensión de solapamiento simple de acuerdo con el método de

Horton *y col*. Gene, 77, p 61 (1989)). Se realizó por separado la amplificación PCR del AlbudAb y de las secuencias IFN usando cebadores con un solapamiento ~15 pares de bases en la región engarzadora TVAAPS. Los cebadores usados son los siguientes:

IFNα2b SOE fragmento 5'	GCCCGGATCCACCGGCTGTGATCTG (SEC ID Nº: 376)
IFNα2b SOE fragmento 3'	GGAGGATGGAGACTGGGTCATCTGGATGTC (SEC ID Nº: 377)
Vk SOE fragmento 5'	GACATCCAGATGACCCAGTCTCCATCCTCC (SEC ID Nº: 378)
Vk SOE fragmento 5' para introducir también una etiqueta myc	GCGCAAGCTTTTATTAATTCAGATCCTCTTC TGAGATGAGTTTTTGTTCTGCGGCCGCCCGT TTGATTTCCACCTTGGTCCC (SEC ID Nº: 379)

Los fragmentos se purificaron por separado y posteriormente se ensamblaron en una reacción SOE (extensión PCR por extensión de solapamiento simple) usando únicamente los cebadores flanqueantes.

IFNα2b SOE fragmento 5'	GCCCGGATCCACCGGCTGTGATCTG (SEC ID Nº: 380)
Vk SOE fragmento 3' para introducir también una etiqueta myc	GCGCAAGCTTTTATTAATTCAGATCCTCTTC TGAGATGAGTTTTTGTTCTGCGGCCGCCCGT TTGATTTCCACCTTGGTCCC (SEC ID Nº: 381)

La digestión del producto PCR ensamblado se realizó con las enzimas de

restricción BamHI y HindIII y el gen se ligó en los sitios correspondientes en el pDOM50, un vector de expresión de mamíferos que es un derivado de pTT5 con una secuencia líder secretora IgG de ratón V-J2-C N-terminal para facilitar la expresión en el medio celular.

Secuencia líder (aminoácidos):

METDTLLLWVLLLWVPGSTG (SEC ID Nº: 382)

Secuencia líder (nucleótidos):

ATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTGCTGTGGGTGCCCGGATCC ACCGGGC (SEC ID Nº: 383)

Se preparó un ADN plasmídico usando QIAfilter megaprep (Qiagen). Se transfectó ADN 1 µg /ml con Fectin-293 en células HEK293E y se cultivaron en medio sin suero. La proteína se expresó en el cultivo durante 5 días y se purificó del sobrenadante del cultivo usando la resina de afinidad a proteína L y se eluyó con glicina 100 mM pH 2. Las proteínas se llevaron a una concentración superior a 1 mg/ml, se intercambió tampón a PBS y las endotoxinas se agotaron usando columnas de giro Q (Vivascience).

Tabla 11: Secuencias Interferón alfa 2b-AlbudAb con y sin etiqueta-myc (como secuencias de aminoácidos y nucleótidos)

El Interferón alfa 2b es N-terminal con respecto a AlbudAb en las siguientes fusiones.

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
DMS7321 (IFNα2b-DOM7h-14)	CDLPQTHSLGS	TGCGACTTGCC	CDLPQTHSLGS	TGCGACTTGCC
	RRTLMLLAQMR	ACAGACACATA	RRTLMLLAQMR	ACAGACACATA
	RISLFSCLKDRH	GTTTGGGATCA	RISLFSCLKDRH	GTTTGGGATCA
	DFGFPQEEFGN	AGAAGAACATT	DFGFPQEEFGN	AGAAGAACATT
	QFQKAETIPVLH	GATGTTATTAG	QFQKAETIPVLH	GATGTTATTAG
	EMIQQIFNLFST	CACAAATGCGT	EMIQQIFNLFST	CACAAATGCGT
	KDSSAAWDETL	AGAATTTCTTT	KDSSAAWDETL	AGAATTTCTTT
	LDKFYTELYQQ	GTTCTCTTGTC	LDKFYTELYQQ	GTTCTCTTGTC
	LNDLEACVIQG	TAAAGGACCGT	LNDLEACVIQG	TAAAGGACCGT
	VGVTETPLMKE	CACGACTTCG	VGVTETPLMKE	CACGACTTCG
	DSILAVRKYFQR	GATTCCCTCAG	DSILAVRKYFQR	GATTCCCTCAG
	ITLYLKEKKYSP	GAAGAGTTTG	ITLYLKEKKYSP	GAAGAGTTTG
	CAWEVVRAEIM	GAAACCAATTC	CAWEVVRAEIM	GAAACCAATTC
	RSFSLSTNLQE	CAAAAAGCAGA	RSFSLSTNLQE	CAAAAAGCAGA
	SLRSKETVAAP	AACTATTCCTG	SLRSKETVAAP	AACTATTCCTG
	SDIQMTQSPSS	TCTTGCACGAA	SDIQMTQSPSS	TCTTGCACGAA
	LSASVGDRVTIT	ATGATCCAGCA	LSASVGDRVTIT	ATGATCCAGCA
	CRASQWIGSQL	AATATTCAATTT	CRASQWIGSQL	AATATTCAATTT
	SWYQQKPGKA	GTTTTCTACAA	SWYQQKPGKA	GTTTTCTACAA
	PKLLIMWRSSL	AGGACTCATCA	PKLLIMWRSSL	AGGACTCATCA
	QSGVPSRFSGS	GCCGCTTGGG	QSGVPSRFSGS	GCCGCTTGGG
	GSGTDFTLTISS	ATGAAACTCTG	GSGTDFTLTISS	ATGAAACTCTG
	LQPEDFATYYC	TTAGATAAATT	LQPEDFATYYC	TTAGATAAATT

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
	AQGAALPRTFG QGTKVEIKR **AAAEQKLISEE DLN*** (SEC ID Nº: 384)	CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA GAAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT	AQGAALPRTFG QGTKVEIKR (SEC ID Nº: 386)	CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA GAAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		CGCTGCTCCAT CTGACATCCAG ATGACCCAGTC TCCATCCTCCC TGTCTGCATCT GTAGGAGACC GTGTCACCATC ACTTGCCGGG CAAGTCAGTG GATTGGGTCTC AGTTATCTTGG TACCAGCAGAA ACCAGGGAAA GCCCCTAAGCT CCTGATCATGT GGCGTTCCTC GTTGCAAAGTG GGGTCCCATC ACGTTTCAGTG GCAGTGGATC TGGGACAGATT TCACTCTCACC ATCAGCAGTCT		CGCTGCTCCAT CTGACATCCAG ATGACCCAGTC TCCATCCTCCC TGTCTGCATCT GTAGGAGACC GTGTCACCATC ACTTGCCGGG CAAGTCAGTG GATTGGGTCTC AGTTATCTTGG TACCAGCAGAA ACCAGGGAAA GCCCCTAAGCT CCTGATCATGT GGCGTTCCTC GTTGCAAAGTG GGGTCCCATC ACGTTTCAGTG GCAGTGGATC TGGGACAGATT TCACTCTCACC ATCAGCAGTCT

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
		GCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTGC GGCGTTGCCT AGGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG**G CGGCCGCAGA ACAAAAACTCA TCTCAGAAGAG GATCTGAATTA A** (SEC ID Nº: 385)		GCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTGC GGCGTTGCCT AGGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG (SEC ID Nº: 387)
DMS732 (IFNα2b-DOM7h-14-10)	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN QFQKAETIPVLH EMIQQIFNLFST KDSSAAWDETL LDKFYTELYQQ	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT GATGTTATTAG CACAAATGCGT AGAATTTCTTT GTTCTCTTGTC	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN QFQKAETIPVLH EMIQQIFNLFST KDSSAAWDETL LDKFYTELYQQ	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT GATGTTATTAG CACAAATGCGT AGAATTTCTTT GTTCTCTTGTC

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
	LNDLEACVIQG VGVTETPLMKE DSILAVRKYFQR ITLYLKEKKYSP CAWEVVRAEIM RSFSLSTNLQE SLRSKETVAAP SDIQMTQSPSS LSASVGDRVTIT CRASQWIGSQL SWYQQKPGKA PKLLIMWRSSL QSGVPSRFSGS GSGTDFTLTISS LQPEDFATYYC AQGLRHPKTFG QGTKVEIKR **AAAEQKLISEE DLN*** (SEC ID Nº: 388)	TAAAGGACCGT CACGACTTCG GATTCCCTCAG GAAGAGTTTG GAAACCAATTC CAAAAAGCAGA AACTATTCCTG TCTTGCACGAA ATGATCCAGCA AATATTCAATTT GTTTTCTACAA AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA	LNDLEACVIQG VGVTETPLMKE DSILAVRKYFQR ITLYLKEKKYSP CAWEVVRAEIM RSFSLSTNLQE SLRSKETVAAP SDIQMTQSPSS LSASVGDRVTIT CRASQWIGSQL SWYQQKPGKA PKLLIMWRSSL QSGVPSRFSGS GSGTDFTLTISS LQPEDFATYYC AQGLRHPKTFG QGTKVEIKR (SEC ID Nº: 390)	TAAAGGACCGT CACGACTTCG GATTCCCTCAG GAAGAGTTTG GAAACCAATTC CAAAAAGCAGA AACTATTCCTG TCTTGCACGAA ATGATCCAGCA AATATTCAATTT GTTTTCTACAA AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA GAAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT CGCTGCTCCAT CTGACATCCAG ATGACCCAGTC TCCATCCTCCC TGTCTGCATCT GTAGGAGACC GTGTCACCATC ACTTGCCGGG		AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA GAAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT CGCTGCTCCAT CTGACATCCAG ATGACCCAGTC TCCATCCTCCC TGTCTGCATCT GTAGGAGACC GTGTCACCATC ACTTGCCGGG

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		CAAGTCAGTG GATTGGGTCTC AGTTATCTTGG TACCAGCAGAA ACCAGGGAAA GCCCCTAAGCT CCTGATCATGT GGCGTTCCTC GTTGCAAAGTG GGGTCCCATC ACGTTTCAGTG GCAGTGGATC TGGGACAGATT TCACTCTCACC ATCAGCAGTCT GCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTTTG AGGCATCCTAA GACGTTCGGC CAAGGGACCA AGGTGGAAATC		CAAGTCAGTG GATTGGGTCTC AGTTATCTTGG TACCAGCAGAA ACCAGGGAAA GCCCCTAAGCT CCTGATCATGT GGCGTTCCTC GTTGCAAAGTG GGGTCCCATC ACGTTTCAGTG GCAGTGGATC TGGGACAGATT TCACTCTCACC ATCAGCAGTCT GCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTTTG AGGCATCCTAA GACGTTCGGC CAAGGGACCA AGGTGGAAATC

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
		AAACGG**GCGG CCGCAGAACA AAAACTCATCT CAGAAGAGGA TCTGAATTAA** (SEC ID Nº: 389)		AAACGG (SEC ID Nº: 391)
DMS7323 (IFNα2b-DOM7h-14-18)	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN QFQKAETIPVLH EMIQQIFNLFST KDSSAAWDETL LDKFYTELYQQ LNDLEACVIQG VGVTETPLMKE DSILAVRKYFQR ITLYLKEKKYSP CAWEVVRAEIM RSFSLSTNLQE SLRSKETVAAP SDIQMTQSPSS LSASVGDRVTIT	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT GATGTTATTAG CACAAATGCGT AGAATTTCTTT GTTCTCTTGTC TAAAGGACCGT CACGACTTCG GATTCCCTCAG GAAGAGTTTG GAAACCAATTC CAAAAAGCAGA AACTATTCCTG TCTTGCACGAA ATGATCCAGCA	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN QFQKAETIPVLH EMIQQIFNLFST KDSSAAWDETL LDKFYTELYQQ LNDLEACVIQG VGVTETPLMKE DSILAVRKYFQR ITLYLKEKKYSP CAWEVVRAEIM RSFSLSTNLQE SLRSKETVAAP SDIQMTQSPSS LSASVGDRVTIT	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT GATGTTATTAG CACAAATGCGT AGAATTTCTTT GTTCTCTTGTC TAAAGGACCGT CACGACTTCG GATTCCCTCAG GAAGAGTTTG GAAACCAATTC CAAAAAGCAGA AACTATTCCTG TCTTGCACGAA ATGATCCAGCA

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
	CRASQWIGSQL SWYQQKPGKA PKLLIMWRSSL QSGVPSRFSGS GSGTDFTLTISS LQPEDFATYYC AQGLMKPMTF GQGTKVEIKR**A AAEQKLISEEDL N*** (SEC ID Nº: 392)	AATATTCAATTT GTTTTCTACAA AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA	CRASQWIGSQL SWYQQKPGKA PKLLIMWRSSL QSGVPSRFSGS GSGTDFTLTISS LQPEDFATYYC AQGLMKPMTF GQGTKVEIKR (SEC ID Nº: 394)	AATATTCAATTT GTTTTCTACAA AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		GAAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT CGCTGCTCCAT CTGACATCCAG ATGACCCAGTC TCCATCCTCCC TGTCTGCATCT GTAGGAGACC GTGTCACCATC ACTTGCCGGG CAAGTCAGTG GATTGGGTCTC AGTTATCTTGG TACCAGCAGAA ACCAGGGAAA GCCCCTAAGCT CCTGATCATGT GGCGTTCCTC GTTGCAAAGTG		GAAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT CGCTGCTCCAT CTGACATCCAG ATGACCCAGTC TCCATCCTCCC TGTCTGCATCT GTAGGAGACC GTGTCACCATC ACTTGCCGGG CAAGTCAGTG GATTGGGTCTC AGTTATCTTGG TACCAGCAGAA ACCAGGGAAA GCCCCTAAGCT CCTGATCATGT GGCGTTCCTC GTTGCAAAGTG

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
		GGGTCCCATC ACGTTTCAGTG GCAGTGGATC TGGGACAGATT TCACTCTCACC ATCAGCAGTCT GCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTCTT ATGAAGCCTAT GACGTTCGGC CAAGGGACCA AGGTGGAAATC AAACGG**GCGG CCGCAGAACA AAAACTCATCT CAGAAGAGGA TCTGAATTAA** (SEC ID Nº: 393)		GGGTCCCATC ACGTTTCAGTG GCAGTGGATC TGGGACAGATT TCACTCTCACC ATCAGCAGTCT GCAACCTGAA GATTTTGCTAC GTACTACTGTG CTCAGGGTCTT ATGAAGCCTAT GACGTTCGGC CAAGGGACCA AGGTGGAAATC AAACGG (SEC ID Nº: 395)
DMS7324 (IFNα2b-DOM7h-14-19)	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH	TGCGACTTGCC ACAGACACATA GTTTGGGATCA	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH	TGCGACTTGCC ACAGACACATA GTTTGGGATCA

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
	DFGFPQEEFGN	AGAAGAACATT	DFGFPQEEFGN	AGAAGAACATT
	QFQKAETIPVLH	GATGTTATTAG	QFQKAETIPVLH	GATGTTATTAG
	EMIQQIFNLFST	CACAAATGCGT	EMIQQIFNLFST	CACAAATGCGT
	KDSSAAWDETL	AGAATTTCTTT	KDSSAAWDETL	AGAATTTCTTT
	LDKFYTELYQQ	GTTCTCTTGTC	LDKFYTELYQQ	GTTCTCTTGTC
	LNDLEACVIQG	TAAAGGACCGT	LNDLEACVIQG	TAAAGGACCGT
	VGVTETPLMKE	CACGACTTCG	VGVTETPLMKE	CACGACTTCG
	DSILAVRKYFQR	GATTCCCTCAG	DSILAVRKYFQR	GATTCCCTCAG
	ITLYLKEKKYSP	GAAGAGTTTG	ITLYLKEKKYSP	GAAGAGTTTG
	CAWEVVRAEIM	GAAACCAATTC	CAWEVVRAEIM	GAAACCAATTC
	RSFSLSTNLQE	CAAAAAGCAGA	RSFSLSTNLQE	CAAAAAGCAGA
	SLRSKETVAAP	AACTATTCCTG	SLRSKETVAAP	AACTATTCCTG
	SDIQMTQSPSS	TCTTGCACGAA	SDIQMTQSPSS	TCTTGCACGAA
	LSASVGDRVTIS	ATGATCCAGCA	LSASVGDRVTIS	ATGATCCAGCA
	CRASQWIGSQL	AATATTCAATTT	CRASQWIGSQL	AATATTCAATTT
	SWYQQKPGEA	GTTTTCTACAA	SWYQQKPGEA	GTTTTCTACAA
	PKLLIMWRSSL	AGGACTCATCA	PKLLIMWRSSL	AGGACTCATCA
	QSGVPSRFSGS	GCCGCTTGGG	QSGVPSRFSGS	GCCGCTTGGG
	GSGTDFTLTISS	ATGAAACTCTG	GSGTDFTLTISS	ATGAAACTCTG
	LQPEDFATYYC	TTAGATAAATT	LQPEDFATYYC	TTAGATAAATT
	AQGAALPRTFG	CTACACTGAAC	AQGAALPRTFG	CTACACTGAAC
	QGTKVEIKR	TATATCAACAA	QGTKVEIKR	TATATCAACAA
	AAAEQKLISEE	CTGAACGATCT	(SEC ID Nº: 398)	CTGAACGATCT

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
	DLN* (SEC ID Nº: 396)	AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA GAAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT CGCTGCTCCAT CTGACATCCAG ATGACCCAGTc		AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA GAAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT CGCTGCTCCAT CTGACATCCAG ATGACCCAGTc

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		TCCATCCTCCC TGTCTGCATCT GTAGGAGACC GTGTCACCATC TCTTGCCGGG CAAGTCAGTG GATTGGGTCTC AGTTATCTTGG TACCAGCAGAA ACCAGGGGAA GCCCCTAAGCT CCTGATCATGT GGCGTTCCTC GTTGCAAAGTG GGGTCCCATC ACGTTTCAGTG GCAGTGGATC TGGGACAGATT TCACTCTCACC ATCAGCAGTCT GCAACCTGAA GATTTTGCTAC GTACTACTGTG		TCCATCCTCCC TGTCTGCATCT GTAGGAGACC GTGTCACCATC TCTTGCCGGG CAAGTCAGTG GATTGGGTCTC AGTTATCTTGG TACCAGCAGAA ACCAGGGGAA GCCCCTAAGCT CCTGATCATGT GGCGTTCCTC GTTGCAAAGTG GGGTCCCATC ACGTTTCAGTG GCAGTGGATC TGGGACAGATT TCACTCTCACC ATCAGCAGTCT GCAACCTGAA GATTTTGCTAC GTACTACTGTG

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
		CTCAGGGTGC GGCGTTGCCT AGGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG**G CGGCCGCAGA ACAAAAACTCA TCTCAGAAGAG GATCTGAATTA A** (SEC ID Nº: 397)		CTCAGGGTGC GGCGTTGCCT AGGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG (SEC ID Nº: 399)
DMS7325 (IFNα2b-DOM7h-11)	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN QFQKAETIPVLH EMIQQIFNLFST KDSSAAWDETL LDKFYTELYQQ LNDLEACVIQG VGVTETPLMKE DSILAVRKYFQR	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT GATGTTATTAG CACAAATGCGT AGAATTTCTTT GTTCTCTTGTC TAAAGGACCGT CACGACTTCG GATTCCCTCAG	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN QFQKAETIPVLH EMIQQIFNLFST KDSSAAWDETL LDKFYTELYQQ LNDLEACVIQG VGVTETPLMKE DSILAVRKYFQR	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT GATGTTATTAG CACAAATGCGT AGAATTTCTTT GTTCTCTTGTC TAAAGGACCGT CACGACTTCG GATTCCCTCAG

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
	ITLYLKEKKYSP CAWEVVRAEIM RSFSLSTNLQE SLRSKETVAAP SDIQMTQSPSS LSASVGDRVTIT CRASRPIGTTLS WYQQKPGKAP KLLIWFGSRLQ SGVPSRFSGSG SGTDFTLTISSL QPEDFATYYCA QAGTHPTTFGQ GTKVEIKR **AAAEQKLISEE DLN*** (SEC ID Nº: 400)	GAAGAGTTTG GAAACCAATTC CAAAAAGCAGA AACTATTCCTG TCTTGCACGAA ATGATCCAGCA AATATTCAATTT GTTTTCTACAA AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA	ITLYLKEKKYSP CAWEVVRAEIM RSFSLSTNLQE SLRSKETVAAP SDIQMTQSPSS LSASVGDRVTIT CRASRPIGTTLS WYQQKPGKAP KLLIWFGSRLQ SGVPSRFSGSG SGTDFTLTISSL QPEDFATYYCA QAGTHPTTFGQ GTKVEIKR (SEC ID Nº: 402)	GAAGAGTTTG GAAACCAATTC CAAAAAGCAGA AACTATTCCTG TCTTGCACGAA ATGATCCAGCA AATATTCAATTT GTTTTCTACAA AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA GAAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT CGCTGCTCCAT CTGACATCCAG ATGACCCAGTC TCCATCCTCCC TGTCTGCATCT GTAGGAGACC GTGTCACCATC ACTTGCCGGG CAAGTCGTCC GATTGGGACG ACGTTAAGTTG		GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA GAAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT CGCTGCTCCAT CTGACATCCAG ATGACCCAGTC TCCATCCTCCC TGTCTGCATCT GTAGGAGACC GTGTCACCATC ACTTGCCGGG CAAGTCGTCC GATTGGGACG ACGTTAAGTTG

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
		GTACCAGCAG AAACCAGGGA AAGCCCCTAAG CTCCTGATCTG GTTTGGTTCCC GGTTGCAAAGT GGGGTCCCAT CACGTTTCAGT GGCAGTGGAT CTGGGACAGA TTTCACTCTCA CCATCAGCAGT CTGCAACCTGA AGATTTTGCTA CGTACTACTGT GCGCAGGCTG GGACGCATCC TACGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG**G** **CGGCCGCAGA** **ACAAAAACTCA**		GTACCAGCAG AAACCAGGGA AAGCCCCTAAG CTCCTGATCTG GTTTGGTTCCC GGTTGCAAAGT GGGGTCCCAT CACGTTTCAGT GGCAGTGGAT CTGGGACAGA TTTCACTCTCA CCATCAGCAGT CTGCAACCTGA AGATTTTGCTA CGTACTACTGT GCGCAGGCTG GGACGCATCC TACGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG (SEC ID Nº: 403)

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
		TCTCAGAAGAG GATCTGAATTA A (SEC ID Nº: 401)		
DMS7326 (IFNα2b-DOM7h-11-12)	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN QFQKAETIPVLH EMIQQIFNLFST KDSSAAWDETL LDKFYTELYQQ LNDLEACVIQG VGVTETPLMKE DSILAVRKYFQR ITLYLKEKKYSP CAWEVVRAEIM RSFSLSTNLQE SLRSKETVAAP SDIQMTQSPSS LSASVGDRVTIT CRASRPIGTML SWYQQKPGKA	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT GATGTTATTAG CACAAATGCGT AGAATTTCTTT GTTCTCTTGTC TAAAGGACCGT CACGACTTCG GATTCCCTCAG GAAGAGTTTG GAAACCAATTC CAAAAAGCAGA AACTATTCCTG TCTTGCACGAA ATGATCCAGCA AATATTCAATTT GTTTTCTACAA	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN QFQKAETIPVLH EMIQQIFNLFST KDSSAAWDETL LDKFYTELYQQ LNDLEACVIQG VGVTETPLMKE DSILAVRKYFQR ITLYLKEKKYSP CAWEVVRAEIM RSFSLSTNLQE SLRSKETVAAP SDIQMTQSPSS LSASVGDRVTIT CRASRPIGTML SWYQQKPGKA	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT GATGTTATTAG CACAAATGCGT AGAATTTCTTT GTTCTCTTGTC TAAAGGACCGT CACGACTTCG GATTCCCTCAG GAAGAGTTTG GAAACCAATTC CAAAAAGCAGA AACTATTCCTG TCTTGCACGAA ATGATCCAGCA AATATTCAATTT GTTTTCTACAA

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
	PKLLILFGSRLQ SGVPSRFSGSG SGTDFTLTISSL QPEDFATYYCA QAGTHPTTFGQ GTKVEIKR **AAAEQKLISEE DLN*** (SEC ID Nº: 404)	AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA GAAATTATGAG GTCCTTCTCTC	PKLLILFGSRLQ SGVPSRFSGSG SGTDFTLTISSL QPEDFATYYCA QAGTHPTTFGQ GTKVEIKR (SEC ID Nº: 406)	AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA GAAATTATGAG GTCCTTCTCTC

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT CGCTGCTCCAT CTGACATCCAG ATGACCCAGTC TCCATCCTCCC TGTCTGCATCT GTAGGAGACC GTGTCACCATC ACTTGCCGGG CAAGTCGTCC GATTGGGACG ATGTTAAGTTG GTACCAGCAG AAACCAGGGA AAGCCCCTAAG CTCCTGATCTT GTTTGGTTCCC GGTTGCAAAGT GGGGTCCCAT CACGTTTCAGT		TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT CGCTGCTCCAT CTGACATCCAG ATGACCCAGTC TCCATCCTCCC TGTCTGCATCT GTAGGAGACC GTGTCACCATC ACTTGCCGGG CAAGTCGTCC GATTGGGACG ATGTTAAGTTG GTACCAGCAG AAACCAGGGA AAGCCCCTAAG CTCCTGATCTT GTTTGGTTCCC GGTTGCAAAGT GGGGTCCCAT CACGTTTCAGT

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
		GGCAGTGGAT CTGGGACAGA TTTCACTCTCA CCATCAGCAGT CTGCAACCTGA AGATTTTGCTA CGTACTACTGT GCGCAGGCTG GGACGCATCC TACGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG**G CGGCCGCAGA ACAAAAACTCA TCTCAGAAGAG GATCTGAATTA A** (SEC ID Nº: 405		GGCAGTGGAT CTGGGACAGA TTTCACTCTCA CCATCAGCAGT CTGCAACCTGA AGATTTTGCTA CGTACTACTGT GCGCAGGCTG GGACGCATCC TACGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG (SEC ID Nº: 407)
DMS7327 (IFNα2b-DOM7h-11-15)	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT	CDLPQTHSLGS RRTLMLLAQMR RISLFSCLKDRH DFGFPQEEFGN	TGCGACTTGCC ACAGACACATA GTTTGGGATCA AGAAGAACATT

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
	QFQKAETIPVLH EMIQQIFNLFST KDSSAAWDETL LDKFYTELYQQ LNDLEACVIQG VGVTETPLMKE DSILAVRKYFQR ITLYLKEKKYSP CAWEVVRAEIM RSFSLSTNLQE SLRSKETVAAP SDIQMTQSPSS LSASVGDRVTIT CRASRPIGTML SWYQQKPGKA PKLLILAFSRLQ SGVPSRFSGSG SGTDFTLTISSL QPEDFATYYCA QAGTHPTTFGQ GTKVEIKR **AAAEQKLISEE DLN*** (SEC ID	GATGTTATTAG CACAAATGCGT AGAATTTCTTT GTTCTCTTGTC TAAAGGACCGT CACGACTTCG GATTCCCTCAG GAAGAGTTTG GAAACCAATTC CAAAAAGCAGA AACTATTCCTG TCTTGCACGAA ATGATCCAGCA AATATTCAATTT GTTTTCTACAA AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC	QFQKAETIPVLH EMIQQIFNLFST KDSSAAWDETL LDKFYTELYQQ LNDLEACVIQG VGVTETPLMKE DSILAVRKYFQR ITLYLKEKKYSP CAWEVVRAEIM RSFSLSTNLQE SLRSKETVAAP SDIQMTQSPSS LSASVGDRVTIT CRASRPIGTML SWYQQKPGKA PKLLILAFSRLQ SGVPSRFSGSG SGTDFTLTISSL QPEDFATYYCA QAGTHPTTFGQ GTKVEIKR (SEC ID Nº: 410)	GATGTTATTAG CACAAATGCGT AGAATTTCTTT GTTCTCTTGTC TAAAGGACCGT CACGACTTCG GATTCCCTCAG GAAGAGTTTG GAAACCAATTC CAAAAAGCAGA AACTATTCCTG TCTTGCACGAA ATGATCCAGCA AATATTCAATTT GTTTTCTACAA AGGACTCATCA GCCGCTTGGG ATGAAACTCTG TTAGATAAATT CTACACTGAAC TATATCAACAA CTGAACGATCT AGAGGCTTGC

	aa + myc	**nt + myc**	**Aminoácidos sin tag**	**Nucleótidos sin tag**
	Nº: 408)	GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA GAAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT CGCTGCTCCAT CTGACATCCAG ATGACCCAGTC TCCATCCTCCC		GTTATTCAGGG TGTAGGAGTTA CTGAAACTCCC CTAATGAAAGA AGATTCAATTC TAGCCGTTAGA AAATACTTTCA GCGTATCACAT TGTATTTAAAG GAAAAGAAATA CTCCCCATGTG CATGGGAGGT GGTTAGAGCA GAAATTATGAG GTCCTTCTCTC TTTCTACGAAT TTGCAAGAATC TTTGAGATCTA AGGAAACCGT CGCTGCTCCAT CTGACATCCAG ATGACCCAGTC TCCATCCTCCC

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		TGTCTGCATCT GTAGGAGACC GTGTCACCATC ACTTGCCGGG CAAGTCGTCC GATTGGGACG ATGTTAAGTTG GTACCAGCAG AAACCAGGGA AAGCCCCTAAG CTCCTGATCCT TGCTTTTTCCC GTTTGCAAAGT GGGGTCCCAT CACGTTTCAGT GGCAGTGGAT CTGGGACAGA TTTCACTCTCA CCATCAGCAGT CTGCAACCTGA AGATTTTGCTA CGTACTACTGC GCGCAGGCTG		TGTCTGCATCT GTAGGAGACC GTGTCACCATC ACTTGCCGGG CAAGTCGTCC GATTGGGACG ATGTTAAGTTG GTACCAGCAG AAACCAGGGA AAGCCCCTAAG CTCCTGATCCT TGCTTTTTCCC GTTTGCAAAGT GGGGTCCCAT CACGTTTCAGT GGCAGTGGAT CTGGGACAGA TTTCACTCTCA CCATCAGCAGT CTGCAACCTGA AGATTTTGCTA CGTACTACTGC GCGCAGGCTG

	aa + myc	nt + myc	Aminoácidos sin tag	Nucleótidos sin tag
		GGACGCATCC TACGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG**G CGGCCGCAGA ACAAAAACTCA TCTCAGAAGAG GATCTGAATTA A** (SEC ID Nº: 409)		GGACGCATCC TACGACGTTCG GCCAAGGGAC CAAGGTGGAA ATCAAACGG (SEC ID Nº: 411)

Las secuencias de aminoácidos y nucleótidos resaltadas en negrita representan el sitio de clonación y la etiqueta MYC. * representa el codon de terminación en el extremo del gen.

Determinación de Afinidad y Caracterización Biofísica:

Para determinar la afinidad de unión (K_D) de las proteínas de fusión AlbudAb-IFNα2b a cada albúmina de suero; las proteínas de fusión purificadas se analizaron por BIAcore sobre albúmina (inmovilizada mediante acoplamiento de amina primaria sobre matrices CM5; BIAcore) usando concentraciones de las proteínas de fusión de 5000 nM a 39 nM (5000 nM, 2500 nM, 1250 nM, 625 nM, 312 nM, 156 nM, 78 nM, 39 nM) en tampón HBS-EP BIAcore.

Tabla 12: Afinidad para SA

AlbudAb	**Fusión**	**Afinidad para SA (nM)**	**Kd**	**Ka**
		Rata		
DOM7h-14	IFNα2b	350	4,500E-02	1,28E+05
DOM7h-14-10	IFNα2b	16	4,970E-03	5,90E+05
DOM 7h-14-18	IFNα2b	780	2,127E-01	5,80E+05
DOM 7h-14-19	IFNα2b	1900	1,206E-01	7,96E+04
DOM 7h-11	IFNα2b	6000	7,500E-01	nd
DOM 7h-11-12	IFNα2b	1700	3,100E-01	1,30E+05
DOM 7h-11-15	IFNα2b	200	1,660E-02	1,50E+05
		Cyno		
DOM 7h-14	IFNα2b	60	1,32E-02	5,0E+05
DOM 7h-14-10	IFNα2b	19	7,05E-03	4,50E+05
DOM 7h-14-18	IFNα2b	sin unión	sin unión	sin unión
DOM 7h-14-19	IFNα2b	520	8,47E-02	2,73E+05
DOM 7h-11	IFNα2b	3300	3,59E-01	1,20E+05
DOM 7h-11-12	IFNα2b	630	3,45E-01	7,00E+05
DOM 7h-11-15	IFNα2b	15	4,86E-03	3,60E+05
		Ratón		

AlbudAb	**Fusión**	**Afinidad para SA (nM)**	**Kd**	**Ka**
DOM 7h-14	IFNα2b	240	3,21E-02	1,50E+06
DOM 7h-14-10	IFNα2b	60	3,45E-02	6,86E+05
DOM 7h-14-18	IFNα2b	180	1,50E-01	9,84E+05
DOM 7h-14-19	IFNα2b	490	4,03E-02	1,19E+05
DOM 7h-11	IFNα2b	6000	1,55E-01	nd
DOM 7h-11-12	IFNα2b	150	9,49E-02	6,30E+05
DOM 7h-11-15	IFNα2b	28	6,69E-03	2,80E+05
		Humano		
DOM 7h-14	IFNα2b	244	2,21E-02	9,89E+04
DOM 7h-14-10	IFNα2b	32	6,58E-03	3,48E+05
DOM 7h-14-18	IFNα2b	470	2,75E-01	6,15E+05
DOM 7h-14-19	IFNα2b	350	4,19E-02	1,55E+05
DOM 7h-11	IFNα2b	670	2,02E-01	7,00E+05
DOM 7h-11-12	IFNα2b	500	1,66E-01	3,90E+05
DOM 7h-11-15	IFNα2b	10	1,87E-03	3,50E+05

Cuando IFNα2b está unido a las variantes AlbudAb, en todos los casos la afinidad de unión de AlbudAb para la albúmina de suero se reduce. DOM7h-14-10 y DOM7-11-15 conservan afinidad de unión mejorada para la albúmina de suero en todas las especies en comparación con el parental. DOM7h-11-12 también muestra afinidad

de unión mejorada para la albúmina de suero en todas las especies en comparación con el parental.

Tabla 13: Caracterización Biofísica

La Caracterización Biofísica se realizó por SEC MALLS y DSC como se ha descrito anteriormente para los AlbudAbs sencillos.

AlbudAb	Fusión	Número DMS	Parámetros biofísicos	
			SEC MALLS	DSC Tm (ºC)
DOM 7h-14	IFNα2b	DMS7321	M/D	58-65
DOM 7h-14-10	IFNα2b	DMS7322	M/D	55-65
DOM 7h-14-18	IFNα2b	DMS7323	M/D	55-65
DOM 7h-14-19	IFNα2b	DMS7324	M/D	59-66
DOM 7h-11	IFNα2b	DMS7325	M/D	65,8-66,2
DOM 7h-11-12	IFNα2b	DMS7326	M/D	67-67,3
DOM 7h-11-15	IFNα2b	DMS7327	M/D	56,3-66,2

M/D indica un equilibrio de monómero/dímero según se detecta por SEC MALLS

En la Tabla 13 se observa la expresión para todos los clones en el intervalo de 17,5 a 54 mg/l en HEK293.

Para las variantes IFNα2b-DOM7h-14 e IFNα2b-DOM7h-11, durante la maduración de afinidad se mantuvieron parámetros biofísicos y niveles de expresión favorables.

Determinación del PK para fusiones AlbudAb-IFNα2b

Las fusiones AlbudAbs IFNα2b DMS7321 (IFNα2b-DOM7h-14) DMS7322 (IFNα2b-DOM7h-14-10) DMS7323 (IFNα2b-DOM7h-14-18), DMS7324 (IFNα2b-DOM7h-14-19), DMS7325 (IFNα2b-DOM7h-11), DMS7326 (IFNα2b-DOM7h-11-12), DMS7327 (IFNα2b-DOM7h-11-15) se expresaron con la etiqueta myc en cantidades de 20-50 mg en células HEK293 y se purificaron del sobrenadante de cultivo usando resina de afinidad a proteína L y se eluyó con glicina 100 mM pH2. Las proteínas se llevaron a una concentración superior a 1 mg/ml, se intercambio de tampón en PBS de Dulbecco y la endotoxina se agotó usando columnas de giro Q (Vivascience).

Para el PK de Rata, se dosificó IFN-AlbudAb como inyecciones i.v. únicas de 2,0 mg/kg usando 3 ratas por compuesto. Se tomaron muestras de suero a 0,16, 1, 4, 8, 24, 48, 72, 120, 168 h. El análisis de los niveles en suero se realizó por EASY ELISA de acuerdo con las instrucciones del fabricante (GE Healthcare, número de catálogo RPN5960).

Para el PK de Ratón, se dosificó DMS7322 (IFN2b-DOM7h-14-10) DMS7325 (IFN2b-DOM7h-11), DMS7326 (IFN2b-DOM7h-11-12), DMS7327 (IFN2b-DOM7h-11-15) todos etiquetados con myc como inyecciones i.v. únicas de 2,0 mg/kg por grupos de dosis de 3 sujetos y las muestras de suero se tomaron a 10 min; 1 h, 8 h; 24 h; 48 h; 72 h; 96 h. El análisis de los niveles en suero se realizó por EASY ELISA de acuerdo con las instrucciones del fabricante (GE Healthcare, número de catálogo RPN5960).

Tabla 14:

Especie	AlbudAb	Fusión	Albúmina K_D (nM)	Parámetros PK

				AUC h x μg/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
Rata	**7h-14**	IFNα2b	350	832,1	2,4	27	94,5
	7h-14-10	IFNα2b	16	1380,7	1,5	35,8	75,2
	7h-14-18	IFNα2b	780	691,2	2,9	22,4	93,7
	7h-14-19	IFNα2b	1900	969,4	2,2	25	78,7
	7h-11	IFNα2b	6000	327,9	6,5	11	101,9
	7h-11-12	IFNα2b	1700	747,1	2,8	25,8	104,7
	7h-11-15	IFNα2b	200	1118,7	1,8	39,5	103,6
Ratón	**7h-14**	IFNα2b	240	761,2	2,6	30,4	115,3
	7h-14-10	IFNα2b	60	750,5	2,7	30,9	118,6
	7h-11	IFNα2b	6000	493,9	4,0	8,8	51,2
	7h-11-12	IFNα2b	150	439,6	4,5	21,5	140,9
	7h-11-15	IFNα2b	28	971,8	2,1	33,6	99,6

Los parámetros farmacocinéticos obtenidos de estudios de rata y ratón se ajustaron usando un modelo no-compartimental. Clave: AUC: Área bajo la curva del tiempo de dosificación extrapolado al infinito; CL: eliminación; t1/2: es el tiempo durante el cual la concentración en sangre se divide en dos; Vz: volumen de distribución en base a la fase terminal.

Se ensayaron IFNα2b-AlbudAbs en rata y ratón. Para todas las proteínas de

fusión de la variante IFNα2b-DOM7h-11 tanto en rata como en ratón, el valor t1/2 mejoró en comparación con el parental. La mejora del t1/2 equivale a una KD mejorada *in vitro* para la albúmina de suero.

Para las variantes IFNα2b-DOM7h-14-10 la mejora de K_D *in vitro* para la albúmina de suero también equivale a una mejora del t1/2 en rata.

Todas las proteínas de fusión IFNα2b-AlbudAbs mostraron una disminución en la unión a RSA de 5 a 10 veces en comparación con AlbudAb sencillo. Este efecto es más pronunciado (es decir, 10 veces) en la serie DOM7h-14 que en la serie DOM7h-11 (únicamente una disminución de 5 veces).

Ejemplo 8: Fusiones AlbudAb adicionales con proteínas, péptidos y NCE.

Se ensayaron diversas AlbudAbs fusionadas a otras entidades químicas concretamente anticuerpos de dominio (dAbs), péptidos y compuestos NCE. Los resultados se muestran en la tabla 15.

Tabla 15:

Especie	AlbudAb	Fusión	Albúmina K_D (nM)	Paráme-tros PK			
				AUC h x µg/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
Rata	DOM7h-14	Exendina-4	2400	18	57,1	11	901,9
	DOM7h-14-10	Exendina-4	19	43,6	23,1	22,1	740,3

Especie	AlbudAb	Fusión	Albúmina K_D (nM)	Paráme-tros PK			
				AUC h x µg/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
	DOM7h-14-18	Exendina-4	16000	16,9	75,7	9,4	1002,5
	DOM7h-14-19	Exendina-4	17000	31,4	32,5	11,9	556,7
	DOM7h-11	Exendina-4	24000	6,1	168	7,1	1684,1
	DOM7h-11-12	Exendina-4	1400	24,2	59,9	13	1068,7
	DOM7h-11-15	Exendina-4	130	36,3	27,6	19,3	765,7
	DOM7h14-10	NCE-GGGGSC	62				
	DOM7h14-10	NCE-TVAAPSC	35				
Humano	DOM7h-14	NCE	204				

Especie	AlbudAb	Fusión	Albúmina K_D (nM)	Paráme-tros PK			
				AUC h x µg/ml	CL ml/h/kg	t1/2 h	Vz ml/kg
Ratón	DOM7h-11	DOM1m-21-23		234	10,7	4,7	72,5
	DOM7h-11-12	DOM1m-21-23		755	3,3	18	86,2
	DOM7h-11-15	DOM1m-21-23		1008	2,5	17,4	62,4

Clave: DOM1m-21-23 es un dAb anti-TNFR1, Exendina-4 es un péptido (un agonista de GLP-1) de 39 aminoácidos de longitud. NCE, NCE-GGGGSC y NCE-TVAAPSC se describen a continuación.

Anteriormente se ha descrito el uso de fusiones genéticas con un dAb de unión a albúmina (AlbudAb) para ampliar la semivida PK del dAbs anti-TNFR1 *in vivo* (véase, por ejemplo los documentos WO04003019, WO2006038027, WO2008149148). En estas solicitudes estas solicitudes PCT se hace referencia a los protocolos. En la tabla anterior, DOM1m-21-23 es un dAb anti-TNFR1 de ratón.

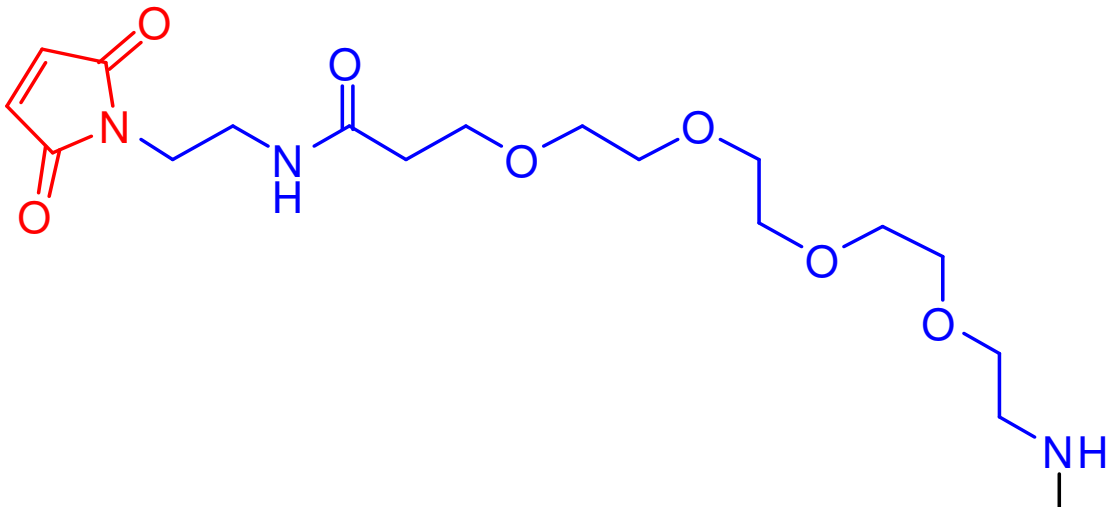
Para producir las fusiones genéticas de exendina-4 o con DOM7h-14 (u otro AlbudAb) que se unen a la albúmina de suero, la secuencia AlbudAb-engarce-exendina-4 se clonó en el vector pTT 5 (obtenible de CNRC, Canadá). En cada caso la exendina-4 estaba en el extremo 5' de la construcción y el dAb en el extremo 3'. El engarce era un engarce $(G_4S)_3$. Se preparó ADN sin endotoxina en *E. coli* usando lisis alcalina (usando

el kit Giga para plásmido sin endotoxina, obtenible de Qiagen CA) y se usó para transfectar células HEK293E (obtenibles de CNRC, Canadá). La transfección se realizó en matraces de células HEK293E / 250 ml a 1,75x10^6 céls/ml usando 333 µl de fectin 293 (Invitrogen) y 250 µg de ADN por matraz y la expresión se realizó a 30ºC durante 5 días. El sobrenadante se recogió por centrifugación y la purificación se realizó por purificación de afinidad en proteína L. La proteína se unió en lotes a la resina, se rellenó en una columna y se lavó con volúmenes de 10 columnas de PBS. La proteína se eluyó con 50 ml de glicina 0,1 M pH 2 y se neutralizó con Tris pH 8. La proteína del tamaño esperado se identificó sobre un gel SDS-PAGE.

Fusiones NCE Albudab:

Se ensayó una fusión de AlbudAb con una nueva entidad química (NEC). La NCE, un inhibidor de ADAMTS-4 de molécula pequeña se sintetizó con un engarce PEG (engarce PEG 4 (es decir, moléculas PEG 4 antes de la maleimida) y un grupo maleimida para la conjugación al AlbudAb. La conjugación del NCE al AlbudAb se realiza mediante un resto de cistina modificado por ingeniería genética en la posición de aminoácido R108C o después de un espaciador de 5 aminoácidos (GGGGSC) o 6 aminoácidos (TVAAPSC) en el extremo del AlbudAb. En resumen, el AlbudAb se redujo con TCEP (Pierce, Catálogo Número 77720), se desalinizó usando una columna PD10 (GE healthcare) en Bis-Tris 25 mM, EDTA 5 mM, glicerol al 10% (v/v) pH 6,5. Se añadió un exceso molar de 5 veces del NCE activado en DMSO no sobrepasando el 10% de concentración final (V/V). La reacción se incubó durante una noche a temperatura ambiente y se dializó exhaustivamente en Tris 20 mM pH 7,4.

Engarce PEG:



Secuencias:

DOM7h-14 R108C:

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKC (SEC ID Nº: 412)

Nucleótidos:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGT CACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTGGTACCAGC AGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTCCTCGTTGCAAAGT GGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCAT CAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGTGCTCAGGGTTTGAGGC ATCCTAAGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAATGC (SEC ID Nº: 413)

Véase la Tabla 5 para las secuencias de DOM7h-14-10/TVAAPSC y DOM7h-14-

10/GGGGSC (es decir, DOM7h-14-10/G4SC).

NCE-AlbudAbs DOM7h-14-10 GGGGSC y DOM7h14-10 TVAAPSC, muestran una disminución de afinidad *in vitro* de 5 a 10 veces (K_D) para RSA según se determina por BIAcore cuando se fusionan a la entidad química. Aún no se dispone de los datos PK para estas moléculas.

Fusión dAb-Albudab: los 2 AlbudAbs DOM7h-11 con la mayor afinidad para RSA experimentaron una disminución de afinidad para RSA de 2 veces en un BIAcore cuando se fusionaron a un anticuerpo de dominio terapéutico (DOM1m-21-23) en comparación con AlbudAb no fusionado. El clon DOM7h-11 muestra una K_D micromolar cuando se fusiona (2,8 μM) así como cuando no se fusiona (~5 μM).

Fusión Exendina-4 AlbudAb: el efecto de la fusión de AlbudAbs a un péptido en la capacidad de unión a RSA es aproximadamente de 10 veces, excepto DOM7h-14-10, que únicamente muestra una disminución de unión de 4 veces. El efecto, sin embargo, es más pronunciado para la serie DOM7h-14 (excepto DOM7h-14-10) que lo que parece ser para la serie DOM7h-11.

Para todos los datos anteriores, el T1/2 de la fusión aumentó con afinidad mejorada para las SA de las especies.

Generalmente se clasifican los efectos terapéuticos de Albudab como que son terapéuticamente susceptibles (para el tratamiento y/o profilaxis de enfermedades, afecciones o indicaciones) cuando las fusiones AlbudAb-fármaco muestran un intervalo de afinidad (K_D) de 0,1 nM a 10 nM para la unión a la albúmina de suero.

Los intervalos terapéuticos de las fusiones AlbudAbs y AlbudAb (Proteína-AlbudAb por ejemplo IFNa2b-DOM7h-14-10; Péptido-AlbudAbs por ejemplo Exendina-4-DOM7h-14-10; dAb-AlbudAbs por ejemplo DOM1m21-23-DOM7h11-15; NCE-AlbudAb por ejemplo ADAMTS-4-DOM7h-14-10) se definen a continuación: se muestran

intervalos de afinidad (K_D) que son útiles para la terapia de afecciones, enfermedades o indicaciones crónicas o agudas que se muestran. También se muestran intervalos de afinidad marcados como “intermedios”. AlbudAb y las fusiones en este intervalo son útiles en enfermedades, afecciones o indicaciones agudas o crónicas. De este modo, la afinidad de la AlbudAb o fusión para la albúmina de suero puede adaptarse o seleccionarse de acuerdo con la enfermedad, afección o indicación a tratar. Como se describe anteriormente, la invención proporciona AlbudAbs con afinidades que permiten que cada AlbudAb se clasifique como “afinidad elevada”, “afinidad media” o “afinidad baja”, permitiendo de esta manera al experto en la materia seleccionar la AlbudAb apropiada de la invención de acuerdo con la terapia en cuestión. Véase la Figura 2.

Ejemplo 9: Secuencias DOM7h-11-15^{S12P}

Secuencia de Aminoácidos de DOM7h-11-15^{S12P}

DIQMTQSPSSLPASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQSGVP SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR (SEC ID Nº: 414)

Un aspecto de la invención proporciona un ácido nucleico que comprende la secuencia de nucleótidos de DOM7h-11-15^{S12P} o una secuencia de nucleótidos tiene una identidad de secuencia de al menos el 80% con respecto a dicha secuencia seleccionada. DOM7h-11-15^{S12P} se produjo usando la siguiente secuencia de ácidos nucleicos (la C subrayada indica el cambio (frente a los ácidos nucleicos que codifican DOM7h-11-15) que conduce una prolina en la posición 12):

GACATCCAGATGACCCAGTCTCCATCCTCCCTG<u>C</u>CTGCATCTGTAGGAGACCGTGT

CACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACCAG
CAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCCCGTTTGCAAAG
TGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCA
TCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGCGCGCAGGCTGGGAC
GCATCCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG (SEC ID Nº: 415)

DOM7h-11-15^{S12P} se construyó usando DOM7h-11-15 como un molde en una PCR en la que se usó un cebador para introducir la mutación S12P. La secuencia del cebador es:

GCAACAGCGTCGACGGACATCCAGATGACCCAGTCTCCATCCTCCCTGCCTGCAT CTGTAGG (SEC ID Nº: 416).

Un aspecto alternativo de la invención proporciona un ácido nucleico que comprende la secuencia de nucleótidos de la SEC ID Nº: 415 o una secuencia de nucleótidos tiene una identidad de secuencia de al menos el 80% con respecto a dicha secuencia seleccionada. En una realización, DOM7h-11-15^{S12P} se codifica por y se expresa a partir de un vector que contiene una región de engarce y una secuencia C-terminal que codifica una proteína o un fármaco peptídico de un dominio variable simple u otro fragmento de anticuerpo para preparar el producto de fusión de proteína *in-line*. El engarce, en una realización, comprende la secuencia de aminoácidos TVA, por ejemplo, TVAAPS. Otros aspectos de la invención son un vector que comprende el ácido nucleico; y una célula huésped aislada que comprende el vector. La invención también proporciona un método de tratamiento o prevención de una enfermedad o trastorno en un paciente, que comprende administrar al menos una dosis de DOM7h-11-15^{S12P} a dicho paciente.

RESUMEN DE LA REVELACIÓN

La invención se refiere a variantes mejoradas del dominio variable sencillo de inmunoglobulina anti-albúmina de suero DOM7h-11, así como a ligandos y conjugados de fármacos que comprenden dichas variantes, composiciones, ácido nucleicos, vectores y huéspedes.

Restos Kabat	'	'	'	'	5	'	'	'	'	10	'	'	'	'	15	'	'	'	'	20
DOM7h-14	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T
DOM7h-14-10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-18	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-36	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Restos Kabat	'	'	'	'	25	'	'	'	'	30	'	'	'	'	35	'	'	'	'	40
DOM7h-14	I	T	C	**R**	**A**	**S**	**Q**	**W**	**I**	**G**	**S**	**Q**	**L**	**S**	W	Y	Q	Q	K	P
DOM7h-14-10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-18	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-19	.	S	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-36	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Restos Kabat	'	'	'	'	45	'	'	'	'	50	'	'	'	'	55	'	'	'	'	60
DOM7h-14	G	K	A	P	K	L	L	I	M	**W**	**R**	**S**	**S**	**L**	**Q**	**S**	G	V	P	S
DOM7h-14-10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-18	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-19	.	E	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-36	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Restos Kabat	'	'	'	'	65	'	'	'	'	70	'	'	'	'	75	'	'	'	'	80
DOM7h-14	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P
DOM7h-14-10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Figura 1A

DOM7h-14-18	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-36	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Restos Kabat	'	'	'	'	85	'	'	'	'	90	'	'	'	'	95	'	'	'	'	100
DOM7h-14	E	D	F	A	T	Y	Y	C	**A**	**Q**	**G**	**A**	**A**	**L**	**P**	**R**	**T**	F	G	Q
DOM7h-14-10	.	.	.	.	.	.	.	.	.	.	.	**L**	**R**	**H**	.	**K**	.	.	.	.
DOM7h-14-18	.	.	.	.	.	.	.	.	.	.	.	**L**	**M**	**K**	.	**M**	.	.	.	.
DOM7h-14-19	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
DOM7h-14-28	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	**K**	.	.	.	.
DOM7h-14-36	.	.	.	.	.	.	.	.	.	.	.	**F**	**K**	**K**	.	.	.	.	.	.
Restos Kabat	'	'	'	'	105	'	'	'												
DOM7h-14	G	T	K	V	E	I	K	R												
DOM7h-14-10	.	.	.	.	.	.	.	.												
DOM7h-14-18	.	.	.	.	.	.	.	.												
DOM7h-14-19	.	.	.	.	.	.	.	.												
DOM7h-14-28	.	.	.	.	.	.	.	.												
DOM7h-14-36	.	.	.	.	.	.	.	.												

Figura 1B

humano	Parámetros cinéticos basados en linajes DOM7h-14 y DOM7h-11 (intervalos confirmados por datos)		
	Intervalos globales		
	KD: 1 to 10000		
	Kd:1.5e-4 to 0.1 ; Ka:2e6 to 1e4		
Agentes terapéuticos :	Crónico	Intermedio	Agudo
	Afinidad elevada	Afinidad media	Afinidad baja
	KD: 0,1-400	KD: 400-2000	KD: 2000-10000
	Kd:1,5e-4 to 8e-3 ; Ka:1e6 to 5e4	Kd: 8e-3 to 0,08 ; Ka: 2e4 to 5e4	Kd:0.08 to 0,1 ; Ka: 5e4 to 1e4
Intervalos opcionales	KD: 1-200	KD: 400-1500	KD: 2000-6000
	Kd:3e-4 to 2e-3; Ka: 1e6 to 5e4	Kd:8e-3 to 0,08; Ka: 2e4 to 6e4	Kd:0.08 to 0,1 ; Ka: 5e4 to 2e4
Ejemplos	DOM7h-11-15, DOM7h-14, DOM7h-14-10, DOM7h-14-18, DOM7h-14-19, DOM7h-11-18, DOM7h-11-19 DMS7321, DMS7322; DMS7324, DMS7327	DMS7325, DMS7326; DMS7323	DOM7h-11

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Figura 2A

Cyno			
	Intervalos globales		
	KD: 1 to 10000		
	Kd:1.5e-4 to 0.1 ; Ka:2e6 to 1e4		
Agentes terapéuticos	crónico	intermedio	agudo
	Afinidad alta	Afinidad media	Afinidad baja
	KD: 0,1-400	KD: 400-2000	KD: 2000-10000
	Kd:1,5e-4 to 8e-3 ; Ka:2e6 to 2e4	Kd: 8e-3 to 0,08 ; Ka: 2e4 to 5e4	Kd:0.08 to 0,1 ; Ka: 5e4 to 1e4
Intervalos opcionales	KD: 1-200	KD: 400-1500	KD: 2000-6000
	Kd:3e-4 to 2e-3; Ka: 1e6 to 1e4	Kd:2e-3 to 0,05; Ka: 2e4 to 1e4	Kd:0.08 to 0,1 ; Ka: 5e4 to 2e4
Ejemplos	DMS7327; DOM7h-11-15; DOM7h-14; DOM7h-14-10; DOM7h-14-18; DOM7h-14-19, DOM7h-14-28, DOM7h-14-36 DMS7321; DMS7322	DOM7h-11; DMS7326; DMS7324;	DOM7h11-12, DOM7h-11-18 DMS7325

Figura 2A

Rata			
	Intervalos globlales		
	KD: 1 to 10000		
	Kd: 2e-3 to 0,15 ; Ka: 2e6 to 1e4		
Agentes terapéuticos	crónico	Intermedio	Agudo
	Afinidad elevada	Afinidad media	Afinidad baja
	KD: 1-300	KD: 300-2000	KD: 2000-10000
	Kd:2e-3 to 5e-2 ; Ka:2e6 to 2e5	Kd:5e-2 to 0,09 ; Ka:2e5 to 4,5e4	Kd:0,09 to 0,15 ; Ka: 4,5e4 to 1,5e4
Intervalos opcionales	KD: 20-200	KD: 400-1800	KD: 2000-6000
	Kd:9e-3 to 2e-2 ; Ka: 1e6 to 1e5	Kd: 4e-2 to 0,09; Ka:1e5 to 5e4	Kd: 0,1 to 0,14 ; Ka: 5e4 to 3e4
Ejemplos	DOM7h-11-15; DOM7h-11-12; DOM7h-11-18, DOM7h-11-19, DOM7h-14-28, DOM7h-14-36, DOM7h-14 DMS7327; DMS7322	DOM7h-14-18; DOM7h-14-19; DMS7321; DMS7323, DMS7324, DMS7326;,	DMS7325; DOM7h-11;

Figura 2C

Ratón			
	Intervalos globales		
	KD: 1 to 10000		
	Kd: 2e-3 to 0.15 ; Ka: 2e6 to 1e4		
Agentes terapéuticos	crónico	intermedio	Agudo
	Afinidad elevada	Afinidad media	Afinidad baja
	KD: 1-100	KD: 100-2000	KD: 2000-10000
	Kd:2e-3 to 1e-2 ; Ka:2e6 to 1e5	Kd:1e-2 to 0,07 ; Ka: 1e5 to 3e4	Kd: 0,08 to 0,15; Ka: 4e4 to 1,5e4
Intervalos opcionales	KD: 1 to 80	KD: 120-2000	KD: 4000-10000
	Kd:2e-3 to 1e-2 ; Ka: 2e6 to 1,5e5	Kd: 9e-3 to 0,07 ; Ka: 1,3e5 to 3e4	Kd:0,1 to 0,15 ; Ka: 2.5e4 to 1,5e4
Ejemplos	DOM7h-11-15;; DOM7h-14; DOM7h-14-10, DOM7h-14-18, DOM7h-14-19, DOM7h-11-18, DOM7h-11-19, DOM7h-14-28, DOM7h-14-36 DMS7322, DMS7327	DMS7321; DMS7323; DMS7324; DOM7h-11-12; DMS7326	DMS7325; DOM7h-11

Figura 2D

CAPÍTULO REIVINDICATORIO

(Solicitud Divisional A)

1. Una variante de dominio variable sencillo de inmunoglobulina anti-albúmina de suero (SA) de DOM7h-11, caracterizado porque la variante comprende mutaciones en la unión FW2/CDR2, en cada una de las posiciones 49, 50 y 51, (numeración de acuerdo con Kabat), donde:

el aminoácido de la posición 49 es Leu;

el aminoácido de la posición 50 es Ala; y

el aminoácido de la posición 51 es Phe;

y en donde la variante tiene de 2 a 8 cambios en comparación con la secuencia de aminoácidos de la proteína DOM7h-11.

2. La variante de la Reivindicación 1, en donde la variante comprende una Met en la posición 32 (numeración de acuerdo con Kabat).

3. La variante de la Reivindicación 1 o 2, donde la variante comprende al menos una mutación seleccionada de las siguientes: Posición 87 = H, y Posición 91 = T.

4. La variante de la Reivindicación 1, donde la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de un dominio variable simple de SEC ID NO: 2 o tiene hasta 4 cambios en comparación con la secuencia de aminoácidos seleccionada, siempre y cuando la secuencia de aminoácidos de la variante tenga mutaciones en la unión FW2/CDR2 en cada una de las posiciones 49, 50 y 51, como se define en la Reivindicación 1.

5. La variante de una cualquier de las Reivindicaciones 1 a 4, donde la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de un dominio variable simple de SEC ID NO: 2.

6. La variante de una cualquier de las Reivindicaciones 1 a 4, donde la variante comprende una secuencia de aminoácidos que es idéntica a la secuencia de aminoácidos de SEC ID NO: 414.

7. La variante de cualquier reivindicación anterior, en el que la variante comprende un sitio de unión que se une específicamente a SA humana con una constante de disociación (KD) de aproximadamente 0,1 a aproximadamente 10000 nM, opcionalmente de

aproximadamente 1 a aproximadamente 6000 nM, como se determina por resonancia de plasmón superficial.

8. La variante de cualquier reivindicación anterior, en la que la variante comprende un sitio de unión que se une específicamente a SA humana con una constante de velocidad de disociación (K_d) de aproximadamente 1,5 x 10^{-4} a aproximadamente 0,1 s^{-1}, opcionalmente de aproximadamente 3 x 10^{-4} a aproximadamente 0,1 s^{-1}, como se determina por resonancia de plasmón superficial.

9. La variante de cualquier reivindicación anterior, en el que la variante comprende un sitio de unión que se une específicamente a SA humana con una constante de velocidad de asociación (K_a) de aproximadamente 2 x 10^6 a aproximadamente 1 x 10^4 $M^{-1}s^{-1}$, opcionalmente de aproximadamente 1 x 10^6 a aproximadamente 2 x 10^4 $M^{-1}s^{-1}$, como se determina por resonancia de plasmón superficial.

10. La variante de cualquier reivindicación anterior, en el que la variante comprende un sitio de unión que se une específicamente a SA de mono *Cynomolgus* con una constante de disociación (KD) de aproximadamente 0,1 a aproximadamente 10000 nM, opcionalmente de aproximadamente 1 a aproximadamente 6000 nM, como se determina por resonancia de plasmón superficial.

11. La variante de cualquier reivindicación anterior, en la que la variante comprende un sitio de unión que se une específicamente a SA de mono *Cynomolgus* con una constante de velocidad de disociación (K_d) de aproximadamente 1,5 x 10^{-4} a aproximadamente 0,1 s^{-1}, opcionalmente de aproximadamente 3 x 10^{-4} a aproximadamente 0,1 s^{-1}, como se determina por resonancia de plasmón superficial.

12. La variante de cualquier reivindicación anterior, en la que la variante comprende un sitio de unión que se une específicamente a SA de mono *Cynomolgus* con una constante de velocidad de asociación (K_a) de aproximadamente 2 x 10^6 a aproximadamente 1 x 10^4 $M^{-1}s^{-1}$, opcionalmente de aproximadamente 1 x 10^6 a aproximadamente 5 x 10^3 $M^{-1}s^{-1}$, como se determina por resonancia de plasmón superficial.

13. Un ligando multiespecífico que comprende una variante anti-SA de cualquier reivindicación anterior y un motivo de unión que se une específicamente a un antígeno blanco distinto de SA.

14. Un ligando multiespecífico como el de la Reivindicación 13, donde el otro antígeno

blanco distinto de SA es TNFR1.

15. Un dominio variable sencillo de variante anti-SA de una cualquiera de las Reivindicaciones 1 a 12, en el que el dominio de variable se conjuga con un fármaco (opcionalmente un fármaco NCE), opcionalmente en el que la variante seleccionada es SEC ID NO: 2 o SEC ID NO: 414.

16. Una proteína de fusión que comprende un fármaco polipeptídico o peptídico fusionado a una variante de acuerdo con una cualquiera de las Reivindicaciones 1 a 12, opcionalmente en el que la variante seleccionada es SEC ID NO: 2 o SEC ID NO: 414.

17. Una proteína de fusión de acuerdo con la Reivindicación 16, en la que la proteína de fusión comprende un enlace, tal como, un enlace que comprende la secuencia de aminoácidos TVA, opcionalmente TVAAPS, entre la variante y el fármaco.

18. Una composición que comprende una variante, proteína de fusión o ligando de cualquier reivindicación anterior y un diluyente, transportador, excipiente o vehículo farmacéuticamente aceptable.

19. Un ácido nucléico que comprende una secuencia de nucleótidos que codifica una variante de acuerdo con una cualquiera de las Reivindicaciones 1 a 12 o un ligando multiespecífico de la Reivindicación 14 o proteína de fusión de la Reivindicación 16 o 17.

20. Un ácido nucléico que comprende la secuencia de nucleótidos seleccionada de la secuencia de nucleótidos SEC ID NO: 7 o una secuencia de nucleótidos que tiene una identidad de secuencia de al menos el 80% con respecto a dicha secuencia seleccionada.

21. Un ácido nucléico que comprende la secuencia de nucleótidos SEC ID NO: 415 o una secuencia de nucleótidos que tiene una identidad de secuencia de al menos el 80% con respecto a dicha secuencia seleccionada.

22. Un vector que comprende el ácido nucléico de las Reivindicaciones 19, 20 o 21.

23. Una célula transformada que comprende el vector de la Reivindicación 22.

****

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<120> IMPROVED ANTI-SERUM ALBUMIN BINDING
VARIANTS

<130> DB63556 WO

<140> PCT/EP2010/052008
<141> 2010-02-17

<150> 61/247136
<151> 2009-09-30

<150> 61/163987
<151> 2009-03-27

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

<160> 420

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

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

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

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

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

<400> 2
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met
20 25 30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Leu Ala Phe Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg

100 105

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

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

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

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

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

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

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

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

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

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

<220>
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<400> 6
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gggcaagtcg tccgattggg acgatgttaa gttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatcttgttt ggttcccggt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgtgcgcag gctgggacgc atcctacgac gttcggccaa 300
gggaccaagg tggaaatcaa acgg 324

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

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

<400> 7
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gggcaagtcg tccgattggg acgatgttaa gttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatccttgct ttttcccgtt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgcgcgcag gctgggacgc atcctacgac gttcggccaa 300
gggaccaagg tggaaatcaa acgg 324

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

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

<400> 8
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gggcaagtcg tccgattggg acgatgttaa gttggtacca gcagaaacca 120
gggaaagccc caaagctcct gatctggttt ggttcccggt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacca ctgtgcgcag gcggggacgc atcctacgac gttcggccaa 300
gggaccaagg tggaaatcaa acgg 324

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

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

<400> 9
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gggcaagtcg tccgattggg acgatgttaa gttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatcttgttt ggttcccggt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacggat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgtgcgcag actgggacgc atcccacgac gttcggccaa 300
gggaccaagg tggaaatcaa acgg 324

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

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

<400> 10
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gggcaagtcg tccgattggg acgacgttaa gttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatcctttgg aattcccgtt tgcaaagtgg ggtcccatca 180

cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgtgcgcag gctgggacgc atcctacgac gttcggccaa 300
gggaccaagg tggaaatcaa acgg 324

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

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

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

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

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

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

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

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

<400> 13
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Met Arg Tyr
            20   25   30
Arg Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Ser Ile Asp Ser Asn Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Asp Arg Thr Glu Arg Ser Pro Val Phe Asp Tyr Trp Gly Gln
            100   105   110
Gly Thr Leu Val Thr Val Ser Ser
        115   120

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

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

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

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

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

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

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

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

<400> 16
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

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

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

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

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

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

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

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

<210> 19
<211> 119
<212> PRT
<213> Artificial Sequence

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<400> 19
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15

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

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

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

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

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

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

<400> 21
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Gly Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Asp Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

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

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

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

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

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

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

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

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

<400> 24
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 25
<211> 119
<212> PRT

<213> Artificial Sequence

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

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

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

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

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

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

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

<400> 27
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

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

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

<400> 28
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp His Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

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

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

<400> 29
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Gly Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Asp Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

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

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

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

100 105 110
Thr Leu Val Thr Val Ser Ser
115

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

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

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

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

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

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

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

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

<400> 33
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

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

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

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

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

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

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

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

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

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

<400> 36
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

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

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

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

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

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

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

<400> 38
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

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

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

<400> 39
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

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


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

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

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


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

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

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


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

<220>
```

<223> Derived from a Human Germline sequence.

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

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

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

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

<210> 44
<211> 119
<212> PRT
<213> Artificial Sequence

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

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

<210> 45
<211> 119

<212> PRT
<213> Artificial Sequence

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

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

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

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

<400> 46
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Glu Arg Arg Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

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

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

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

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

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

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

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

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

<400> 49
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Lys Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

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

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

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

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

<210> 51
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 51
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 52
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 52
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 53
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 53
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60

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

<210> 54
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 54
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Lys Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 55
<211> 119
<212> PRT
<213> Artificial Sequence

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

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

<210> 56
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 56
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30

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

<210> 57
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 57
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 58
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 58
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 59
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 59

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


<210> 60
<211> 119
<212> PRT
<213> Artificial Sequence

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

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


<210> 61
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 61
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115


<210> 62
<211> 119
<212> PRT
<213> Artificial Sequence
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<220>
<223> Derived from a Human Germline sequence.

<400> 62
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 63
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 63
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 64
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 64
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Lys Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 65

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

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

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

<210> 66
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 66
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 67
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 67
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser

115

<210> 68
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 68
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Phe
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 69
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 69
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 70
<211> 119
<212> PRT
<213> Artificial Sequence

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

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

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

<210> 71
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 71
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 72
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 72
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ala Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Pro Asp Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 73
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 73
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ser Val

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

<210> 74
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 74
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Pro Asp Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 75
<211> 119
<212> PRT
<213> Artificial Sequence

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

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

<210> 76
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 76
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr

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


<210> 77
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 77
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Pro Asp Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115


<210> 78
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 78
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Ala Trp Gly Asp Arg Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115


<210> 79
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.
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<400> 79
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Gly Gly Gln Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 80
<211> 119
<212> PRT
<213> Artificial Sequence

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

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

<210> 81
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 81
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Gly Gly Thr Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 82
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 82
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Lys Gly Thr Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 83
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 83
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35   40   45
Ser Gln Ile Ser Glu Thr Gly Arg Arg Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 84
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 84
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Asn Asn Thr Gly Ser Thr Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Asp Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 85
<211> 119
<212> PRT
<213> Artificial Sequence

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

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

<210> 86
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 86
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Pro Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 87
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 87
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
        115

<210> 88
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 88
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 89
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 89
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 90
<211> 119
<212> PRT
<213> Artificial Sequence

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

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

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

<210> 91
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 91
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Arg Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 92
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 92
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Leu Asn Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 93
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 93
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

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

<210> 94
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 94
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Arg Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 95
<211> 119
<212> PRT
<213> Artificial Sequence

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

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

<210> 96
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 96
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15

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

<210> 97
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 97
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Leu Tyr Thr Gly Arg Trp Val Ser Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 98
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 98
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Val Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 99
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 99
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Leu Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 100
<211> 119
<212> PRT
<213> Artificial Sequence

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

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

<210> 101
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 101
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Ala Asp Arg Arg Tyr Tyr Ala Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 102
<211> 119
<212> PRT

<213> Artificial Sequence

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

<400> 102
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Asp Arg Arg Tyr Tyr Ala His Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 103
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 103
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asn Thr Ala Asp Arg Arg Tyr Tyr Ala Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 104
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 104
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala His Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 105
<211> 119
<212> PRT
<213> Artificial Sequence

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

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

<210> 106
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 106
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asn Thr Ala Asp Arg Arg Tyr Tyr Ala His Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 107
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 107
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Val Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly

100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 108
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 108
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ala Asn Thr Gly Asp Arg Arg Tyr Tyr Ala Asp Ala Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 109
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 109
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 110
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 110
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

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

<210> 111
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 111
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 112
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 112
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ser His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 113
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 113
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

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

<210> 114
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 114
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Thr Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 115
<211> 119
<212> PRT
<213> Artificial Sequence

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

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

<210> 116
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 116
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

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


<210> 117
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 117
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ala Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115


<210> 118
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 118
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115


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

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

<400> 119
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 120
<211> 119
<212> PRT
<213> Artificial Sequence

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

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

<210> 121
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 121
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Arg Tyr Tyr Asp Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 122
<211> 119

<212> PRT
<213> Artificial Sequence

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

<400> 122
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asp Thr Gly Asp Arg Arg Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 123
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 123
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asp Thr Gly Asp Arg Arg Tyr Tyr Asp Asp Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 124
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 124
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Gly Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 125
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 125
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Ala Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 126
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 126
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Gly Pro Phe Gln Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 127
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 127
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

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

<210> 128
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 128
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 129
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 129
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Gln Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 130
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 130
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60

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

<210> 131
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 131
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 132
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 132
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
20 25 30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> 133
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 133
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
20 25 30

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

<210> 134
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 134
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 135
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 135
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Arg Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 136
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 136

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

<210> 137
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 137
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 138
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 138
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ser His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 139
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 139
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ser His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 140
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 140
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Thr His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 141
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 141
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Thr His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 142

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

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

<400> 142
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 143
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 143
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 144
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 144
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Leu Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser

115

<210> 145
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 145
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 146
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 146
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 147
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 147
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

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

<210> 148
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 148
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Thr Tyr Tyr Asp His Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 149
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 149
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Arg Tyr Tyr Ala His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 150
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 150
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Arg Tyr Tyr Ala His Ala Val

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

<210> 151
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 151
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Arg Tyr Tyr Ala His Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 152
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 152
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Arg Tyr Tyr Asp His Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 153
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 153
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr

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


<210> 154
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 154
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ala Asp Thr Ala Asp Arg Arg Tyr Tyr Asp His Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115


<210> 155
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 155
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20                  25                  30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Arg Tyr Tyr Asp Asp Ala Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Thr Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Ile Tyr Thr Gly Arg Trp Glu Pro Phe Val Tyr Trp Gly Gln Gly
            100                 105                 110
Thr Leu Val Thr Val Ser Ser
        115


<210> 156
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 156
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Ala Asp Arg Thr Tyr Tyr Ala His Ala Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Val Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 157
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 157
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Val Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asn Thr Gly Gly His Thr Tyr Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Tyr Thr Gly Arg Trp Glu Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 158
<211> 119
<212> PRT
<213> Artificial Sequence

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

<400> 158
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Phe Lys Tyr
            20   25   30
Ser Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gln Ile Ser Asp Thr Gly Asp Arg Arg Tyr Tyr Asp His Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Ile Tyr Thr Gly Arg Trp Ala Pro Phe Glu Tyr Trp Gly Gln Gly
            100   105   110
Thr Leu Val Thr Val Ser Ser
        115

<210> 159
<211> 360
<212> DNA
<213> Artificial Sequence

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

<400> 159
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttatg aggtatagga tgcattgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcatcg attgattcta atggttctag tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaagatcgt 300
acggagcgtt cgccggtttt tgactactgg ggtcagggaa ccctggtcac cgtctcgagc 360

<210> 160
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 160
gaggtgcagc tgttggagtc tgggggaggc ttggtgcagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt gattatgaga tgcattgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcatct attagtgaga gtggtacgac gacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaacgtcgt 300
ttttctgctt ctacgtttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 161
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 161
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 300
ggtcattggg agcctttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 162
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 162
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 300
ggtcgttggg agccttatga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 163
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 163
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 164
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 164
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 300
ggtcgttggg agccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 165
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 165
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 166
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 166
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 167
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 167
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tgggatgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcacagt ctcgagc 357

<210> 168
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 168
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccata tcccgcgaca attccaagaa cacgctgtat 240

atgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 169
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 169
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttggt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg atctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 170
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 170
gaggtgcagc tgttggagtc aggggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtggtca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 300
ggtcgttggg agccttttga ccactggggt caggggaccc tggtcaccgt ctcgagc 357

<210> 171
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 171
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 172
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 172
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 173
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 173
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60

tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 174
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 174
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttTgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 175
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 175
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttTgtt aagtattcga tgggatgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcacagt ctcgagc 357

<210> 176
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 176
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttTgtt aagtattcga tgggatgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcgaata cgggtgatca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcacagt ctcgagc 357

<210> 177
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 177
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttTggt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg atctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 178
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 178
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttggt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg atctagagtg ggtctcacag atttcgaata cgggtgatca tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 179
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 179
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 180
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 180
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 181
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 181
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcggactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga agccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 182
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 182
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 183
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 183
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 184
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 184
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggcat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 185
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 185
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttta ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 186
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 186
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 187
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 187
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa ctcgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg tgcctttga caactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 188

<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 188
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttatt acgtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttca gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 189
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 189
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttggt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcggactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 190
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 190
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaagac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 191
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 191
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 192
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 192
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300

ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 193
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 193
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttaa gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 194
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 194
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttagt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgagcg tagatactac 180
gcagactcag tgaagggccg gttcaccatc tcccgcgaca atcccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg agcctttga atactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 195
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 195
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aactattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tacatactac 180
gcggactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttatga gtactggggt cagggaaccc tggtcaccgt cacgagc 357

<210> 196
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 196
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgata attccaagaa cacactgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 197
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 197
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120

ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga agccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 198
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 198
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 199
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 199
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 200
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 200
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 201
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 201
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc ggtatatacg 300
ggtcgttggg agcctttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 202
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 202
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga agccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 203
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 203
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 204
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 204
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 205
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 205
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 206
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 206
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 207
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 207
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggcc 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga agccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 208
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 208
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 209
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 209
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 210
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 210
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 211
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 211
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 212
<211> 357

<212> DNA
<213> Artificial Sequence

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

<400> 212
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga agccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 213
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 213
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggcc 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaagac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 214
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 214
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 215
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 215
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 216
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 216
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttg aagttttcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 217
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 217
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttTg aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 218
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 218
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttTc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 219
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 219
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttTg aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 220
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 220
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt caccTttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggcat attactgtgc gatatatacg 300
ggtcggtggc ccgactttga ctactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 221
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 221
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt caccTttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180

gcagactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggcat attactgtgc gatatatacg 300
ggtcggtggc ccgactttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 222
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 222
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggc ccgactttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 223
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 223
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggc ccgactttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 224
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 224
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggc ccgactttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 225
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 225
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggc ccgactttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 226
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 226

gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tgggatgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcggcct ggggtgacag gacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 227
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 227
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcggacg gcggtcagag gacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 228
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 228
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tgggatgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcggact ccggttaccg cacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 229
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 229
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtccagagtg ggtctcacag atttcggacg ggggtacgcg gacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 230
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 230
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tgggatgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcggaca agggtacgcg cacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 231
<211> 357
<212> DNA
<213> Artificial Sequence

<220>

<223> Derived from a Human Germline sequence.

<400> 231
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tgggatgggt ccgccaggct 120
ccagggaaag gtccagagtg ggtctcacag atttcggaga ccggtcgcag gacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 232
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 232
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attaacaata cgggttcgac cacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttga ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 233
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 233
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtccagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 234
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 234
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtccagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 235
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 235
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 236
<211> 357
<212> DNA

<213> Artificial Sequence

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

<400> 236
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 237
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 237
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 238
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 238
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
acacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 239
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 239
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg cagatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 240
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 240
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attttgaata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 241
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 241
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 242
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 242
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 243
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 243
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 244
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 244
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc ggtatatact 300
gggcgttggg tgtcttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 245
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 245
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gctatatact 300
gggcgttggg tgtcttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 246
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 246
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gtttaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc ggtatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 247
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 247
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gctatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 248
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 248
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata ctgctgatcg tagatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 249
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 249
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 250
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 250
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60

tcctgtgcgg cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata cgggcgatcg tagatactac 180
gcacacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 251
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 251
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttTgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata ctgctgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 252
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 252
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttTgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcacacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 253
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 253
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttTgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcgaata ctgctgatcg tagatactac 180
gcacacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 254
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 254
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttTgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cggctgatcg tagatactac 180
gcacacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 255
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 255
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgtgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 256
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 256
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcgaata cgggtgatcg tagatactac 180
gcagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 257
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 257
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 258
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 258
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 259
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 259
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 260
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 260
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
tcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 261
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 261
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
acacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 262
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 262
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
acagacgcgg tgaaggggcg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agcctttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 263
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 263
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 264
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 264
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttttg aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 265

<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 265
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata cgggtgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 266
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 266
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 267
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 267
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgcctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatcactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg aacctttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 268
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 268
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata cgggtgatcg tagatactac 180
gatgacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 269
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 269
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac 180
gatgactctg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300

ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 270
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 270
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata cgggtgatcg tagatactac 180
gatcactctg tgaagggccg gttcactatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 271
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 271
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata cgggtgatcg tagatactac 180
gatgacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 272
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 272
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg ggccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 273
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 273
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg tgcctttgc ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 274
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 274
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120

ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg gacctttttca gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 275
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 275
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttca gtactggggt cagggaactc tggtcaccgt ctcgagc 357

<210> 276
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 276
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 277
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 277
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg cgccttttca gtactggggt cagggaactc tggtcaccgt ctcgagc 357

<210> 278
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 278
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg tgcctttttca gtactggggt cagggcaccc tggtcaccgt ctcgagc 357

<210> 279
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 279
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ccggtgatcg tagatactac 180
gatcactctg tgaagggccg gttcactatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 280
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 280
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttg aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 281
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 281
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgcctttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 282
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 282
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttg aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 283
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 283
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttgga ggccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 284
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 284
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttttTC aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 285
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 285
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttttTG aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 286
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 286
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttttTG aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
tcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 287
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 287
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttttTC aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
tcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 288
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 288
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGTC cctgcgtctc 60
tcctgtgcag cctccggatt caccttttTC aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
acacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 289
<211> 357

<212> DNA
<213> Artificial Sequence

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

<400> 289
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttg aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
acacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 290
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 290
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 291
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 291
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttg aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 292
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 292
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttg aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ccggtgatcg tagatactac 180
gatcactctg tgaagggccg gttcactatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 293
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 293
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ccggtgatcg tagatactac 180
gatcactctg tgaagggccg gttcactatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 294
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 294
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tacatactac 180
gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgcgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 295
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 295
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttTt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tacatactac 180
gcacacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 296
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 296
gaggtgcagc tgttggagtc tgggggaggc ttggtgcagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tacatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 297
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 297
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tacatactac 180
gatcacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgctgaggac accgcggtat attactgtgc gatatatact 300
gggcgttggg tgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc   357

<210> 298
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 298
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggGtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac 180

gcacactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 299
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 299
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180
gcacacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 300
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 300
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac 180
gcacacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 301
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 301
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180
gatcacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 302
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 302
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac 180
gatcacgcgg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt caggggaccc tggtcaccgt ctcgagc 357

<210> 303
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 303

gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgtt aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag attgcggata ctgctgatcg tagatactac 180
gatcactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcggtggg cgccttttga gtactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 304
<211> 357
<212> DNA
<213> Artificial Sequence

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

<400> 304
gaggtgcagc tgctggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt caccttttc aagtattcga tggggtgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacag atttcggata ctgctgatcg tagatactac 180
gatgacgcgg tgaagggccg gttcaccatc acccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gatatatacg 300
ggtcgttggg agccttttgt ctactggggt cagggaaccc tggtcaccgt ctcgagc 357

<210> 305
<211> 163
<212> PRT
<213> Artificial Sequence

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

<400> 305
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1   5   10   15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20   25   30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    50   55   60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
65   70   75   80
Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln Gln Lys Pro Gly
                85   90   95
Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser Leu Gln Ser Gly
            100   105   110
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        115   120   125
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala
    130   135   140
Gln Gly Ala Ala Leu Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu
145   150   155   160
Ile Lys Arg

<210> 306
<211> 489
<212> DNA
<213> Artificial Sequence

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

<400> 306
catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60
ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120
ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180
cagtctccat cctccctgtc tgcatctgta ggagaccgtg tcaccatcac ttgccgggca 240
agtcagtgga ttgggtctca gttatcttgg taccagcaga aaccagggaa agcccctaag 300
ctcctgatca tgtggcgttc ctcgttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg 420
tactactgtg ctcagggtgc ggcgttgcct aggacgttcg gccaagggac caaggtggaa 480
atcaaacgg 489

<210> 307
<211> 163

<212> PRT
<213> Artificial Sequence

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

<400> 307
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1   5   10   15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20   25   30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    50   55   60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
65   70   75   80
Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln Gln Lys Pro Gly
                85   90   95
Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser Leu Gln Ser Gly
            100   105   110
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        115   120   125
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala
    130   135   140
Gln Gly Leu Arg His Pro Lys Thr Phe Gly Gln Gly Thr Lys Val Glu
145   150   155   160
Ile Lys Arg

<210> 308
<211> 489
<212> DNA
<213> Artificial Sequence

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

<400> 308
catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60
ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120
ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180
cagtctccat cctccctgtc tgcatctgta ggagaccgtg tcaccatcac ttgccgggca 240
agtcagtgga ttgggtctca gttatcttgg taccagcaga aaccagggaa agcccctaag 300
ctcctgatca tgtggcgttc ctcgttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg 420
tactactgtg ctcagggttt gaggcatcct aagacgttcg gccaagggac caaggtggaa 480
atcaaacgg   489

<210> 309
<211> 163
<212> PRT
<213> Artificial Sequence

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

<400> 309
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1   5   10   15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20   25   30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    50   55   60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
65   70   75   80
Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln Gln Lys Pro Gly
                85   90   95
Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser Leu Gln Ser Gly
            100   105   110
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        115   120   125
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala
    130   135   140

Gln Gly Leu Met Lys Pro Met Thr Phe Gly Gln Gly Thr Lys Val Glu
145 150 155 160
Ile Lys Arg

<210> 310
<211> 489
<212> DNA
<213> Artificial Sequence

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

<400> 310
catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60
ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120
ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180
cagtctccat cctccctgtc tgcatctgta ggagaccgtg tcaccatcac ttgccgggca 240
agtcagtgga ttgggtctca gttatcttgg taccagcaga aaccagggaa agcccctaag 300
ctcctgatca tgtggcgttc ctcgttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg 420
tactactgtg ctcagggtct tatgaagcct atgacgttcg gccaagggac caaggtggaa 480
atcaaacgg 489

<210> 311
<211> 163
<212> PRT
<213> Artificial Sequence

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

<400> 311
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
50 55 60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Ser Cys Arg Ala
65 70 75 80
Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln Gln Lys Pro Gly
85 90 95
Glu Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser Leu Gln Ser Gly
100 105 110
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
115 120 125
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala
130 135 140
Gln Gly Ala Ala Leu Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu
145 150 155 160
Ile Lys Arg

<210> 312
<211> 489
<212> DNA
<213> Artificial Sequence

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

<400> 312
catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60
ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120
ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180
cagtctccat cctccctgtc tgcatctgta ggagaccgtg tcaccatctc ttgccgggca 240
agtcagtgga ttgggtctca gttatcttgg taccagcaga aaccagggga agcccctaag 300
ctcctgatca tgtggcgttc ctcgttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg 420
tactactgtg ctcagggtgc ggcgttgcct aggacgttcg gccaagggac caaggtggaa 480
atcaaacgg 489

<210> 313
<211> 163
<212> PRT
<213> Artificial Sequence

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

<400> 313
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1   5   10   15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20   25   30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    50   55   60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
65   70   75   80
Ser Arg Pro Ile Gly Thr Thr Leu Ser Trp Tyr Gln Gln Lys Pro Gly
                85   90   95
Lys Ala Pro Lys Leu Leu Ile Trp Phe Gly Ser Arg Leu Gln Ser Gly
            100   105   110
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        115   120   125
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala
    130   135   140
Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly Thr Lys Val Glu
145   150   155   160
Ile Lys Arg

<210> 314
<211> 489
<212> DNA
<213> Artificial Sequence

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

<400> 314
catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60
ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120
ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180
cagtctccat cctccctgtc tgcatctgta ggagaccgtg tcaccatcac ttgccgggca 240
agtcgtccga ttgggacgac gttaagttgg taccagcaga aaccagggaa agcccctaag 300
ctcctgatct ggtttggttc ccggttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg 420
tactactgtg cgcaggctgg gacgcatcct acgacgttcg gccaagggac caaggtggaa 480
atcaaacgg   489

<210> 315
<211> 163
<212> PRT
<213> Artificial Sequence

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

<400> 315
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1   5   10   15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20   25   30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    50   55   60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
65   70   75   80
Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln Gln Lys Pro Gly
                85   90   95
Lys Ala Pro Lys Leu Leu Ile Leu Phe Gly Ser Arg Leu Gln Ser Gly
            100   105   110
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        115   120   125

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala
    130   135   140
Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly Thr Lys Val Glu
145   150   155   160
Ile Lys Arg

<210> 316
<211> 489
<212> DNA
<213> Artificial Sequence

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

<400> 316
catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60
ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120
ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180
cagtctccat cctccctgtc tgcatctgta ggagaccgtg tcaccatcac ttgccgggca 240
agtcgtccga ttgggacgat gttaagttgg taccagcaga aaccagggaa agcccctaag 300
ctcctgatct tgtttggttc ccggttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg 420
tactactgtg cgcaggctgg gacgcatcct acgacgttcg gccaagggac caaggtggaa 480
atcaaacgg   489

<210> 317
<211> 163
<212> PRT
<213> Artificial Sequence

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

<400> 317
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1   5   10   15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20   25   30
Ser Gly Ala Pro Pro Pro Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly
        35   40   45
Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    50   55   60
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
65   70   75   80
Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln Gln Lys Pro Gly
                85   90   95
Lys Ala Pro Lys Leu Leu Ile Leu Ala Phe Ser Arg Leu Gln Ser Gly
            100   105   110
Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        115   120   125
Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Ala
    130   135   140
Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly Thr Lys Val Glu
145   150   155   160
Ile Lys Arg

<210> 318
<211> 489
<212> DNA
<213> Artificial Sequence

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

<400> 318
catggtgaag gaacatttac cagtgacttg tcaaaacaga tggaagagga ggcagtgcgg 60
ttatttattg agtggcttaa gaacggagga ccaagtagcg gggcacctcc gccatcgggt 120
ggtggaggcg gttcaggcgg aggtggcagc ggcggtggcg ggtcggacat ccagatgacc 180
cagtctccat cctccctgtc tgcatctgta ggagaccgtg tcaccatcac ttgccgggca 240
agtcgtccga ttgggacgat gttaagttgg taccagcaga aaccagggaa agcccctaag 300
ctcctgatcc ttgctttttc ccgtttgcaa agtggggtcc catcacgttt cagtggcagt 360
ggatctggga cagatttcac tctcaccatc agcagtctgc aacctgaaga ttttgctacg 420
tactactgcg cgcaggctgg gacgcatcct acgacgttcg gccaagggac caaggtggaa 480

atcaaacgg 489

<210> 319
<211> 114
<212> PRT
<213> Artificial Sequence

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

<400> 319
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln
            20   25   30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Met Trp Arg Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Gly Leu Arg His Pro Lys
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Gly Gly Gly Gly
            100   105   110
Ser Cys

<210> 320
<211> 345
<212> DNA
<213> Artificial Sequence

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

<400> 320
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gggcaagtca gtggattggg tctcagttat cttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatcatgtgg cgttcctcgt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgtgctcag ggtttgaggc atcctaagac gttcggccaa 300
gggaccaagg tggaaatcaa acggggtggc ggagggggtt cctgt 345

<210> 321
<211> 115
<212> PRT
<213> Artificial Sequence

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

<400> 321
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln
            20   25   30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Met Trp Arg Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Gly Leu Arg His Pro Lys
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100   105   110
Pro Ser Cys
        115

<210> 322
<211> 345
<212> DNA
<213> Artificial Sequence

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

<400> 322
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gggcaagtca gtggattggg tctcagttat cttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatcatgtgg cgttcctcgt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgtgctcag ggtttgaggc atcctaagac gttcggccaa 300
gggaccaagg tggaaatcaa acggaccgtc gctgctccat cttgt 345

<210> 323
<211> 235
<212> PRT
<213> Artificial Sequence

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

<400> 323
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
            20   25   30
Ser Met Gly Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Arg Ile Asp Ser Tyr Gly Arg Gly Thr Tyr Tyr Glu Asp Pro Val
    50   55   60
Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Ile Ser Gln Phe Gly Ser Asn Ala Phe Asp Tyr Trp Gly Gln
            100   105   110
Gly Thr Gln Val Thr Val Ser Ser Ala Ser Thr Ser Gly Pro Ser Asp
        115   120   125
Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
    130   135   140
Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Thr Leu
145   150   155   160
Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Trp
                165   170   175
Phe Gly Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
            180   185   190
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
        195   200   205
Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr
    210   215   220
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
225   230   235

<210> 324
<211> 249
<212> PRT
<213> Artificial Sequence

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

<400> 324
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
            20   25   30
Ser Met Gly Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Arg Ile Asp Ser Tyr Gly Arg Gly Thr Tyr Tyr Glu Asp Pro Val
    50   55   60
Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Ile Ser Gln Phe Gly Ser Asn Ala Phe Asp Tyr Trp Gly Gln
            100   105   110
Gly Thr Gln Val Thr Val Ser Ser Ala Ser Thr Ser Gly Pro Ser Asp
        115   120   125

Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
    130   135   140
Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Thr Leu
145   150   155   160
Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Trp
                165   170   175
Phe Gly Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
            180   185   190
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
        195   200   205
Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr
    210   215   220
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln
225   230   235   240
Lys Leu Ile Ser Glu Glu Asp Leu Asn
                245

<210> 325
<211> 705
<212> DNA
<213> Artificial Sequence

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

<400> 325
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttaat aggtatagta tggggtggct ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacgg attgattctt atggtcgtgg tacatactac 180
gaagaccccg tgaagggccg gttcagcatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgccgtat attactgtgc gaaaatttct 300
cagtttgggt caaatgcgtt tgactactgg ggtcagggaa cccaggtcac cgtctcgagc 360
gctagcacca gtggtccatc ggacatccag atgacccagt ctccatcctc cctgtctgca 420
tctgtaggag accgtgtcac catcacttgc cgggcaagtc gtccgattgg gacgacgtta 480
agttggtacc agcagaaacc agggaaagcc cctaagctcc tgatctggtt tggttcccgg 540
ttgcaaagtg gggtcccatc acgtttcagt ggcagtggat ctgggacaga tttcactctc 600
accatcagca gtctgcaacc tgaagatttt gctacgtact actgtgcgca ggctgggacg 660
catcctacga cgttcggcca agggaccaag gtggaaatca aacgg   705

<210> 326
<211> 750
<212> DNA
<213> Artificial Sequence

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

<400> 326
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttaat aggtatagta tggggtggct ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacgg attgattctt atggtcgtgg tacatactac 180
gaagaccccg tgaagggccg gttcagcatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgccgtat attactgtgc gaaaatttct 300
cagtttgggt caaatgcgtt tgactactgg ggtcagggaa cccaggtcac cgtctcgagc 360
gctagcacca gtggtccatc ggacatccag atgacccagt ctccatcctc cctgtctgca 420
tctgtaggag accgtgtcac catcacttgc cgggcaagtc gtccgattgg gacgacgtta 480
agttggtacc agcagaaacc agggaaagcc cctaagctcc tgatctggtt tggttcccgg 540
ttgcaaagtg gggtcccatc acgtttcagt ggcagtggat ctgggacaga tttcactctc 600
accatcagca gtctgcaacc tgaagatttt gctacgtact actgtgcgca ggctgggacg 660
catcctacga cgttcggcca agggaccaag gtggaaatca aacgggcggc cgcagaacaa 720
aaactcatct cagaagagga tctgaattaa   750

<210> 327
<211> 235
<212> PRT
<213> Artificial Sequence

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

<400> 327
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
            20   25   30
Ser Met Gly Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

```
        35                  40                  45
Ser Arg Ile Asp Ser Tyr Gly Arg Gly Thr Tyr Tyr Glu Asp Pro Val
    50                  55                  60
Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Lys Ile Ser Gln Phe Gly Ser Asn Ala Phe Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Gln Val Thr Val Ser Ser Ala Ser Thr Ser Gly Pro Ser Asp
        115                 120                 125
Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
    130                 135                 140
Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu
145                 150                 155                 160
Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu
                165                 170                 175
Phe Gly Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
            180                 185                 190
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
        195                 200                 205
Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr
    210                 215                 220
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
225                 230                 235


<210> 328
<211> 249
<212> PRT
<213> Artificial Sequence

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

<400> 328
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
            20                  25                  30
Ser Met Gly Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Arg Ile Asp Ser Tyr Gly Arg Gly Thr Tyr Tyr Glu Asp Pro Val
    50                  55                  60
Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Lys Ile Ser Gln Phe Gly Ser Asn Ala Phe Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Gln Val Thr Val Ser Ser Ala Ser Thr Ser Gly Pro Ser Asp
        115                 120                 125
Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
    130                 135                 140
Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu
145                 150                 155                 160
Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu
                165                 170                 175
Phe Gly Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
            180                 185                 190
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
        195                 200                 205
Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr
    210                 215                 220
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln
225                 230                 235                 240
Lys Leu Ile Ser Glu Glu Asp Leu Asn
                245


<210> 329
<211> 705
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.
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<400> 329
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttaat aggtatagta tggggtggct ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacgg attgattctt atggtcgtgg tacatactac 180
gaagaccccg tgaagggccg gttcagcatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgccgtat attactgtgc gaaaatttct 300
cagtttgggt caaatgcgtt tgactactgg ggtcagggaa cccaggtcac cgtctcgagc 360
gctagcacca gtggtccatc ggacatccag atgacccagt ctccatcctc cctgtctgca 420
tctgtaggag accgtgtcac catcacttgc cgggcaagtc gtccgattgg gacgatgtta 480
agttggtacc agcagaaacc agggaaagcc cctaagctcc tgatcttgtt tggttcccgg 540
ttgcaaagtg gggtcccatc acgtttcagt ggcagtggat ctgggacaga tttcactctc 600
accatcagca gtctgcaacc tgaagatttt gctacgtact actgtgcgca ggctgggacg 660
catcctacga cgttcggcca agggaccaag gtggaaatca aacgg 705

<210> 330
<211> 750
<212> DNA
<213> Artificial Sequence

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

<400> 330
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttaat aggtatagta tggggtggct ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacgg attgattctt atggtcgtgg tacatactac 180
gaagaccccg tgaagggccg gttcagcatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgccgtat attactgtgc gaaaatttct 300
cagtttgggt caaatgcgtt tgactactgg ggtcagggaa cccaggtcac cgtctcgagc 360
gctagcacca gtggtccatc ggacatccag atgacccagt ctccatcctc cctgtctgca 420
tctgtaggag accgtgtcac catcacttgc cgggcaagtc gtccgattgg gacgatgtta 480
agttggtacc agcagaaacc agggaaagcc cctaagctcc tgatcttgtt tggttcccgg 540
ttgcaaagtg gggtcccatc acgtttcagt ggcagtggat ctgggacaga tttcactctc 600
accatcagca gtctgcaacc tgaagatttt gctacgtact actgtgcgca ggctgggacg 660
catcctacga cgttcggcca agggaccaag gtggaaatca aacgggcggc cgcagaacaa 720
aaactcatct cagaagagga tctgaattaa 750

<210> 331
<211> 235
<212> PRT
<213> Artificial Sequence

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

<400> 331
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
            20   25   30
Ser Met Gly Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Arg Ile Asp Ser Tyr Gly Arg Gly Thr Tyr Tyr Glu Asp Pro Val
    50   55   60
Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Ile Ser Gln Phe Gly Ser Asn Ala Phe Asp Tyr Trp Gly Gln
            100   105   110
Gly Thr Gln Val Thr Val Ser Ser Ala Ser Thr Ser Gly Pro Ser Asp
        115   120   125
Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
    130   135   140
Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu
145   150   155   160
Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu
                165   170   175
Ala Phe Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
            180   185   190
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
        195   200   205
Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr
    210   215   220
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
225   230   235

<210> 332
<211> 249
<212> PRT
<213> Artificial Sequence

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

<400> 332
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
            20   25   30
Ser Met Gly Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Arg Ile Asp Ser Tyr Gly Arg Gly Thr Tyr Tyr Glu Asp Pro Val
    50   55   60
Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Lys Ile Ser Gln Phe Gly Ser Asn Ala Phe Asp Tyr Trp Gly Gln
            100   105   110
Gly Thr Gln Val Thr Val Ser Ser Ala Ser Thr Ser Gly Pro Ser Asp
        115   120   125
Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp
    130   135   140
Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu
145   150   155   160
Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu
                165   170   175
Ala Phe Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
            180   185   190
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
        195   200   205
Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr
    210   215   220
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln
225   230   235   240
Lys Leu Ile Ser Glu Glu Asp Leu Asn
                245

<210> 333
<211> 705
<212> DNA
<213> Artificial Sequence

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

<400> 333
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttaat aggtatagta tggggtggct ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacgg attgattctt atggtcgtgg tacatactac 180
gaagaccccg tgaagggccg gttcagcatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgccgtat attactgtgc gaaaatttct 300
cagtttgggt caaatgcgtt tgactactgg ggtcagggaa cccaggtcac cgtctcgagc 360
gctagcacca gtggtccatc ggacatccag atgacccagt ctccatcctc cctgtctgca 420
tctgtaggag accgtgtcac catcacttgc cgggcaagtc gtccgattgg gacgatgtta 480
agttggtacc agcagaaacc agggaaagcc cctaagctcc tgatccttgc tttttcccgt 540
ttgcaaagtg gggtcccatc acgtttcagt ggcagtggat ctgggacaga tttcactctc 600
accatcagca gtctgcaacc tgaagatttt gctacgtact actgcgcgca ggctgggacg 660
catcctacga cgttcggcca agggaccaag gtggaaatca aacgg   705

<210> 334
<211> 750
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 334
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60

tcctgtgcag cctccggatt cacctttaat aggtatagta tggggtggct ccgccaggct 120
ccagggaagg gtctagagtg ggtctcacgg attgattctt atggtcgtgg tacatactac 180
gaagaccccg tgaagggccg gttcagcatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgccgtat attactgtgc gaaaatttct 300
cagtttgggt caaatgcgtt tgactactgg ggtcagggaa cccaggtcac cgtctcgagc 360
gctagcacca gtggtccatc ggacatccag atgacccagt ctccatcctc cctgtctgca 420
tctgtaggag accgtgtcac catcacttgc cgggcaagtc gtccgattgg gacgatgtta 480
agttggtacc agcagaaacc agggaaagcc cctaagctcc tgatccttgc tttttcccgt 540
ttgcaaagtg gggtcccatc acgtttcagt ggcagtggat ctgggacaga tttcactctc 600
accatcagca gtctgcaacc tgaagatttt gctacgtact actgcgcgca ggctgggacg 660
catcctacga cgttcggcca agggaccaag gtggaaatca aacgggcggc cgcagaacaa 720
aaactcatct cagaagagga tctgaattaa 750

<210> 335
<211> 9
<212> PRT
<213> Homo Sapiens

<400> 335
Ser Gln Ser Ile Ser Ser Tyr Leu Asn
 1   5

<210> 336
<211> 8
<212> PRT
<213> Homo Sapiens

<400> 336
Tyr Ala Ala Ser Ser Leu Gln Ser
 1   5

<210> 337
<211> 9
<212> PRT
<213> Homo Sapiens

<400> 337
Gln Gln Ser Tyr Ser Thr Pro Asn Thr
 1   5

<210> 338
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 338
Ser Arg Pro Ile Gly Thr Thr Leu Ser
 1   5

<210> 339
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 339
Trp Phe Gly Ser Arg Leu Gln Ser
 1   5

<210> 340
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 340
Ala Gln Ala Gly Thr His Pro Thr Thr
 1   5

<210> 341
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 341
Ser Arg Pro Ile Gly Thr Met Leu Ser
 1   5

<210> 342
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 342
Leu Phe Gly Ser Arg Leu Gln Ser
 1   5

<210> 343
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 343
Ala Gln Ala Gly Thr His Pro Thr Thr
 1   5

<210> 344
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 344
Ser Arg Pro Ile Gly Thr Met Leu Ser
 1   5

<210> 345
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 345
Leu Ala Phe Ser Arg Leu Gln Ser
 1   5

<210> 346
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 346
Ala Gln Ala Gly Thr His Pro Thr Thr
 1   5

<210> 347
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 347
Ser Arg Pro Ile Gly Thr Met Leu Ser
 1   5

<210> 348
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 348
Trp Phe Gly Ser Arg Leu Gln Ser
 1   5

<210> 349
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 349
Ala Gln Ala Gly Thr His Pro Thr Thr
 1   5

<210> 350
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 350
Ser Arg Pro Ile Gly Thr Met Leu Ser
 1   5

<210> 351
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 351
Leu Phe Gly Ser Arg Leu Gln Ser
 1   5

<210> 352
<211> 9
<212> PRT

<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 352
Ala Gln Thr Gly Thr His Pro Thr Thr
 1   5

<210> 353
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 353
Ser Arg Pro Ile Gly Thr Thr Leu Ser
 1   5

<210> 354
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 354
Leu Trp Phe Ser Arg Leu Gln Ser
 1   5

<210> 355
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 355
Ala Gln Ala Gly Thr His Pro Thr Thr
 1   5

<210> 356
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 356
Ser Gln Trp Ile Gly Ser Gln Leu Ser
 1   5

<210> 357
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 357
Met Trp Arg Ser Ser Leu Gln Ser
 1   5

<210> 358
<211> 9

<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 358
Ala Gln Gly Ala Ala Leu Pro Arg Thr
 1   5

<210> 359
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 359
Ser Gln Trp Ile Gly Ser Gln Leu Ser
 1   5

<210> 360
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 360
Met Trp Arg Ser Ser Leu Gln Ser
 1   5

<210> 361
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 361
Ala Gln Gly Leu Arg His Pro Lys Thr
 1   5

<210> 362
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 362
Ser Gln Trp Ile Gly Ser Gln Leu Ser
 1   5

<210> 363
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 363
Met Trp Arg Ser Ser Leu Gln Ser
 1   5

<210> 364

<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 364
Ala Gln Gly Leu Met Lys Pro Met Thr
 1   5

<210> 365
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 365
Ser Gln Trp Ile Gly Ser Gln Leu Ser
 1   5

<210> 366
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 366
Met Trp Arg Ser Ser Leu Gln Ser
 1   5

<210> 367
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 367
Ala Gln Gly Ala Ala Leu Pro Arg Thr
 1   5

<210> 368
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 368
Ser Gln Trp Ile Gly Ser Gln Leu Ser
 1   5

<210> 369
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 369
Met Trp Arg Ser Ser Leu Gln Ser
 1   5

<210> 370
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 370
Ala Gln Gly Ala Ala Leu Pro Lys Thr
 1   5

<210> 371
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 371
Ser Gln Trp Ile Gly Ser Gln Leu Ser
 1   5

<210> 372
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 372
Met Trp Arg Ser Ser Leu Gln Ser
 1   5

<210> 373
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 373
Ala Gln Gly Phe Lys Lys Pro Arg Thr
 1   5

<210> 374
<211> 165
<212> PRT
<213> Homo Sapiens

<400> 374
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160
Leu Arg Ser Lys Glu
165

<210> 375
<211> 495
<212> DNA
<213> Homo Sapiens

<400> 375
tgtgatctgc ctcaaaccca cagcctgggt agcaggagga ccttgatgct cctggcacag 60
atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120
gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180
cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240
ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300
caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360
aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420
gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480
ttaagaagta aggaa 495

<210> 376
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 376
gcccggatcc accggctgtg atctg 25

<210> 377
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 377
ggaggatgga gactgggtca tctggatgtc 30

<210> 378
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 378
gacatccaga tgacccagtc tccatcctcc 30

<210> 379
<211> 82
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 379
gcgcaagctt ttattaattc agatcctctt ctgagatgag tttttgttct gcggccgccc 60
gtttgatttc caccttggtc cc 82

<210> 380
<211> 56
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 380

gcccggatcc accggctgtg atctggcgca agcttttatt aattcagatc ctcttc 56

<210> 381
<211> 51
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 381
tgagatgagt ttttgttctg cggccgcccg tttgatttcc accttggtcc c 51

<210> 382
<211> 1
<212> PRT
<213> Murine

<400> 382
Gly
 1

<210> 383
<211> 61
<212> DNA
<213> Murine

<400> 383
atggagaccg acaccctgct gctgtgggtg ctgctgctgt gggtgcccgg atccaccggg 60
c 61

<210> 384
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 384
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165   170   175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180   185   190
Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln
        195   200   205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser
    210   215   220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225   230   235   240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245   250   255
Tyr Tyr Cys Ala Gln Gly Ala Ala Leu Pro Arg Thr Phe Gly Gln Gly
            260   265   270

Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser
275 280 285
Glu Glu Asp Leu Asn
290

<210> 385
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 385
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccagggaaag cccctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtgcgg cgttgcctag gacgttcggc caagggacca aggtggaaat caaacgggcg 840
gccgcagaac aaaaactcat ctcagaagag gatctgaatt aa 882

<210> 386
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 386
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
165 170 175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
180 185 190
Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln
195 200 205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser
210 215 220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225 230 235 240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
245 250 255
Tyr Tyr Cys Ala Gln Gly Ala Ala Leu Pro Arg Thr Phe Gly Gln Gly
260 265 270
Thr Lys Val Glu Ile Lys Arg
275

<210> 387
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 387
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactcccctа atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccagggaaag cccctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtgcgg cgttgcctag gacgttcggc caagggacca aggtggaaat caaacgg   837

<210> 388
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 388
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165   170   175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180   185   190
Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln
        195   200   205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser
    210   215   220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225   230   235   240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245   250   255
Tyr Tyr Cys Ala Gln Gly Leu Arg His Pro Lys Thr Phe Gly Gln Gly
            260   265   270
Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser
        275   280   285
Glu Glu Asp Leu Asn
    290

<210> 389
<211> 882
<212> DNA

<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 389
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccagggaaag cccctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtttga ggcatcctaa gacgttcggc caagggacca aggtggaaat caaacgggcg 840
gccgcagaac aaaaactcat ctcagaagag gatctgaatt aa   882

<210> 390
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 390
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165   170   175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180   185   190
Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln
        195   200   205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser
    210   215   220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225   230   235   240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245   250   255
Tyr Tyr Cys Ala Gln Gly Leu Arg His Pro Lys Thr Phe Gly Gln Gly
            260   265   270
Thr Lys Val Glu Ile Lys Arg
        275

<210> 391
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 391
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccagggaaag cccctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtttga ggcatcctaa gacgttcggc caagggacca aggtggaaat caaacgg 837

<210> 392
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 392
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165   170   175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180   185   190
Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln
        195   200   205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser
    210   215   220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225   230   235   240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245   250   255
Tyr Tyr Cys Ala Gln Gly Leu Met Lys Pro Met Thr Phe Gly Gln Gly
            260   265   270
Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser
        275   280   285
Glu Glu Asp Leu Asn
    290

<210> 393
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 393
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180

cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccagggaaag cccctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtctta tgaagcctat gacgttcggc caagggacca aggtggaaat caaacgggcg 840
gccgcagaac aaaaactcat ctcagaagag gatctgaatt aa 882

<210> 394
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 394
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165   170   175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180   185   190
Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln
        195   200   205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser
    210   215   220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225   230   235   240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245   250   255
Tyr Tyr Cys Ala Gln Gly Leu Met Lys Pro Met Thr Phe Gly Gln Gly
            260   265   270
Thr Lys Val Glu Ile Lys Arg
        275

<210> 395
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 395
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480

ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccagggaaag cccctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtctta tgaagcctat gacgttcggc caagggacca aggtggaaat caaacgg 837

<210> 396
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 396
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165   170   175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180   185   190
Ser Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln
        195   200   205
Gln Lys Pro Gly Glu Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser
    210   215   220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225   230   235   240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245   250   255
Tyr Tyr Cys Ala Gln Gly Ala Ala Leu Pro Arg Thr Phe Gly Gln Gly
            260   265   270
Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser
        275   280   285
Glu Glu Asp Leu Asn
    290

<210> 397
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 397
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatctctt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccagggaaag cccctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720

gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtgcgg cgttgcctag gacgttcggc caagggacca aggtggaaat caaacgggcg 840
gccgcagaac aaaaactcat ctcagaagag gatctgaatt aa 882

<210> 398
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 398
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165   170   175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180   185   190
Ser Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln Leu Ser Trp Tyr Gln
        195   200   205
Gln Lys Pro Gly Glu Ala Pro Lys Leu Leu Ile Met Trp Arg Ser Ser
    210   215   220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225   230   235   240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245   250   255
Tyr Tyr Cys Ala Gln Gly Ala Ala Leu Pro Arg Thr Phe Gly Gln Gly
            260   265   270
Thr Lys Val Glu Ile Lys Arg
        275

<210> 399
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 399
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatctctt gccgggcaag tcagtggatt 600
gggtctcagt tatcttggta ccagcagaaa ccaggggaag cccctaagct cctgatcatg 660
tggcgttcct cgttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgct 780
cagggtgcgg cgttgcctag gacgttcggc caagggacca aggtggaaat caaacgg 837

<210> 400
<211> 293

<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 400
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165   170   175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180   185   190
Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Thr Leu Ser Trp Tyr Gln
        195   200   205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Trp Phe Gly Ser Arg
    210   215   220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225   230   235   240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245   250   255
Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly
            260   265   270
Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser
        275   280   285
Glu Glu Asp Leu Asn
    290

<210> 401
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 401
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcgtccgatt 600
gggacgacgt taagttggta ccagcagaaa ccagggaaag cccctaagct cctgatctgg 660
tttggttccc ggttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgcg 780
caggctggga cgcatcctac gacgttcggc caagggacca aggtggaaat caaacgggcg 840
gccgcagaac aaaaactcat ctcagaagag gatctgaatt aa   882

<210> 402
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 402
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165   170   175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180   185   190
Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Thr Leu Ser Trp Tyr Gln
        195   200   205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Trp Phe Gly Ser Arg
    210   215   220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225   230   235   240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245   250   255
Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly
            260   265   270
Thr Lys Val Glu Ile Lys Arg
        275

<210> 403
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 403
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcgtccgatt 600
gggacgacgt taagttggta ccagcagaaa ccagggaaag cccctaagct cctgatctgg 660
tttggttccc ggttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgcg 780
caggctggga cgcatcctac gacgttcggc caagggacca aggtggaaat caaacgg   837

<210> 404
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 404
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35   40   45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50   55   60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65   70   75   80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85   90   95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100   105   110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115   120   125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130   135   140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145   150   155   160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165   170   175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180   185   190
Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln
        195   200   205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu Phe Gly Ser Arg
    210   215   220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225   230   235   240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245   250   255
Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly
            260   265   270
Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser
        275   280   285
Glu Glu Asp Leu Asn
    290

<210> 405
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 405
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcgtccgatt 600
gggacgatgt taagttggta ccagcagaaa ccagggaaag cccctaagct cctgatcttg 660
tttggttccc ggttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgcg 780
caggctggga cgcatcctac gacgttcggc caagggacca aggtggaaat caaacgggcg 840
gccgcagaac aaaaactcat ctcagaagag gatctgaatt aa   882

<210> 406
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 406
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1   5   10   15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20   25   30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln

```
        35                  40                  45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165                 170                 175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180                 185                 190
Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln
        195                 200                 205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu Phe Gly Ser Arg
    210                 215                 220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225                 230                 235                 240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245                 250                 255
Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly
            260                 265                 270
Thr Lys Val Glu Ile Lys Arg
        275
```

<210> 407
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 407
```
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcgtccgatt 600
gggacgatgt taagttggta ccagcagaaa ccagggaaag cccctaagct cctgatcttg 660
tttggttccc ggttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgtgcg 780
caggctggga cgcatcctac gacgttcggc caagggacca aggtggaaat caaacgg    837
```

<210> 408
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 408
```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1               5                  10                  15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
```

```
                85                  90                  95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165                 170                 175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180                 185                 190
Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln
        195                 200                 205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu Ala Phe Ser Arg
    210                 215                 220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225                 230                 235                 240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245                 250                 255
Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly
            260                 265                 270
Thr Lys Val Glu Ile Lys Arg Ala Ala Ala Glu Gln Lys Leu Ile Ser
        275                 280                 285
Glu Glu Asp Leu Asn
    290
```

<210> 409
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 409

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tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcgtccgatt 600
gggacgatgt taagttggta ccagcagaaa ccagggaaag cccctaagct cctgatcctt 660
gctttttccc gtttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgcgcg 780
caggctggga cgcatcctac gacgttcggc caagggacca aggtggaaat caaacgggcg 840
gccgcagaac aaaaactcat ctcagaagag gatctgaatt aa                    882
```

<210> 410
<211> 279
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 410

```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
 1               5                  10                  15
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45
Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80
Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95
Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110
```

```
Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125
Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140
Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160
Leu Arg Ser Lys Glu Thr Val Ala Ala Pro Ser Asp Ile Gln Met Thr
                165                 170                 175
Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
            180                 185                 190
Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met Leu Ser Trp Tyr Gln
        195                 200                 205
Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Leu Ala Phe Ser Arg
    210                 215                 220
Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
225                 230                 235                 240
Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
                245                 250                 255
Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr Thr Phe Gly Gln Gly
            260                 265                 270
Thr Lys Val Glu Ile Lys Arg
        275


<210> 411
<211> 837
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 411
tgcgacttgc cacagacaca tagtttggga tcaagaagaa cattgatgtt attagcacaa 60
atgcgtagaa tttctttgtt ctcttgtcta aaggaccgtc acgacttcgg attccctcag 120
gaagagtttg gaaaccaatt ccaaaaagca gaaactattc ctgtcttgca cgaaatgatc 180
cagcaaatat tcaatttgtt ttctacaaag gactcatcag ccgcttggga tgaaactctg 240
ttagataaat tctacactga actatatcaa caactgaacg atctagaggc ttgcgttatt 300
cagggtgtag gagttactga aactccccta atgaaagaag attcaattct agccgttaga 360
aaatactttc agcgtatcac attgtattta aaggaaaaga aatactcccc atgtgcatgg 420
gaggtggtta gagcagaaat tatgaggtcc ttctctcttt ctacgaattt gcaagaatct 480
ttgagatcta aggaaaccgt cgctgctcca tctgacatcc agatgaccca gtctccatcc 540
tccctgtctg catctgtagg agaccgtgtc accatcactt gccgggcaag tcgtccgatt 600
gggacgatgt taagttggta ccagcagaaa ccagggaaag cccctaagct cctgatcctt 660
gctttttccc gtttgcaaag tggggtccca tcacgtttca gtggcagtgg atctgggaca 720
gatttcactc tcaccatcag cagtctgcaa cctgaagatt ttgctacgta ctactgcgcg 780
caggctggga cgcatcctac gacgttcggc caagggacca aggtggaaat caaacgg    837

<210> 412
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 412
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1                  5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Trp Ile Gly Ser Gln
            20                  25                  30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Met Trp Arg Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Gly Leu Arg His Pro Lys
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Cys
            100                 105


<210> 413
<211> 324
<212> DNA
<213> Artificial Sequence
```

<220>
<223> Derived from a Human Germline sequence.

<400> 413
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gggcaagtca gtggattggg tctcagttat cttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatcatgtgg cgttcctcgt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgtgctcag ggtttgaggc atcctaagac gttcggccaa 300
gggaccaagg tggaaatcaa atgc 324

<210> 414
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 414
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Pro Ala Ser Val Gly
 1   5   10   15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Pro Ile Gly Thr Met
            20   25   30
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45
Leu Ala Phe Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Ala Gln Ala Gly Thr His Pro Thr
                85   90   95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100   105

<210> 415
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 415
gacatccaga tgacccagtc tccatcctcc ctgcctgcat ctgtaggaga ccgtgtcacc 60
atcacttgcc gggcaagtcg tccgattggg acgatgttaa gttggtacca gcagaaacca 120
gggaaagccc ctaagctcct gatccttgct ttttcccgtt tgcaaagtgg ggtcccatca 180
cgtttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240
gaagattttg ctacgtacta ctgcgcgcag gctgggacgc atcctacgac gttcggccaa 300
gggaccaagg tggaaatcaa acgg 324

<210> 416
<211> 62
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 416
gcaacagcgt cgacggacat ccagatgacc cagtctccat cctccctgcc tgcatctgta 60
gg 62

<210> 417
<211> 360
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 417
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttagt cagtatagga tgcattgggt ccgccaggct 120
ccagggaaga gtctagagtg ggtctcaagt attgatacta ggggttcgtc tacatactac 180

gcagaccccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaagctgtg 300
acgatgtttt ctccttttt tgactactgg ggtcagggaa ccctggtcac cgtctcgagc 360

<210> 418
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 418
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggtc cctgcgtctc 60
tcctgtgcag cctccggatt cacctttgct gattatggga tgcgttgggt ccgccaggct 120
ccagggaagg gtctagagtg ggtctcatct attacgcgga ctggtcgtgt tacatactac 180
gcagactccg tgaagggccg gttcaccatc tcccgcgaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgcg tgccgaggac accgcggtat attactgtgc gaaatggcgg 300
aatcggcatg gtgagtatct tgctgatttt gactactggg gtcagggaac cctggtcacc 360
gtctcgagc 369

<210> 419
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Derived from a Human Germline sequence.

<400> 419
Thr Val Ala Ala Pro Ser Cys
 1   5

<210> 420
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Linker Sequence

<400> 420
Gly Gly Gly Gly Ser Cys
 1   5