SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-064214- -00000-0000
Fecha: 2011-05-24 17:24:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALII
Act. 411 PRESENTACION Folios: 1286

Industria y Comercio

SUPERINTENDENCIA

PCT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 11-064214

54. **TÍTULO** Moléculas Biespecíficas de unión a EGFR/IGFIR.

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** Bristol Myers Squibb Company.

DOMICILIO Estados Unidos.

74. **APODERADO** Alvaro Correa Ordoñez.

22. **BOGOTÁ, D.C.,** Mayo 24, 2011.

Con Reserva
24-06-2011

(FORMA P-10)

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-064214- -00000-0000
Fecha: 2011-05-24 17:24:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1286

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

[X]	Patente de Invención	[ ]	Patente de Modelo de Utilidad
[X]	Capítulo I.	[ ]	Capítulo II.

(2) SOLICITANTE (71)

Nombre: BRISTOL-MYERS SQUIBB COMPANY

Dirección: Route 206 & Province Line Road Princeton, NJ 08543-4000

Nacionalidad o Domicilio: Estados Unidos de América

Lugar de Constitución: Estados Unidos de América

Teléfono: Fax:

E-Mail

IDENTIFICACION

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número

(3) REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ

Dirección: Avenida 82 No. 10-62 Piso 5

Teléfono: 6341500 Fax: 3762211

E-Mail: alvaro.correa@bakermckenzie.com

IDENTIFICACION

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número 79.143.366 Usaquén TP 20281

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de propiedad Industrial, sírvase indicar el número de radicación (del poder).

(4) INVENTOR (ES) (72)

Nombre: EMANUEL, Stuart; ENGLE, Linda; CAMPHAUSEN, Ray; WRIGHT, Martin, C.; RAKESTRAW, Ginger Chao; GOTTARDIS, Marco; CARBONI, Joan.

Dirección: Route 206 & Province Line Road Princeton, NJ 08543-4000 (US)

Nacionalidad o Domicilio: Estados Unidos de América

(5) PCT (85)

Solicitud Internacional No. PCT/US2009/065765 Fecha 24/11/2009

Publicación Internacional No. WO/2010/060095 Fecha 27/05/2010

(6) Título (54) MOLECULAS BIESPECIFICAS DE UNION A EGFR/IGFIR

(7) Clasificación Internacional (51) C07K 14/78; C07K 16/28

(8) Prioridad SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	24/11/2008	61/200,164
US	26/11/2008	61/200,282
US	17/04/2009	61/212,966
US	14/05/2009	61/178,279
US	21/07/2009	61/227,330

(9) Comprobante de pago No. 11-0024589, 11-0042461, 11-0042558, 11-00425559, 11-0046266,11-0046172 **Fecha** 18/03/2011,05/05/2011,05/05/2011,05/05/2011,16/05/2011,16/05/2011

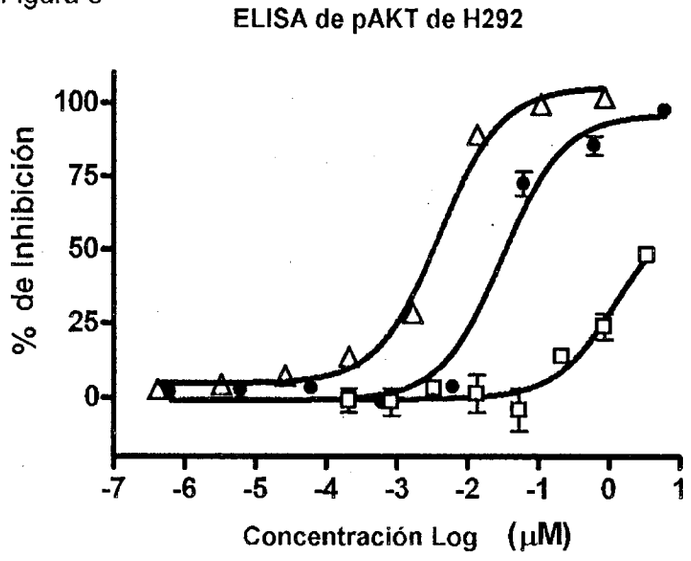
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso. *Ver documento de Poder General radicado en el Expediente No. 08. 129.339*
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [X] 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: Extractos, listado de secuencias

(11) **FIGURA CARATERISTICA**

Figura 6



(12) Solicito la concesión de la patente.

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén T.P. 20.281

~~Instrucciones para la presentación de los anexos, ver reverso de esta página~~

2011/0043

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0024589

Bogotá D.C., Marzo 18 de 2011 - 06:45:57

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	325068785	17/03/2011	113.170.000.00

*** Conceptos Pagados ***

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

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

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

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-064214- -00000-0000
Fecha: 2011-05-24 17:24:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1286

2011/006

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0042461

Bogotá D.C., Mayo 05 de 2011 - 07:17:18

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	444391496	04/05/2011	78.375.000.00

*** Conceptos Pagados ***

CANT	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	3.000.00	3.000.00
				$3.000.00

SON: **TRES MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-064214- -00000-0000

Fecha: 2011-05-24 17:24:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1286

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0042558

Bogotá D.C., Mayo 05 de 2011 - 07:17:18

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	444391496	04/05/2011	78.375.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	10.000.00	10.000.00
				$10.000.00

SON: **DIEZ MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-****-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-064214- -00000-0000

Fecha: 2011-05-24 17:24:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1286

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0042559

Bogotá D.C., Mayo 05 de 2011 - 07:17:18

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	444391496	04/05/2011	78.375.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	10.000.00	10.000.00
				$10.000.00

SON: **DIEZ MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-064214- -00000-0000

Fecha: 2011-05-24 17:24:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1286

2011/007

7

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0046266

Bogotá D.C., Mayo 16 de 2011 - 07:37:16

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	182258694	13/05/2011	56.320.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr UNDITARIO	Vr CONCEPTO
1	50005-01-01 SOLICITUDES	3 PROC. REGISTRO DE MARCAS Y LEMAS COMERCIALES	728.000.00	728.000.00
				$728.000.00

SON: **SETECIENTOS VEINTIOCHO MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-****-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-064214- -00000-0000
Fecha: 2011-05-24 17:24:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1286

7A.

2011/007

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0046172

Bogotá D.C., Mayo 16 de 2011 - 07:37:16

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	182258694	13/05/2011	56.320.000,00

*** Conceptos Pagados ***

CANT	RENTISTICO	CONCEPTO	Vr UNDITARIO	Vr CONCEPTO
1	50005-01-08 PRORROGA DE TERMINOS	1608 N CREACION PRORROGA DE TERMINOS O PLAZO ADICIONAL	86.000.00	86.000.00
				$86.000.00

SON: **OCHENTA Y SEIS MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-064214- -00000-0000
Fecha: 2011-05-24 17:24:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ____ PCT X MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s) BRISTOL-MYERS SQUIBB COMPANY

(72) Inventor(es) EMANUEL, Stuart; ENGLE, Linda; CAMPHAUSEN, Ray; WRIGHT, Martin, C.; RAKESTRAW, Ginger Chao; GOTTARDIS, Marco; CARBONI, Joan.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	61/200,164	24/11/2008	US
	61/200,282	26/11/2008	US
	61/212,966	17/04/2009	US
	61/178,279	14/05/2009	US
	61/227,330	21/07/2009	US

(85) Fecha inicio fase nacional: 24/06/2011
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 24/11/2009
No. de solicitud PCT/US2009/065765

(87) Publicación internacional
Fecha: 27/05/2010
N° publicación: WO/2010/060095

(54) Titulo: Moléculas Biespecificas de unión a EGFR/IGFIR

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO TEMATICO

PATENTE DE INVENCION ____ PCT X MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ____

(21) N° de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s) BRISTOL-MYERS SQUIBB COMPANY

(72) Inventor(es) EMANUEL, Stuart; ENGLE, Linda; CAMPHAUSEN, Ray; WRIGHT, Martin, C.; RAKESTRAW, Ginger Chao; GOTTARDIS, Marco; CARBONI, Joan.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

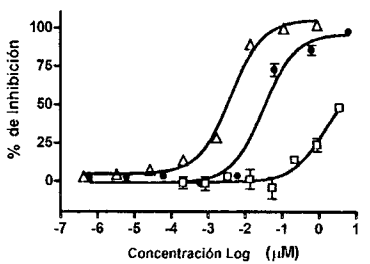
(30) Prioridad

(31) *No. Prioridad*	32) *Fecha*	(33) *País*
61/200,164	24/11/2008	US
61/200,282	26/11/2008	US
61/212,966	17/04/2009	US
61/178,279	14/05/2009	US
61/227,330	21/07/2009	US

(85) Fecha límite inicio fase nacional: 24/06/2011
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 24/11/2009
No. de solicitud PCT/US2009/065765

(87) Publicación internacional:
Fecha: 27/05/2010
No. Publicación : WO/2010/060095

Figura 6



(54) Titulo: Moléculas Biespecificas de unión a EGFR/IGFIR

(57) Resumen:

La presente invención se refiere a moléculas biespecificas que comprenden un dominio de unión a EGFR y un dominio de unión a IGFIR distinto para el uso en aplicaciones de diagnóstico, investigación y terapéuticas. La invención se refiere además a células que comprenden tales proteínas, a polinucleótidos que codifican tales proteínas o fragmentos de las mismas y a vectores que comprenden los polinucleótidos que codifican las proteínas innovadoras. Ejemplos de moléculas biespecificas incluyen dímeros de proteína similar a anticuerpo basados en el décimo dominio de fibronectina de tipo III.

CONTINUA AL RESPALDO ...

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCION

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
61/200,164	24/11/2008	US	
61/200,282	26/11/2008	US	
61/212,966	17/04/2009	US	
61/178,279	14/05/2009	US	
61/227,330	21/07/2009	US	

(51) Int Cl:

(71)Solicitante(s) EMANUEL, Stuart; ENGLE, Linda; CAMPHAUSEN, Ray; WRIGHT, Martin, C.; RAKESTRAW, Ginger Chao; GOTTARDIS, Marco; CARBONI, Joan.

(72) Inventor(es) BRISTOL-MYERS SQUIBB COMPANY

(74) Apoderado: **ALVARO CORREA ORDOÑEZ**

(54) Titulo: Moléculas Biespecificas de unión a EGFR/IGFIR

Reivindicación(es):

1. Un dímero de proteína similar a anticuerpo caracterizado porque comprende a) un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une a IGF-IR con una K_D menor de 500 nM unido covalentemente o no covalentemente con b) un ^{10}Fn3 que se une a EGFR con una K_D menor de 500 nM;

en el que el ^{10}Fn3 de unión a IGF-IR comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID Nº: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID Nº: 3 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-83 de la SEC ID Nº: 3 y

en el que el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID Nº: 112, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID Nº: 112 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-92 de la SEC ID Nº: 112.

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

PODER OTORGADO POR BRISTOL-MYERS SQUIBB COMPANY

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
SALLY B. HANSEN

3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA JERSEY

4. LLEVA EL SELLO DE:
SALLY B. HANSEN, NOTARIO

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY

6. EL 28 DE JUNIO DE 2007

7. POR BRADLEY ABELOW, TESORERO DE NUEVA JERSEY

8. N° A295716

9. SELLO (APARECE ADHERIDO SELLO DORADO)

10. FIRMA (FIRMADO) BRADLEY ABELOW

Texto en inglés y en español mediante el cual **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en Nueva York, Nueva York, otorga poder a **ALVARO CORREA ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA**

Dado y suscrito el 30 de mayo de 2007

(Firmado) Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior)

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
RES. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito Notario certifica el 30 de mayo de 2007 la existencia legal de la sociedad **BRISTOL-MYERS SQUIBB COMPANY** así como las funciones y firma de su representante autorizado Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior) para lo cual se basó en los documentos relacionados en inglés en el punto 6 de la certificación los cuales se traducen aquí al español, a saber:

Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.

Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado mayo 24, 2005.

[Firmado] SALLY B. HANSEN, Notario Público

[Sello en tinta que dice: "SALLY B. HANSEN. Notario Público de Nueva Jersey. Mi comisión vence el 6 de junio de 2010"]

[Aparece sello realzado]

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 82106

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
SALLY B HANSEN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
SALLY B HANSEN, NOTARY

CERTIFIED

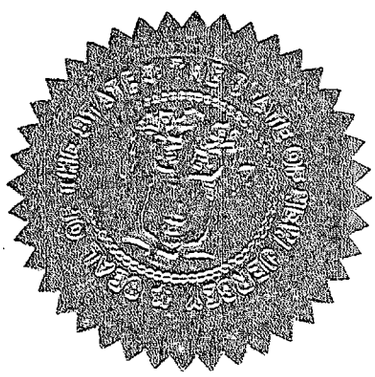
5. AT TRENTON, NEW JERSEY

6. THE 28TH DAY OF JUNE 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A295716

9. SEAL/STAMP:



10. SIGNATURE

Bradley Abelow

Raisbeck, Lara, Rodriguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.066.640-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bskemet.com

POWER OF ATTORNEY

The undersigned.

BRISTOL-MYERS SQUIBB COMPANY

domiciled in

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America

declares that it hereby grants to

ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA

with domicile at Av. 82 No. 10 – 62, 6Th floor, of Bogotá D. C., Colombia, a full and sufficient power of attorney to obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b)Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

the 30 day of May of 2007

Signature of the person issuing the Power

Anastasia P. Winslow
Senior Patent Counsel

PODER DE ABOGADO

La abajo firmada,

BRISTOL-MYERS SQUIBB COMPANY

domiciliada en

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América

declara por el presente que otorga a

ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA

con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en

A los 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder

NOTARIAL CERTIFICATION

On this 30 day of May

2007 , the undersigned Notary

CERTIFIES

1. That **Name of the person issuing the power**
Anastasia P. Winslow
of legal age and domiciled in
Princeton, NJ USA
Address, city, state, country
set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as
Senior Patent Counsel
Position of the person issuing the Power
of the judicial person **BRISTOL-MYERS SQUIBB COMPANY**

4. That the judicial person **BRISTOL-MYERS SQUIBB COMPANY**
having its home office in
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America
is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
(Please indicate here the documents such as the articles of incorporation, by laws or resolution from the Board of Directors and their dates, on which the notary relied to grant the certification)
- Certification executed by Sr. Vice President and General Counsel of Bristol-Myers Squibb Company on April 7, 2007
- Amended and Restated Certificate of Incorporation of Bristol-Myers Squibb Company dated May 24, 2005

Notary Public
SALLY B. HANSEN
Notary Public of New Jersey
My Commission Expires June 6, 2010

CERTIFICACION NOTARIAL

A los 30 días del mes de mayo

de 2007 , el suscrito Notario

DA FE

1 Que Anastasia P. Winslow

mayor y domiciliado en Princeton, NJ
Estados Unidos de América

suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de
Abogados de Patentes Senior
de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

4 Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**
con sede en
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América
está legalmente constituída, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
- Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.
- Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado el 4 de mayo de 2005.

El Notario Público

PATENT COOPERATION TREATY PCT/US2009/065765

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

VARMA, Anita
Ropes & Gray LLP
Prudential Tower
800 Boylston Street
Boston, MA 02199-3600
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
06 April 2011 (06.04.2011)

Applicant's or agent's file reference
COTH-526-WO1

IMPORTANT NOTIFICATION

International application No.
PCT/US2009/065765

International filing date *(day/month/year)*
24 November 2009 (24.11.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
CHAO, Ginger
345 Franklin St., #105
Cambridge, MA 02139
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
RAKESTRAW, Ginger Chao
345 Franklin St., #105
Cambridge, MA 02139
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:
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4. A copy of this notification has been sent to:

☒ the receiving Office
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The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 71 30

Authorized officer
Fahy Laurence
e-mail pt09.pct@wipo.int
Telephone No. +41 22 338 74 09

Form PCT/IB/306 (January 2009) 1/TJTRNEJ60

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 May 2010 (27.05.2010)

PCT

(10) International Publication Number
WO 2010/060095 A1

(51) International Patent Classification:
C07K 14/78 (2006.01) *C07K 16/28* (2006.01)

(21) International Application Number:
PCT/US2009/065765

(22) International Filing Date:
24 November 2009 (24.11.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/200,164	24 November 2008 (24.11.2008)	US
61/200,282	26 November 2008 (26.11.2008)	US
61/212,966	17 April 2009 (17.04.2009)	US
61/178,279	14 May 2009 (14.05.2009)	US
61/227,330	21 July 2009 (21.07.2009)	US

(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 & Province Line Road, Princeton, NJ 08543-4000 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **EMANUEL, Stuart** [US/US]; 5678 South Deer Run Road, Doylestown, PA 18902 (US). **ENGLE, Linda** [US/US]; 19 Randy Road, Framingham, MA 01701 (US). **CAMPHAUSEN, Ray** [US/US]; 7 Bayfield Road, Wayland, MA 01778 (US). **WRIGHT, Martin, C.** [GB/US]; 12 Cumberland St.#4, Boston, MA 02115 (US). **CHAO, Ginger** [US/US]; 345 Franklin St., #105, Cambridge, MA 02139 (US). **GOTTARDIS, Marco** [US/US]; 9 Harris Road, Princeton, NJ 08540 (US). **CARBONI, Joan** [US/US]; 311 Michael Road, Yardley, PA 19067 (US).

(74) Agents: **VARMA, Anita** et al.; ROPES & GRAY LLP, One International Place, Boston, MA 02110 (US).

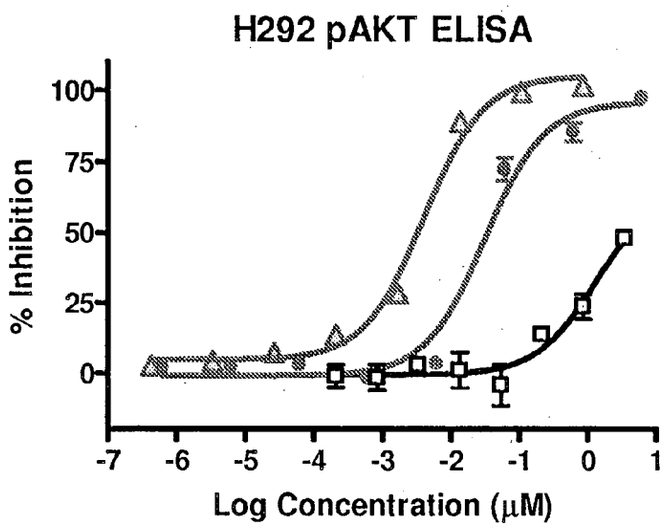
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE,

[Continued on next page]

(54) Title: BISPECIFIC EGFR/IGFIR BINDING MOLECULES

Figure 6



(57) Abstract: The present invention relates to bispecific molecules comprising an EGFR binding domain and a distinct IGFIR binding domain for use in diagnostic, research and therapeutic applications. The invention further relates to cells comprising such proteins, polynucleotide encoding such proteins or fragments thereof, and vectors comprising the polynucleotides encoding the innovative proteins. Exemplary bispecific molecules include antibody-like protein dimers based on the tenth fibronectin type III domain.

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ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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

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

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

BISPECIFIC EGFR/IGFIR BINDING MOLECULES

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on November 23, 2009, is named COTH52WO.txt, and is 552,529 bytes in size.

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Nos. 61/200,164, filed November 24, 2008; 61/200,282, filed November 26, 2008; 61/212,966, filed April 17, 2009; 61/178,279, filed May 14, 2009; and 61/227,330, filed July 21, 2009, which applications are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The present invention relates to EGFR binding domains and bispecific molecules comprising an EGFR binding domain and a distinct IGFIR binding domain for use in diagnostic, research and therapeutic applications. The invention further relates to cells comprising such proteins, polynucleotide encoding such proteins or fragments thereof, and vectors comprising the polynucleotides encoding the innovative proteins. Exemplary EGFR binding domains and bispecific molecules include antibody-like protein dimers based on the tenth fibronectin type III domain.

INTRODUCTION

Activation of receptor tyrosine kinase signaling is central to cancer development (see e.g., Grimberg A. Cancer Biol Ther. 2003 2(6):630-5 and Mendelsohn J. J Clin Oncol. 2003 21(14):2787-99). Receptor tyrosine kinases have a conserved domain structure including an extracellular domain, a transmembrane domain and an intracellular tyrosine kinase domain. The extracellular domain can bind to a ligand, such as to a polypeptide growth factor or to a cell membrane-

associated molecule. Typically, either ligand binding or ligand binding induced dimerization of receptor tyrosine kinases activates the intracellular catalytic tyrosine kinase domain of the receptor and subsequent signal transduction.

Examples of receptor tyrosine kinases include, but are not limited to ERBB receptors (e.g., EGFR, ERBB2, ERBB3, ERBB4), erythropoietin-producing hepatocellular (EPH) receptors, fibroblast growth factor (FGF) receptors (e.g., FGFR1, FGFR2, FGFR3, FGFR4, FGFR5), platelet-derived growth factor (PDGF) receptors (e.g., PDGFR-A, PDGFR-B), vascular endothelial growth factor (VEGF) receptors (e.g., VEGFR1/FLT1, VEGFR2/FLK1, VEGF3), tyrosine kinase with immunoglobulin-like and EGF-like domains (TIE) receptors , insulin-like growth factor (IGF) receptors (e.g., INS-R, IGFIR, IR-R), Discoidin Domain (DD) receptors , receptor for c-Met (MET), recepteur d'origine nantais (RON); also known as macrophage stimulating 1 receptor, Flt3 fins-related tyrosine kinase 3 (Flt3), colony stimulating factor 1(CSF1) receptor, adhesion related kinase receptor (e.g., Axl), receptor for c-kit (KIT) and insulin receptor related (IRR) receptors.

Inhibition of receptor tyrosine kinases has emerged as an effective treatment strategy for certain human malignancies (for a review see Roussidis AE, In Vivo. 2002 16(6):459-69).

While targeted monotherapy may initially be effective in treating cancer, therapeutic resistance often follows, possibly as a result of upregulation of other signaling cascades (see e.g., Nahta R et al., Breast Cancer Res. 2006 8(6):215 and Horn L et al., Clin Lung Cancer. 2007 8:S68-73). Accordingly, there exists a need for developing improved cancer therapeutics.

SUMMARY OF THE INVENTION

In one aspect, the application provides EGFR binding tenth fibronectin type III domains (^{10}Fn3) having novel sequences. EGFR binding ^{10}Fn3 having a consensus sequence are also provided. Such EGFR binding ^{10}Fn3 may be monomeric or may be included as part of a fusion protein.

In another aspect, the application provides bispecific molecules that bind EGFR and IGFIR, referred to herein as "E/I binders". E/I binders encompassed by the invention include bispecific antibodies and dimers of ligand binding scaffold

proteins (e.g., tendamistat, affibody, fibronectin type III domain, anticalin, tetranectin, and ankyrin). When constructed as a single polypeptide chain, the E/I binders may be constructed in any orientation, e.g., from N-terminus to C-terminus either in the E-I arrangement or the I-E arrangement.

In one aspect, antibody-like protein dimers are provided comprising an EGFR binding ^{10}Fn3 covalently or non-covalently linked to an IGFIR binding ^{10}Fn3. The ^{10}Fn3 bind their target (EGFR or IGFIR) with a K_D of less than 500 nM. Each of the individual ^{10}Fn3 independently has an amino acid sequence at least 70, 80, 85, 90, 95, 98, or 100% identical to SEQ ID NO: 32, wherein n is an integer from 1-20, o is an integer from 1-20, and p is an integer from 1-40. In some embodiments, n is an integer from 8-12, o is an integer from 4-8, and p is an integer from 4-28. In some embodiments, n is 10, o is 6, and p is 12.

In some embodiments, the antibody-like protein dimers comprise IGFIR binding ^{10}Fn3 covalently linked to EGFR binding ^{10}Fn3 via a polypeptide linker or a polyethylene glycol moiety. In some embodiments, the antibody-like protein dimer comprises an amino acid sequence at least 80, 90, 95, or 100% identical to any one of SEQ ID NOs: 20-31, 53-58, 87-92, 98-105, 118-133, 149-154, 164-169, 179-184, 192-197, 205-210 and 211-216.

In some embodiments, the E/I binder comprises an amino acid sequence having any one of SEQ ID NOs: 20-31, 53-58, 87-92, 98-105, 118-133, 149-154, 164-169, 179-184, 192-197, 205-210 and 211-216, wherein (i) the EGFR binding ^{10}Fn3 and/or the IGF-IR binding ^{10}Fn3 comprises a ^{10}Fn3 scaffold having from has anywhere from 0 to 20, from 0 to 15, from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 substitutions, conservative substitutions, deletions or additions relative to the corresponding scaffold amino acids of SEQ ID NO: 1, and/or (ii) the EGFR binding ^{10}Fn3 has anywhere from 0 to 15, from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 substitutions, conservative substitutions, deletions or additions relative to the corresponding loop sequences of any one of SEQ ID NOs: 5-8, 52, 66-68, 106-108, 112-114, 140-142, 155-157, 170-172, 182, 185-187, 198-200, or 219-327 and/or the IGF-IR binding ^{10}Fn3 has anywhere from 0 to 15, from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0

to 1 substitutions, conservative substitutions, deletions or additions relative to the corresponding loop sequences of SEQ ID NO: 3.

In one aspect, pharmaceutically acceptable compositions are provided comprising an antibody-like protein dimer as described herein and a pharmaceutically acceptable carrier, wherein the composition is essentially pyrogen free.

In a further aspect, methods for treating hyperproliferative disorders, such as cancer, in a subject are provided comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutically acceptable composition comprising an antibody-like protein dimer as described herein.

In another aspect, the application provides a nucleic acid encoding an antibody-like protein dimer as described herein. Also provided is a vector comprising a nucleic acid encoding an antibody-like dimer as described herein. Suitable vectors include, for example, expression vectors. Also provided are host cells comprising a nucleic, vector, or expression vector, comprising a nucleic acid encoding an antibody-like protein dimer as described herein. Suitable host cells include prokaryotic and eukaryotic host cells. Exemplary prokaryotic cells are bacterial cells, such as E. coli. Exemplary eukaryotic cells are mammalian cells, such as CHO cells. Also provided are methods for producing an antibody-like protein dimer as described herein, comprising culturing a host cell comprising a nucleic, vector, or expression vector, comprising a nucleic acid encoding the antibody-like protein dimer and recovering the expressed antibody-like protein dimer from the culture.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. SDS-PAGE Analysis of I1-GS10-E2. Samples from the lysis of HMS174(DE3) bacterial cell pellet from which I1-GS10-E2 was expressed and purified by a HisTrap chromatography column were run on a 4-12% NuPAGE minigel and stained by Sypro-Orange and visualized by STORM imager. Mark 12 molecular weight standards (Lane 1); Lysate-soluble (Lane 2); Lysate- insoluble (Lane 3); HisTrap load (Lane 4); HisTrap non-bound (Lane 5); Pooled HisTrap

Eluate (Lane 6); Dialyzed into 50mM NaOAc, 150mM NaCl, pH 4.5 (Lane 7); Dialyzed into PBS (Lane 8); Dialyzed into Tris, 150mM NaCl, pH 8.5 (Lane 9).

Figure 2. A. SEC Analysis of midscale purified I1-GS10-E2. 22 μg of HisTrap purified I1-GS10-E2 dialyzed into PBS, pH 7.4 was loaded onto a Superdex 200 10/30 SEC Column (GE Healthcare) with a mobile phase of 100 mM $NaPO_4$, 100 mM $NaSO_4$, 150 mM NaCl, pH 6.8 and measured using A280. I1-GS10-E2 eluted predominantly as a single monomeric species at a molecular weight range of approximately 24.6 kDa vs. globular Gel Filtration standards (BioRad). B. SEC analysis of E2-GS10-I1.

Figure 3. A. Differential Scanning Calorimetry (DSC) of midscale purified I1-GS10-E2 in PBS was performed to determine the T_m. A 1 mg/mL solution of I1-GS10-E2 was scanned from 5 °C to 95 °C at a rate of 1 degree per minute under 3 atm pressure. The data was analyzed versus a control run of the PBS buffer. B. DSC of E2-GS10-I1.

Figure 4. Inhibition of IGFR activity in H292 cells. Cells were stimulated with 100 ng/mL of IGF-1 and 100ng/mL of EGF and treated with either • I1, □ E1, or Δ E1-GS10- I1 HTPP preparations. Phosphorylation of IGFIR on tyrosine 1131 was determined by ELISA.

Figure 5. Inhibition of EGFR activity in H292 cells. Cells were stimulated with 100ng/mL of IGF-1 and 100ng/mL of EGF and treated with either • I1, □ E1, or Δ E1-GS10-I1 HTPP preparations. Phosphorylation of EGFR on tyrosine 1068 was determined by ELISA.

Figure 6. Inhibition of AKT phosphorylation in H292 cells. Cells were stimulated with 100ng/mL of IGF-1 and 100ng/mL of EGF and treated with either • I1, □ E1, or Δ E1-GS10-I1 HTPP preparations. Phosphorylation of AKT on serine 473 was determined by ELISA.

Figure 7. Inhibition of RH41 cell proliferation. Cells were treated with either • I1, □ E1, or Δ E1-GS10-I1 HTPP preparations and percent inhibition of proliferation was determined.

Figure 8. Inhibition of H292 cell proliferation. Cells were treated with either • I1, □ E1, or Δ E1-GS10-I1 HTPP preparations and percent inhibition of proliferation was determined.

Figure 9. Summarizes IC50 values in cell based functional assays for isolated EGFR mononectins, E/I ^{10}Fn3-based binders with serine at the C-terminal position without PEG added and E/I ^{10}Fn3-based binders with cysteine at the C-terminal position conjugated to a 40 kDa branched PEG. Representative data is shown.

Figure 10. Immunoblot analysis of PEGylated E/I ^{10}Fn3-based binder with E2 in the N-terminal and C-terminal positions. Despite both constructs demonstrating comparable activity in the H292 cell assay for inhibiting EGFR, the E/I ^{10}Fn3-based binder with E2 at the C-terminal position did not degrade EGFR while the E/I ^{10}Fn3-based binder with E2 at the N-terminal position did. Both constructs show very weak to no IGFR degradation in this cell line. β-actin was included to demonstrate equal loading across all lanes. The phosphorylation state of EGFR, ERK and Shc was also examined.

Figure 11. Inhibition of EGF-stimulated EGFR phosphorylation in H292 cells. Both constructs demonstrated comparable activity in the H292 cell assay for inhibiting EGFR. E2-GS10-I1 (with PEG) (○), I1-GS10-E2 (with PEG) (□), panitumumab (----).

Figure 12. Results of tumor xenograft studies. Figure 12A: Preclinical anti-tumor activity in the H292 human tumor xenograft model. Mean tumor sizes calculated from groups of 8 mice is shown in mg for control animals (■), E3-GS10-I1 (w/ PEG) dosed at 100mg/kg (○), E2-GS10-I1 (with PEG) dosed at 100 mg/kg (□), panitumumab dosed at 1mg/mouse (△) or 0.1mg/mouse (▽). The letter a on the x-axis indicates doses of E/I binders administered and the p indicates doses of panitumumab administered. Figure 12B: Average weight change is shown for each group over the course of the study. Symbols are as described in Figure 12A legend.

Figure 13. Pharmacodynamic effects in the H292 NSCLC tumor xenograft model. Levels of the indicated analytes were determined in tumor lysates as described in Example 12. (A) phosph-EGFR, (B) phospho-ErbB2, (C) phospho-IGFR, and (D) total EGFR. Checkered bars = panitumumab, empty bars = E2-GS10-I1 (with PEG), hatched bats = E3-GS10-I1 (with PEG).

Figure 14. Western blot analysis of MCF7r cells compared to MCF7 parental cells.

Figure 15. MCF7 (Panel A) and MCF7r (Panel B) human tumor xenograft studies in nude mice. Mean tumor size is shown for both studies calculated from 8 mice per group.

Figure 16. GEO human tumor xenograft studies in nude mice.

Figure 17. H292 human tumor xenograft studies in nude mice.

Figure 18. Colony formation assay with H292 NSCLC cells. A. Representative data is shown from a single plate. B. IC50 from one E/I ^{10}Fn3-based binder is shown with error bars calculated from triplicate measurements.

Figure 19. Epitope mapping assay. Location of epitope binding for various EGFR binding antibodies are shown in panel A. A description of the antibodies is provided in Example 18, Table 11. The left column of table 11 provides a number for each anti-EGFR antibody which correlates with the numbered antibodies shown in panel A. Panel B shows an exemplany epitope mapping assay as described in Example 18.

Figure 20. DSC analysis of the E/I ^{10}Fn3-based binder, I1-GS10-E5 pegylated, measured with a scan range of 15-95 °C at 1mg/ml protein concentration in PBS, resulted in a Tm measurement of 55.2 °C

Figure 21. Evaluation of E/I ^{10}Fn3-based binders for inhibition of AKT phosphorylation in H292 cells as measured by ELISA. I1-GS10-E5-pegylated (○) was more potent than I1-pegylated alone (■) or E5-pegylated alone (▲) for blocking IGF1-stimulated AKT phosphorylation.

Figure 22. Evaluation of E/I ^{10}Fn3-based binders for inhibition of cell proliferation in H292 cells. I1-GS10-E5-pegylated (□) was more potent than I1-pegylated alone (▲) and E5-pegylated alone (●) had only weak effects for inhibiting the growth of H292 cells. Assays were carried out in triplicate. Representative data is shown.

Figure 23. Evaluation of E/I ^{10}Fn3-based binders for inhibition of cell proliferation in RH41 cells. I1-GS10-E5-pegylated (□) was slightly more potent than I1-pegylated alone (▲) and E5-pegylated alone (●) or panitumumab (dashed line) had almost no effect for inhibiting the growth of RH41 cells. Assays were carried out in triplicate. Representative data is shown.

Figure 24. Inhibition of ligand stimulated signaling by ^{10}Fn3-based binders (pegylated). Effect of E/I ^{10}Fn3-based binder (I1-GS10-E5 pegylated) on receptor activation and cell signaling in DiFi (Panel A), H292 (Panel B) or BxPC3 (Panel C) cells. Cells were serum starved and treated for 2 hours with 1 μM ^{10}Fn3-based binders before stimulation with either EGF, IGF1 or a combination of EGF + IGF1. GAPDH was probed to illustrate equal loading in all lanes.

Figure 25. Inhibition of ligand stimulated signaling in H292 cells by ^{10}Fn3-based binders (unpegylated). Effect of E/I ^{10}Fn3-based binder (E2-GS10-I1) on receptor activation and cell signaling in H292 cells. Cells were serum starved and treated for 2 hours with 1 μM ^{10}Fn3-based binders before stimulation with either EGF, IGF1 or a combination of EGF + IGF1. GAPDH was probed to illustrate equal loading in all lanes

Figure 26. Competition binding studies with E/I ^{10}Fn3-based binders. A. The EGFR ^{10}Fn3-based binder does not compete for binding of EGFR antibodies to EGFR. Initial injection of the EGFR ^{10}Fn3-based binder shows binding to EGFR on the surface of the chip. A second injection of EGFR ^{10}Fn3-based binder mixed with an equal amount of cetuximab, panitumumab, or nimotuzumab shows no competition for binding of antibodies to EGFR by the EGFR ^{10}Fn3-based binder. B. The E/I ^{10}Fn3-based binder can bind EGFR and IGF-IR simultaneously. Initial injection of the E/I ^{10}Fn3-based binder shows binding to EGFR immobilized on the chip surface. A second injection of the E/I ^{10}Fn3-based binder soluble IGF-IR shows binding of sIGF-IR to other end of the immobilized E/I ^{10}Fn3-based binder.

Figure 27. TGFα plasma levels 4 hours after last dose of xenograft studies. Plasma samples taken at the end of treatment from the BxPC3 (Panel A), GEO (Panel B) and H441 (Panel C) xenograft studies described in Table 24 were analyzed for circulating levels of TGFα.

Figure 28. TGFα and IGF1 plasma levels in non tumor bearing nude mice after dosing with I1-GS10-E5 pegylated. Non-tumor bearing mice were given a single dose of I1-GS10-E5 pegylated ^{10}Fn3-based binder and analyzed for circulating levels of TGFα (Panel A) and IGF1 (Panel B).

Figure 29. H292 xenograft study using E/I 10Fn3-based binders as compared to panitumumab. H292 xenografts were either untreated (■) or dosed three times a

week with ^{10}Fn3-based binders formulated in PBS with the individual constructs as described in the figure or dosed every three days i.p. with panitumumab at 1 mg/mouse (○) or 0.1 mg/mouse (□). Actual doses of ^{10}Fn3-based binders and panitumumab (▲) are indicated on the x-axis with the panitumumab doses closest to the x-axis below the triangles indicating doses of ^{10}Fn3-based binders. Figure 29A shows measurements out to day 43. Figure 29B shows measurements out to day 27.

Figure 30. Pharmaokinectic parameters profile of E2-GS10-I1 pegylated in mice.

Figure 31. Comparison of half-life at 100 mg/kg and 10 mg/kg IP, and 10 mg/kg and 64 mg/kg SC in various E/I ^{10}Fn3-based binders.

Figure 32. Antitumor efficacy of E2-GS10-I1 pegylated in the RH41 model.

Figure 33. Measurement of pharmacodynamic endpoints in tumors. At the end of treatment, tumors were removed 4 hours following the final dose from DiFi xenograft model (panel A) and H292 xenograft model (panel B) and examined for levels of phospho-EGFR, phospho-IGFR, total EGFR and total IGFR. Equal amounts of total protein lysate was loaded into each lane of the gels and blots were also probed with GAPDH to demonstrate equal loading across all lanes.

Figure 34. Sequence of anti-EGFR binder 679F09 (SEQ ID NO: 490). Loop residues which were varied are underlined.

Figure 35. BC loop Sequence Analysis I. Frequency of amino acids at each position in the BC loop from EGFR binding sequences. Image created using WebLogo (Crooks GE, Hon G, Chandonia JM, Brenner SE. WebLogo: A sequence logo generator. *Genome Research*, 14:1188-1190, 2004).

Figure 36. DE loop Sequence Analysis 1. Frequency of amino acids at each position in the DE loop from EGFR binding sequences (263 unique DE loop sequences analyzed).

Figure 37. FG loop (10-aa length) Sequence Analysis I. Frequency of amino acids at each position in the FG loop from EGFR binding sequences with 10-amino acid long FG loops (228 unique 10-amino acid long FG loops analyzed).

Figure 38. FG loop (15-aa length) Sequence Analysis I. Frequency of amino acids at each position in the FG loop from EGFR binding sequences with 15-amino acid long FG loops (349 unique 15-amino acid long FG loops analyzed).

Figure 39. BC loop Sequence Analysis II. Frequency of amino acids at each position in the BC loop from all "potent" sequences (85 unique BC loop sequences analyzed).

Figure 40. DE loop Sequence Analysis II. Frequency of amino acids at each position in the DE loop from all "potent" sequences (60 unique DE loop sequences analyzed).

Figure 41. FG loop (10-aa length) Sequence Analysis II. Frequency of amino acids at each position in the FG loop from all "potent" sequences with 10-amino acid long FG loops (6 unique 10-amino acid long FG loops analyzed).

Figure 42. FG loop (15-aa length) Sequence Analysis II. Frequency of amino acids at each position in the FG loop from all "potent" sequences with 15-amino acid long FG loops (65 unique 15-amino acid long FG loops analyzed).

Figure 43. Table summarizing various characteristics of E/I ^{10}Fn3-based binders as described in Example 22.

Figure 44. Table summarizing various pharmacokinetic parameters of E/I ^{10}Fn3-based binders as described in Example 30.

Figure 45. Amino acid sequences of E monomers as described in Example 32. The BC, DE and FG loops in each sequence are underlined.

Figure 46. Alignment of wild-type core sequence (amino acids 9-94 of SEQ ID NO: 1) with I1 core (SEQ ID NO:65), E1 core (SEQ ID NO:66), E2 core (SEQ ID NO:67), E3 core (SEQ ID NO:68), E4 core (SEQ ID NO:108), E5 core (SEQ ID NO:114), E85 core (SEQ ID NO:141), E90 core (SEQ ID NO:156), E96 core (SEQ ID NO:171), E105 core (SEQ ID NO:186), and E112 core (SEQ ID NO:199). The BC, DE and FG loops in the wild-type sequences are shown in bold and underlined. The amino acid residues actually changed in comparison to wild-type for the I and E cores are shown i bold and underlined.

Figure 47. Nucleic acid sequences of E and I monomers. Unless otherwise specified, the nucleotide sequences encode a monomer having an N+10 N-terminal extension, a Ser tail, and a his tag.

Figure 48. Nucleic acid sequence of E/I ^{10}Fn3-based binders. All nucleotide sequences encode an E/I ^{10}Fn3-based binder having an N+10 N-terminal extension on the first monomer in the construct and a Cys tail and his tag on the second

monomer in the construct. GS10 is SEQ ID NO: 11; GSGCGS8 is SEQ ID NO: 218; and GSGC is SEQ ID NO: 489.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein, the following terms and phrases shall have the meanings set forth below. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art.

The singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

The terms "comprise" and "comprising" are used in the inclusive, open sense, meaning that additional elements may be included.

The term "including" is used to mean "including but not limited to". "Including" and "including but not limited to" are used interchangeably.

The term "antibody-like protein" refers to a non-immunoglobulin protein having an "immunoglobulin-like fold", i.e., comprises about 80-150 amino acid residues that are structurally organized into a set of beta or beta-like strands, forming beta sheets, where the beta or beta-like strands are connected by intervening loop portions. The beta sheets form the stable core of the antibody-like protein, while creating two "faces" composed of the loops that connect the beta or beta-like strands. As described herein, these loops can be varied to create customized ligand binding sites, and such variations can be generated without disrupting the overall stability of the protein. An example of such an antibody-like protein is a "fibronectin-based scaffold protein", by which is meant a polypeptide based on a fibronectin type III domain (Fn3). In one aspect, an antibody-like protein is based on a tenth fibronectin type III domain (^{10}Fn3).

By a "polypeptide" is meant any sequence of two or more amino acids, regardless of length, post-translation modification, or function. "Polypeptide," "peptide," and "protein" are used interchangeably herein.

"Percent (%) amino acid sequence identity" herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in a selected sequence, after aligning the sequences and

introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are obtained as described below by using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087, and is publicly available through Genentech, Inc., South San Francisco, Calif. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

For purposes herein, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows: 100 times the fraction X/Y where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

The term "therapeutically effective amount" refers to an amount of a drug effective to treat a disease or disorder in a mammal. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer

cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the disorder. To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy in vivo can, for example, be measured by assessing the time to disease progression (TTP) and/or determining the response rates (RR).

The half-life of an amino acid sequence or compound can generally be defined as the time taken for the serum concentration of the polypeptide to be reduced by 50% in vivo due to, e.g., degradation of the sequence or compound and/or clearance or sequestration of the sequence or compound by natural mechanisms. The half-life can be determined in any manner known in the art, such as by pharmacokinetic analysis. See e.g., M Gibaldi & D Perron "Pharmacokinetics", published by Marcel Dekker, 2nd Rev. edition (1982).

The term "E/I binder" refers to a bispecific molecule that comprises an EGFR binding domain and a distinct IGFIR binding domain. The two domains may be covalently or non-covalently linked. An exemplary E/I binder is an antibody-like dimer comprising an EGFR binding ^{10}Fn3 and an IGFIR binding ^{10}Fn3, i.e., an E/I ^{10}Fn3 based binder.

Overview

The epidermal growth factor receptor (EGFR) and insulin-like growth factor receptor (IFGR) play key roles in the tumorigenesis of several types of human cancer. Inhibition of either receptor effectively reduces tumor growth in preclinical models as well as clinically. Blocking the EGFR pathway induces switching to the IGFR pathway to drive growth with in vitro tumor models. Therefore, blocking both receptors simultaneously may achieve superior efficacy to blocking either pathway alone by overcoming pathway switching. In exemplary embodiments, the activity of an E/I binder is synergistic in comparison to the monomeric components of the E/I binder.

The specification describes, *inter alia*, bispecific molecules that bind EGFR and IGFIR, referred to herein as "E/I binders". Applicants have discovered that such bispecific molecules inhibit proliferation of a cancer model cell line with greater

potency than the corresponding. monospecific binders (see e.g., Example 9 and Figure 8).

E/I binders will be useful in numerous therapeutic applications, especially in the treatment of cancer. In addition to therapeutic applications, E/I binders may be used in any circumstance where it is desirable to detect EGFR and/or IGFIR.

E/I binders have an EGFR binding domain and a distinct IGFIR binding domain. Typical binding domains include antibodies; therefore, bispecific antibodies may be generated to function as E/I binders. Bispecific antibodies comprising complementary pairs of V_H and V_L regions are known in the art. These bispecific antibodies comprise two pairs of V_H and V_L, each $V_{H/L}$ pair binding to a single antigen. (see e.g., Hu et al., Cancer Res. 1996 56:3055-306; Neri et al., J. Mol. Biol. 1995 246:367-373; Atwell et al., Mol. Immunol. 1996 33:1301-1312; and Carter et al., Protein Sci. 1997 6:781-788). An exemplary bispecific antibody is a diabody, i.e., a small antibody fragment with two antigen-binding sites, which fragments comprise a heavy-chain variable domain connected to a light-chain variable domain in the same polypeptide chain (Hollinger et al., Proc. Natl. Acad. Sci. USA 1993 90: 6444-6448).

E/I binders also encompass dimers of ligand binding scaffold proteins. Scaffold proteins are well described in the literature and include, e.g., tendamistat, affibody, fibroncectin type III domain, anticalin, tetranectin, and ankyrin. Additional scaffold proteins that may be used to generate E/I binders are reviewed in Binz et al., Nature Biotech 23:1257-1268 (2005). Scaffold proteins are based on a rigid core structure or 'framework' that is important in determining and stabilizing the three-dimensional structure. In between the fixed or conserved residues of the scaffold lie variable regions such as loops, surfaces or cavities that can be randomized to alter ligand binding. A large diversity of amino acids is provided in the variable regions between the fixed scaffold residues to provide specific binding to a target molecule.

An exemplary ligand binding scaffold protein is based on a fibronectin type III domain (Fn3). Fibronectin is a large protein which plays essential roles in the formation of extracellular matrix and cell-cell interactions; it consists of many repeats of three types (types I, II, and III) of small domains.

Fn3 is small, monomeric, soluble, and stable. It lacks disulfide bonds and, therefore, is stable under reducing conditions. The overall structure of Fn3 resembles the immunoglobulin fold. Fn3 domains comprise, in order from N-terminus to C-terminus, a beta or beta-like strand, A; a loop, AB; a beta or beta-like strand, B; a loop, BC; a beta or beta-like strand, C; a loop, CD; a beta or beta-like strand, D; a loop, DE; a beta or beta-like strand, E; a loop, EF; a beta or beta-like strand, F; a loop, FG; and a beta or beta-like strand, G. The seven antiparallel β-strands are arranged as two beta sheets that form a stable core, while creating two "faces" composed of the loops that connect the beta or beta-like strands. Loops AB, CD, and EF are located at one face and loops BC, DE, and FG are located on the opposing face. Any or all of loops AB, BC, CD, DE, EF and FG may participate in ligand binding. There are at least 15 different modules of Fn3, and while the sequence homology between the molecules is low, they all share a high similarity in tertiary structure.

Adnectins™ (Adnexus, a Bristol-Myers Squibb R&D Company) are ligand binding scaffold proteins based on the tenth fibronectin type III domain, i.e., the tenth module of Fn3, (^{10}Fn3). The amino acid sequence of a naturally occurring human ^{10}Fn3 is set forth in SEQ ID NO: 1.

VSDVPRDLEVVAATPTSLLI**SWDAPAVTVR**YYRITYGETGGNSPVQEFTV**P**
GSKST ATISGLKPGVDYTITVYAV**TGRGDSPASSKP**ISINYRT (SEQ ID NO:1) (BC, FG, and DE loops are emphasized)

In SEQ ID NO:1, the AB loop corresponds to residues 15-16, the BC loop corresponds to residues 21-30, the CD loop corresponds to residues 39-45, the DE loop corresponds to residues 51-56, the EF loop corresponds to residues 60-66, and the FG loop corresponds to residues 76-87. (Xu et al., Chemistry & Biology 2002 9:933-942). The BC, DE and FG loops align along one face of the molecule and the AB, CD and EF loops align along the opposite face of the molecule. In SEQ ID NO: 1, beta strand A corresponds to residues 9-14, beta strand B corresponds to residues 17-20, beta strand C corresponds to residues 31-38, beta strand D corresponds to residues 46-50, beta strand E corresponds to residues 57-59, beta strand F corresponds to residues 67-75, and beta strand G corresponds to residues 88-94. The strands are connected to each other through the corresponding loop, e.g.,

strands A and B are connected via loop AB in the formation strand A, loop AB, strand B, etc. Residues involved in forming the hydrophobic core (the "core amino acid residues") include the amino acids corresponding to the following amino acids of SEQ ID NO: 1: L8, V10, A13, L18, I20, W22, Y32, I34, Y36, F48, V50, A57, I59, L62, Y68, I70, V72, A74, I88, I90 and Y92, wherein the core amino acid residues are represented by the single letter amino acid code followed by the position at which they are located within SEQ ID NO: 1. See e.g., Dickinson et al., J. Mol. Biol. 236: 1079-1092 (1994).

As described above, amino acid residues corresponding to residues 21-30, 51-56, and 76-87 of SEQ ID NO: 1 define the BC, DE and FG loops, respectively. However, it should be understood that not every residue within the loop region needs to be modified in order to achieve a ^{10}Fn3 binder having strong affinity for a desired target, such as IGF-IR or EGFR. For example, in many of the examples described herein, only residues corresponding to amino acids 23-30, 52-55 and 77-86 of SEQ ID NO: 1 were modified to produce high affinity ^{10}Fn3 binders (see Figure 46. Accordingly, in certain embodiments, the BC loop may be defined by amino acids corresponding to residues 23-30 of SEQ ID NO: 1, the DE loop may be defined by amino acids corresponding to residues 52-55 of SEQ ID NO: 1, and the FG loop may be defined by amino acids corresponding to residues 77-86 of SEQ ID NO: 1.

^{10}Fn3 are structurally and functionally analogous to antibodies, specifically the variable region of an antibody. While ^{10}Fn3 domains may be described as "antibody mimics" or "antibody-like proteins", they do offer a number of advantages over conventional antibodies. In particular, they exhibit better folding and thermostability properties as compared to antibodies, and they lack disulphide bonds, which are known to impede or prevent proper folding under certain conditions. Exemplary E/I ^{10}Fn3 based binders are predominantly monomeric with Tm's averaging ~50 °C.

The BC, DE, and FG loops of ^{10}Fn3 are analogous to the complementary determining regions (CDRs) from immunoglobulins. Alteration of the amino acid sequence in these loop regions changes the binding specificity of ^{10}Fn3. The protein sequences outside of the CDR-like loops are analogous to the framework regions

from immunoglobulins and play a role in the structural conformation of the ^{10}Fn3. Alterations in the framework-like regions of ^{10}Fn3 are permissible to the extent that the structural conformation is not so altered as to disrupt ligand binding. Methods for generating ^{10}Fn3 ligand specific binders have been described in PCT Publication Nos. WO 00/034787, WO 01/64942, and WO 02/032925, disclosing high affinity TNFα binders, PCT Publication No. WO 2008/097497, disclosing high affinity VEGFR2 binders, and PCT Publication No. WO 2008/066752, disclosing high affinity IGFIR binders. Additional references discussing ^{10}Fn3 binders and methods of selecting binders include PCT Publication Nos. WO 98/056915, WO 02/081497, and WO 2008/031098 and U.S. Publication No. 2003186385.

Antibody-like proteins based on the ^{10}Fn3 scaffold can be defined generally by the sequence:
VSDVPRDLEVVAATPTSLLI$(X)_n$YYRITYGETGGNSPVQEFTV$(X)_o$ATISGLKP GVDYTITVYAV$(X)_p$ISINYRT (SEQ ID NO: 32), wherein n is an integer from 1-20, o is an integer from 1-20, and p is an integer from 1-40. The BC, DE, and FG loops are represented by $(X)_n$, $(X)_o$, and $(X)_p$, respectively.

^{10}Fn3 generally begin with the amino acid residue corresponding to number 1 of SEQ ID NO: 1. However, domains with amino acid deletions are also encompassed by the invention. In some embodiments, amino acid residues corresponding to the first eight amino acids of SEQ ID NO: 1 are deleted. Additional sequences may also be added to the N- or C-terminus. For example, an additional MG sequence may be placed at the N-terminus of ^{10}Fn3. The M will usually be cleaved off, leaving a G at the N-terminus. In some embodiments, sequences may be placed at the C-terminus of the ^{10}Fn3 domain, e.g., EIDKPSQ (SEQ ID NO: 9), EIDKPCQ (SEQ ID NO: 10), EGSGS (SEQ ID NO: 96) or EGSGC (SEQ ID NO: 97).

The non-ligand binding sequences of ^{10}Fn3, i.e., the "^{10}Fn3 scaffold", may be altered provided that the ^{10}Fn3 retains ligand binding function and/or structural stability. In some embodiments, one or more of Asp 7, Glu 9, and Asp 23 are replaced by another amino acid, such as, for example, a non-negatively charged amino acid residue (e.g., Asn, Lys, etc.). These mutations have been reported to have the effect of promoting greater stability of the mutant ^{10}Fn3 at neutral pH as

compared to the wild-type form (See, PCT Publication No. WO 02/04523). A variety of additional alterations in the ^{10}Fn3 scaffold that are either beneficial or neutral have been disclosed. See, for example, Batori et al., Protein Eng. 2002 15(12):1015-20; Koide et al., Biochemistry 2001 40(34):10326-33.

The ^{10}Fn3 scaffold may be modified by one or more conservative substitutions. As many as 5%, 10%, 20% or even 30% or more of the amino acids in the ^{10}Fn3 scaffold may be altered by a conservative substitution without substantially altering the affinity of the ^{10}Fn3 for a ligand. For example, the scaffold modification preferably reduces the binding affinity of the ^{10}Fn3 binder for a ligand by less than 100-fold, 50-fold, 25-fold, 10-fold, 5-fold, or 2-fold. It may be that such changes will alter the immunogenicity of the ^{10}Fn3 in vivo, and where the immunogenicity is decreased, such changes will be desirable. As used herein, "conservative substitutions" are residues that are physically or functionally similar to the corresponding reference residues. That is, a conservative substitution and its reference residue have similar size, shape, electric charge, chemical properties including the ability to form covalent or hydrogen bonds, or the like. Preferred conservative substitutions are those fulfilling the criteria defined for an accepted point mutation in Dayhoff et al., Atlas of Protein Sequence and Structure 5:345-352 (1978 & Supp.). Examples of conservative substitutions are substitutions within the following groups: (a) valine, glycine; (b) glycine, alanine; (c) valine, isoleucine, leucine; (d) aspartic acid, glutamic acid; (e) asparagine, glutamine; (f) serine, threonine; (g) lysine, arginine, methionine; and (h) phenylalanine, tyrosine.

E Binders

In one aspect, the disclosure provides antibody-like proteins comprising an EGFR binding ^{10}Fn3 domain. In certain embodiments, an EGFR binding ^{10}Fn3 may be provided as part of a fusion protein or multimer. For example, an EGFR binding ^{10}Fn3 may be covalently or non-covalently linked to at least a second ^{10}Fn3 binding domain. The second ^{10}Fn3 binding domain may bind to EGFR or to a different target. In an exemplary embodiment, an EGFR binding ^{10}Fn3 may be covalently or non-covalently linked to an IGF-IR binding ^{10}Fn3.

In exemplary embodiments, the EGFR binding ^{10}Fn3 proteins described herein bind to EGFR with a K_D of less than 500 nM, 100 nM, 50 nM, 10 nM, 1 nM, 500 pM, 100 pM. 100 pM, 50 pM or 10 pM.

In exemplary embodiments, the BC loop of the EGFR binding ^{10}Fn3 proteins correspond to amino acids 23-30 of SEQ ID NO: 1, the DE loop of the EGFR binding ^{10}Fn3 proteins correspond to amino acids 52-55 of SEQ ID NO: 1, and the FG loop of the EGFR binding ^{10}Fn3 proteins correspond to amino acids 77-86 of SEQ ID NO: 1.

In one embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop having a YQ at the positions corresponding to amino acids 29 and 30 of SEQ ID NO: 1.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop having a YQ at the positions corresponding to amino acids 29 and 30 of SEQ ID NO: 1 and an FG loop that is fifteen amino acids in length, e.g., an FG loop that is extended in length by five amino acids due to an insertion of five amino acids between residues corresponding to amino acids 77-86 of SEQ ID NO: 1.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop having a YQ at the positions corresponding to amino acids 29 and 30 of SEQ ID NO: 1 and a DE loop having a V, I, L, M or A residue at the position corresponding to amino acid 54 of SEQ ID NO: 1.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop having a YQ at the positions corresponding to amino acids 29 and 30 of SEQ ID NO: 1, a DE loop having a V, I, L, M or A residue at the position corresponding to amino acid 54 of SEQ ID NO: 1, and an FG loop that is fifteen amino acids in length, e.g., an FG loop that is extended in length by five amino acids due to an insertion of five amino acids between residues corresponding to amino acids 77-86 of SEQ ID NO: 1.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop having a YQ at the positions corresponding to amino acids 29 and 30 of SEQ ID NO: 1 and an FG loop comprising a D or N at the position corresponding to amino acid 77 of SEQ ID NO: 1.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop having a YQ at the positions corresponding to amino acids 29 and 30 of SEQ ID NO: 1 and an FG loop (i) that is fifteen amino acids in length, e.g., an FG loop that is extended in length by five amino acids due to an insertion of five amino acids between residues corresponding to amino acids 77-86 of SEQ ID NO: 1 and (ii) comprises a D or N at the position corresponding to amino acid 77 of SEQ ID NO: 1.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a DE loop comprising a V, I, L, M or A residue at the position corresponding to amino acid 54 of SEQ ID NO: 1 and an FG loop comprising a D or N at the position corresponding to amino acid 77 of SEQ ID NO: 1.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a DE loop comprising a V, I, L, M or A residue at the position corresponding to amino acid 54 of SEQ ID NO: 1 and an FG loop (i) that is fifteen amino acids in length, e.g., an FG loop that is extended in length by five amino acids due to an insertion of five amino acids between residues corresponding to amino acids 77-86 of SEQ ID NO: 1 and (ii) comprises a D or N at the position corresponding to amino acid 77 of SEQ ID NO: 1.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop having a YQ at the positions corresponding to amino acids 29 and 30 of SEQ ID NO: 1, a DE loop comprising a V, I, L, M or A residue at the position corresponding to amino acid 54 of SEQ ID NO: 1, and an FG loop comprising a D or N at the position corresponding to amino acid 77 of SEQ ID NO: 1.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop having a YQ at the positions corresponding to amino acids 29 and 30 of SEQ ID NO: 1, a DE loop comprising a V, I, L, M or A residue at the position corresponding to amino acid 54 of SEQ ID NO: 1, and an FG loop (i) that is fifteen amino acids in length, e.g., an FG loop that is extended in length by five amino acids due to an insertion of five amino acids between residues corresponding to amino acids 77-86 of SEQ ID NO: 1 and (ii) comprises a D or N at the position corresponding to amino acid 77 of SEQ ID NO: 1.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop comprising the amino acid sequence XXXXXXYQ, a DE loop comprising the amino acid sequence XX(V/I/L/M/A)X, and an FG loop comprising the amino acid sequence (D/N)X_n, wherein X is any amino acid and n is 9-14 amino acids. In an exemplary embodiment, n is 14 amino acids.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop corresponding to amino acids 23-30 of SEQ ID NO: 1 comprising the amino acid sequence XXXXXXYQ, a DE loop corresponding to amino acids 52-55 of SEQ ID NO: 1 comprising the amino acid sequence XX(V/I/L/M/A)X, and an FG loop corresponding to amino acids 77-86 of SEQ ID NO: 1comprising the amino acid sequence (D/N)X_n, wherein X is any amino acid and n is 9-14 amino acids. In an exemplary embodiment, n is 14 amino acids.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop comprising the amino acid sequence XXXXXXYQ, a DE loop comprising the amino acid sequence XX(V/I/L/M/A)X, and an FG loop comprising an amino acid sequence selected from:

i.

(D/N)(Y/M)(Y/A/M)(Y/H/F)(K/Q/V)(E/P/R)(Y/T/K)X(E/Y/Q)(Y/G/H); and

ii.

D(Y/F/W)(Y/F/K)(N/D/P)(P/H/L)(A/T/V)(T/D/S)(H/Y/G)(E/P/V)(Y/H)(T/K/I)(Y/F)(H/N/Q)(T/Q/E)(T/S/I);

wherein X is any amino acid.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop comprising the amino acid sequence XXXXXXYQ, a DE loop comprising the amino acid sequence (G/Y/H)(D/M/G)(V/L/I)X, and an FG loop comprising an amino acid sequence (D/N)(Y/M)(Y/A/M)(Y/H/F)(K/Q/V)(E/P/R)(Y/T/K)X(E/Y/Q)(Y/G/H), wherein X is any amino acid.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop comprising the amino acid sequence XXXXXXYQ, a DE loop comprising the amino acid sequence (G/Y/H)(D/M/G)(V/L/I)X, and an FG loop comprising an amino acid sequence

D(Y/F/W)(Y/F/K)(N/D/P)(P/H/L)(A/T/V)(T/D/S)(H/Y/G)(E/P/V)(Y/H)(T/K/I)(Y/F)(H/N/Q)(T/Q/E)(T/S/I), wherein X is any amino acid.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop comprising the amino acid sequence XXXXXXYQ, a DE loop comprising the amino acid sequence XX(V/I/L/M/A)X, and an FG loop comprising an amino acid sequence selected from:

i. DY(A/Y)GKPYXEY (SEQ ID NO: 473);

ii. DY(A/Y)Y(K/R/Q/T)PYXEY (SEQ ID NO: 474);

iii. (D/N)Y(A/Y)(Y/F)(K/R/Q/T)EYXE(Y/H) (SEQ ID NO: 475);

iv. DYY(H/Y)X(R/K)X(E/T)YX (SEQ ID NO: 476);

v. DYY(H/Y)(K/H/Q)(R/K)T(E/T)Y(G/P) (SEQ ID NO: 477);

vi. (D/N)MMHV(E/D)YXEY (SEQ ID NO: 478);

vii. DYMHXXYXEY (SEQ ID NO: 479); and

viii. D(M/Y)YHX(K/R)X(V/I/L/M)YG (SEQ ID NO: 480);

wherein X is any amino acid.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop comprising the amino acid sequence XXXXXXYQ, a DE loop comprising the amino acid sequence XX(V/I/L/M/A)X, and an FG loop comprising an amino acid sequence selected from:

i. D(Y/F)(Y/F)NPXTHEYXYXXX (SEQ ID NO: 481);

ii. D(Y/F)(Y/F)D(P/L)X(T/S)HXYXYXXX (SEQ ID NO: 482); and

iii. D(Y/F)(K/R)PHXDGPH(T/I)YXE(S/Y) (SEQ ID NO: 483);

wherein X is any amino acid.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop comprising the amino acid sequence XXXXXXYQ, a DE loop comprising the amino acid sequence XX(V/I/L/M/A)X, and an FG loop comprising the amino acid sequence (D/N)(M/Y)(M/A/W)(H/F/Y)(V/K)EY(A/Q/R/S/T)E(Y/H/D), wherein X is any amino acid.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop comprising the amino acid sequence XXXXXXYQ, a DE loop comprising the amino acid sequence XX(V/I/L/M/A)X, and an FG loop

comprising the amino acid sequence D(Y/F/W)(Y/F/K)(N/P/D)(P/H/L)X(T/D/S)(H/G/Y)(E/P/Y)(Y/H)XYXXX, wherein X is any amino acid.

In various embodiments, the DE loop of the EGFR binding ^{10}Fn3 may comprise the sequence (G/Y/H)(D/M/G)(V/L/I)X.

In another embodiment, the invention provides an EGFR binding ^{10}Fn3 comprising an FG loop comprising an amino acid sequence selected from:

i. D(Y/F)(Y/F)NPXTHEYXYXXX (SEQ ID NO: 481);

ii. D(Y/F)(Y/F)D(P/L)X(T/S)HXYXYXXX (SEQ ID NO: 482); and

iii. D(Y/F)(K/R)PHXDGPH(T/I)YXE(S/Y) (SEQ ID NO: 483);

wherein X is any amino acid.

In certain embodiments, the EGFR binding ^{10}Fn3 comprises any of the consensus sequences provided above, with the proviso that the EGFR binding ^{10}Fn3 does not comprise one or more of the following sequences:

i.

VSDVPRDLEVVAATPTSLLISWQVPRPMYQRYYRITYGETGGNSPVQ EFTVPGGVRTATISGLKPGVDYTITVYAVTDYMHSEYRQYPISINYRT (SEQ ID NO: 484), and

ii.

VSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQE FTVPGGVRTATISGLKPGVDYTITVYAVTDYMHSEYRQYPISINYRT (SEQ ID NO: 485), and

iii.

VSDVPRDLEVVAATPTSLLISWQVPRPMYQRYYRITYGETGGNSPVQ EFTVPGGVRTATISGLKPGVDYTITVYAVTDYMHSEYRQYPISINYRTEIDKP CQ (SEQ ID NO: 486).

In certain embodiments, an EGFR binding ^{10}Fn3 comprising one of the consensus sequences provided above has at least 40%, 50%, 60%, 70%, 75%, or 80% identity to SEQ ID NO: 1. In certain embodiments, the overall structure of an EGFR binding ^{10}Fn3 comprising one of the consensus sequences provided above resembles the immunoglobulin fold. In certain embodiment, an EGFR binding ^{10}Fn3 comprising one of the consensus sequences provided above further comprises

the core amino acid residues of the scaffold. In certain embodiments, an EGFR binding ^{10}Fn3 comprising one of the consensus sequences provided above has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, or 99% identity to any one of SEQ ID NOs: 5-8, 52, 66-68, 106-108, 112-114, 140-142, 155-157, 170-172, 182, 185-187, 198-200, or 219-327. In certain embodiments, an EGFR binding ^{10}Fn3 comprising one of the consensus sequences provided above has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, or 99% identity to the amino acid sequence of amino acid residues corresponding to E9 of SEQ ID NO: 1 through T94 of SEQ ID NO: 1 of any one of SEQ ID NOs: 5-8, 52, 66-68, 106-108, 112-114, 140-142, 155-157, 170-172, 182, 185-187, 198-200, or 219-327. In certain embodiments, the EGFR binding ^{10}Fn3 comprising one of the consensus sequences provided above comprises a ^{10}Fn3 scaffold having from has anywhere from 0 to 20, from 0 to 15, from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 substitutions, conservative substitutions, deletions or additions relative to the scaffold amino acids residues of SEQ ID NO: 1.

In certain embodiments, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 23-30, a DE loop having the amino acid sequence set forth in amino acids 52-55, and an FG loop having the amino acid sequence set forth in amino acids 77-86 of any one of SEQ ID NOs: 219-327. In certain embodiments, the invention provides an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30, a DE loop having the amino acid sequence set forth in amino acids 51-56, and an FG loop having the amino acid sequence set forth in amino acids 76-87 of any one of SEQ ID NOs: 219-327. In certain embodiments, the invention provides an EGFR binding ^{10}Fn3 comprising an amino acid sequence at least 60%, 75%, 80%, 85%, 90%, 95%, or 98% identical to any one of SEQ ID NOs: 219-327.

In one embodiment, an antibody-like protein is provided comprising a tenth fibronectin type III domain (^{10}Fn3) that binds EGFR with a K_D of less than 500 nM and comprises a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 5, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 5, and an FG loop having the amino acid sequence set forth in amino acids 76-92 of SEQ ID NO: 5. In some embodiments,

the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_gDSGRGSYQX_h$ (SEQ ID NO: 40), a DE loop having the amino acid sequence X_iGPVHX_j (SEQ ID NO: 42), and an FG loop having the amino acid sequence $X_kDHKPHADGPHTYHEX_l$ (SEQ ID NO: 44); wherein X is any amino acid and g, h, i, j, k, and l are integers independently selected from 0 to 5. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWDSGRGSYQ (SEQ ID NO: 39), a DE loop having the amino acid sequence PGPVHT (SEQ ID NO: 41), and an FG loop having the amino acid sequence TDHKPHADGPHTYHESP (SEQ ID NO: 43). In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, or 100% identical to SEQ ID NOs: 5 or 6.

In one embodiment, an antibody-like protein is provided comprising a tenth fibronectin type III domain (^{10}Fn3) that binds EGFR with a K_D of less than 500 nM and comprises a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 7, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 7, and an FG loop having the amino acid sequence set forth in amino acids 76-87 of SEQ ID NO: 7. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_mVAGAEDYQX_n$ (SEQ ID NO: 34), a DE loop having the amino acid sequence X_oHDLVX_p (SEQ ID NO: 36), and an FG loop having the amino acid sequence $X_qDMMHVEYTEHX_r$ (SEQ ID NO: 38); wherein X is any amino acid and m, n, o, p, q, and r are integers independently selected from 0 to 5. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWVAGAEDYQ (SEQ ID NO: 33), a DE loop having the amino acid sequence PHDLVT (SEQ ID NO: 35), and an FG loop having the amino acid sequence TDMMHVEYTEHP (SEQ ID NO: 37). In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, or 100% identical to SEQ ID NO: 7 or 8.

In one embodiment, an antibody-like protein is provided comprising a tenth fibronectin type III domain (^{10}Fn3) that binds EGFR with a K_D of less than 500 nM and comprises a BC loop having the amino acid sequence set forth in amino acids 23-30 of SEQ ID NO: 82, a DE loop having the amino acid sequence set forth in

amino acids 51-55 of SEQ ID NO: 82, and an FG loop having the amino acid sequence set forth in amino acids 76-86 of SEQ ID NO: 82. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_sLPGKLRYQX_t$ (SEQ ID NO: 60), a DE loop having the amino acid sequence X_uHDLRX_w (SEQ ID NO: 62), and an FG loop having the amino acid sequence $X_yNMMHVEYSEYX_z$ (SEQ ID NO: 64); wherein X is any amino acid and s, t, u, w, y and z are integers independently selected from 0 to 5. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence LPGKLRYQ (resdiues 3-13 of SEQ ID NO: 59), a DE loop having the amino acid sequence PHDLR (residues 1-5 of SEQ ID NO: 61), and an FG loop having the amino acid sequence TNMMHVEYSEY (residues 1-11 of SEQ ID NO: 63). In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, or 100% identical to SEQ ID NO: 52 or 82.

In one embodiment, an antibody-like protein is provided comprising a tenth fibronectin type III domain (^{10}Fn3) that binds EGFR with a K_D of less than 500 nM and comprises a BC loop having the amino acid sequence set forth in amino acids 23-30 of SEQ ID NO: 106, a DE loop having the amino acid sequence set forth in amino acids 51-55 of SEQ ID NO: 106, and an FG loop having the amino acid sequence set forth in amino acids 76-86 of SEQ ID NO: 106. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_gHERDGSRQX_h$ (SEQ ID NO: 134), a DE loop having the amino acid sequence X_iGGVRX_j (SEQ ID NO: 135), and an FG loop having the amino acid sequence $X_kDYFNPTTHEYIYQTTX_l$ (SEQ ID NO: 136); wherein X is any amino acid and g, h, i, j, k and l are integers independently selected from 0 to 5. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWHERDGSRQ (SEQ ID NO: 109), a DE loop having the amino acid sequence PGGVRT (SEQ ID NO: 110), and an FG loop having the amino acid sequence TDYFNPTTHEYIYQTTP (SEQ ID NO: 111). In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, or 100% identical to any one of SEQ ID NOs: 106-108.

In one embodiment, an antibody-like protein is provided comprising a tenth fibronectin type III domain (^{10}Fn3) that binds EGFR with a K_D of less than 500 nM

and comprises a BC loop having the amino acid sequence set forth in amino acids 23-30 of SEQ ID NO: 112, a DE loop having the amino acid sequence set forth in amino acids 51-55 of SEQ ID NO: 112, and an FG loop having the amino acid sequence set forth in amino acids 76-86 of SEQ ID NO: 112. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_gWAPVDRYQX_h$ (SEQ ID NO: 137), a DE loop having the amino acid sequence X_iRDVYX_j (SEQ ID NO: 138), and an FG loop having the amino acid sequence $X_kDYKPHADGPHTYHESX_l$ (SEQ ID NO: 139); wherein X is any amino acid and g, h, i, j, k and l are integers independently selected from 0 to 5. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWWAPVDRYQ (SEQ ID NO: 115), a DE loop having the amino acid sequence PRDVYT (SEQ ID NO: 116), and an FG loop having the amino acid sequence TDYKPHADGPHTYHESP (SEQ ID NO: 117). In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, or 100% identical to any one of SEQ ID NOs: 112-114.

In one embodiment, an antibody-like protein is provided comprising a tenth fibronectin type III domain (^{10}Fn3) that binds EGFR with a K_D of less than 500 nM and comprises a BC loop having the amino acid sequence set forth in amino acids 13-22 of SEQ ID NO: 141, a DE loop having the amino acid sequence set forth in amino acids 43-48 of SEQ ID NO: 141, and an FG loop having the amino acid sequence set forth in amino acids 68-84 of SEQ ID NO: 141. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_gTQGSTHYQX_h$ (SEQ ID NO: 146), a DE loop having the amino acid sequence X_iGMVYX_j (SEQ ID NO: 147), and an FG loop having the amino acid sequence $X_kDYFDRSTHEYKYRTTX_l$ (SEQ ID NO: 148); wherein X is any amino acid and g, h, i, j, k and l are integers independently selected from 0 to 5. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWTQGSTHYQ (SEQ ID NO: 143), a DE loop having the amino acid sequence PGMVYT (SEQ ID NO: 144), and an FG loop having the amino acid sequence TDYFDRSTHEYKYRTTP (SEQ ID NO: 145). In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, or 100% identical to any one of SEQ ID NOs: 140-142.

In one embodiment, an antibody-like protein is provided comprising a tenth fibronectin type III domain (^{10}Fn3) that binds EGFR with a K_D of less than 500 nM and comprises a BC loop having the amino acid sequence set forth in amino acids 13-22 of SEQ ID NO: 156, a DE loop having the amino acid sequence set forth in amino acids 43-48 of SEQ ID NO: 156, and an FG loop having the amino acid sequence set forth in amino acids 68-84 of SEQ ID NO: 156. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence X_gYWEGLPYQX_h (SEQ ID NO: 161), a DE loop having the amino acid sequence X_iRDVNX_j (SEQ ID NO: 162), and an FG loop having the amino acid sequence X_kDWYNPDTHEYIYHTIX_l (SEQ ID NO: 163); wherein X is any amino acid and g, h, i, j, k and l are integers independently selected from 0 to 5. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWYWEGLPYQ (SEQ ID NO: 158), a DE loop having the amino acid sequence PRDVNT (SEQ ID NO: 159), and an FG loop having the amino acid sequence TDWYNPDTHEYIYHTIP (SEQ ID NO: 160). In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, or 100% identical to any one of SEQ ID NOs: 155-157.

In one embodiment, an antibody-like protein is provided comprising a tenth fibronectin type III domain (^{10}Fn3) that binds EGFR with a K_D of less than 500 nM and comprises a BC loop having the amino acid sequence set forth in amino acids 13-22 of SEQ ID NO: 171, a DE loop having the amino acid sequence set forth in amino acids 43-48 of SEQ ID NO: 171, and an FG loop having the amino acid sequence set forth in amino acids 68-84 of SEQ ID NO: 171. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence X_gASNRGTYQX_h (SEQ ID NO: 176), a DE loop having the amino acid sequence X_iGGVSX_j (SEQ ID NO: 177), and an FG loop having the amino acid sequence X_kDAFNPTTHEYNYFTTX$_l$ (SEQ ID NO: 178); wherein X is any amino acid and g, h, i, j, k and l are integers independently selected from 0 to 5. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWASNRGTYQ (SEQ ID NO: 173), a DE loop having the amino acid sequence PGGVST (SEQ ID NO: 174), and an FG loop having the amino acid sequence TDAFNPTTHEYNYFTTP (SEQ ID NO: 175). In some embodiments, the

EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, or 100% identical to any one of SEQ ID NOs: 170-172.

In one embodiment, an antibody-like protein is provided comprising a tenth fibronectin type III domain (^{10}Fn3) that binds EGFR with a K_D of less than 500 nM and comprises a BC loop having the amino acid sequence set forth in amino acids 13-22 of SEQ ID NO: 186, a DE loop having the amino acid sequence set forth in amino acids 43-48 of SEQ ID NO: 186, and an FG loop having the amino acid sequence set forth in amino acids 68-84 of SEQ ID NO: 186. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_gDAPTSRYQX_h$ (SEQ ID NO: 190), a DE loop having the amino acid sequence X_iGGLSX_j (SEQ ID NO: 191), and an FG loop having the amino acid sequence $X_kDYKPHADGPHTYHESX_l$ (SEQ ID NO: 139); wherein X is any amino acid and g, h, i, j, k and l are integers independently selected from 0 to 5. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWDAPTSRYQ (SEQ ID NO: 188), a DE loop having the amino acid sequence PGGLST (SEQ ID NO: 189), and an FG loop having the amino acid sequence TDYKPHADGPHTYHESP (SEQ ID NO: 117). In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, or 100% identical to any one of SEQ ID NOs: 185-187.

In one embodiment, an antibody-like protein is provided comprising a tenth fibronectin type III domain (^{10}Fn3) that binds EGFR with a K_D of less than 500 nM and comprises a BC loop having the amino acid sequence set forth in amino acids 13-22 of SEQ ID NO: 199, a DE loop having the amino acid sequence set forth in amino acids 43-48 of SEQ ID NO: 199, and an FG loop having the amino acid sequence set forth in amino acids 68-84 of SEQ ID NO: 199. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_gDAGAVTYQX_h$ (SEQ ID NO: 203), a DE loop having the amino acid sequence X_iGGVRX_j (SEQ ID NO: 135), and an FG loop having the amino acid sequence $X_kDYKPHADGPHTYHEYX_l$ (SEQ ID NO: 204); wherein X is any amino acid and g, h, i, j, k and l are integers independently selected from 0 to 5. In some embodiments, the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWDAGAVTYQ (SEQ ID NO: 201), a DE loop having the amino acid

sequence PGGVRT (SEQ ID NO: 110), and an FG loop having the amino acid sequence TDYKPHADGPHTYHEYP (SEQ ID NO: 202). In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, or 100% identical to any one of SEQ ID NOs: 198-200.

In certain embodiments, an EGFR binding ^{10}Fn3 domain is covalently or non-covalently linked to an EGF-IR binding ^{10}Fn3 domain. In exemplary embodiments, the IGF-IR binding ^{10}Fn3 may comrpise a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 3, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 3, and an FG loop having the amino acid sequence set forth in amino acids 76-83 of SEQ ID NO: 3. In some embodiments, the IGF-IR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_aSARLKVAX_b$ (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX_d (SEQ ID NO: 48), and an FG loop having the amino acid sequence $X_eRFRDYQX_f$ (SEQ ID NO: 50), wherein X is any amino acid and a, b, c, d, e, f, g, h, i, j, k, and l are integers independently selected from 0 to 5, or wherein a is 2 and b-f are 1, or wherein a-f are zero. In some embodiments, the IGF-IR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, 99, or 100% identical to SEQ ID NO: 3. In certain embodiments, the IGF-IR binding ^{10}Fn3 comprises a ^{10}Fn3 scaffold having from has anywhere from 0 to 20, from 0 to 15, from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 substitutions, conservative substitutions, deletions or additions relative to the scaffold amino acid residues of SEQ ID NO: 1. In certain embodiments, the IGF-IR binding ^{10}Fn3 has anywhere from 0 to 15, from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 substitutions, conservative substitutions, deletions or additions relative to the corresponding loop sequences of SEQ ID NO: 3.

^{10}Fn3 E/I Binders

One aspect of the disclosure provides E/I binders constructed from antibody-like protein multimers. In some embodiments, an antibody-like protein multimer comprises at least one EGFR binding ^{10}Fn3 covalently or non-covalently linked to at least one IGFIR binding ^{10}Fn3. In certain embodiments, the E/I binders described

herein may be constructed as a single polypeptide chain wherein the E and I subunits may be in either orientation, e.g., from N-terminus to C-terminus, in the E-I orientation or in the I-E orientation.

The disclosure relates, in part, to the surprising discovery that multiple ^{10}Fn3 joined via a polypeptide linker correctly fold independently of each other, retain high affinity binding, and that each of the domains retains its functional properties (see e.g., Examples 5-10). Additionally, these E/I ^{10}Fn3 based binders demonstrate desirable biophysical properties such as low aggregation and high melting temperature (T_m) (see e.g., Example 4). The Examples characterize a variety of E/I ^{10}Fn3 based binders. An exemplary IGFIR binding ^{10}Fn3 is set forth in SEQ ID NO: 4. Exemplary EGFR binding ^{10}Fn3 are set forth in SEQ ID NOs: 6, 8, 52, 107, 113, 140, 155, 170, 185 and 198.

In some embodiments, an E/I binder comprises an EGFR binding ^{10}Fn3 and an IGFIR binding ^{10}Fn3, independently having an amino acid sequence at least 40, 50, 60, 70, or 80% identical to the human ^{10}Fn3 domain, shown in SEQ ID NO: 1. Much of the variability will generally occur in one or more of the loops.

In some embodiments, an E/I binder comprises an EGFR binding ^{10}Fn3 and an IGFIR binding ^{10}Fn3, independently having an amino acid sequence at least 70, 80, 85, 90, 95, 98, or 100% identical to SEQ ID NO: 32, wherein n is an integer from 1-20, o is an integer from 1-20, and p is an integer from 1-40. In some embodiments, n is an integer from 8-12, o is an integer from 4-8, and p is an integer from 4-28. In some embodiments, n is 10, o is 6, and p is 12.

In some embodiments, the disclosure provides multimers of ^{10}Fn3 having at least one loop selected from loop BC, DE, and FG with an altered amino acid sequence relative to the sequence of the corresponding loop of the human ^{10}Fn3. By "altered" is meant one or more amino acid sequence alterations relative to a template sequence (corresponding human fibronectin domain) and includes amino acid additions, deletions, and substitutions. Altering an amino acid sequence may be accomplished through intentional, blind, or spontaneous sequence variation, generally of a nucleic acid coding sequence, and may occur by any technique, for example, PCR, error-prone PCR, or chemical DNA synthesis. In some

embodiments, an amino acid sequence is altered by substituting with or adding naturally occurring amino acids.

In some embodiments, one or more loops selected from BC, DE, and FG may be extended or shortened in length relative to the corresponding human fibronectin loop. In particular, the FG loop of the human ^{10}Fn3 is 12 residues long, whereas the corresponding loop in antibody heavy chains ranges from 4-28 residues. To optimize antigen binding, therefore, the length of the FG loop of ^{10}Fn3 may be altered in length as well as in sequence to obtain the greatest possible flexibility and affinity in antigen binding.

In some embodiments of the ^{10}Fn3 molecules, the altered BC loop has up to 10 amino acid substitutions, up to 9 amino acid deletions, up to 10 amino acid insertions, or a combination of substitutions and deletions or insertions. In some embodiments, the altered DE loop has up to 6 amino acid substitutions, up to 5 amino acid deletions, up to 14 amino acid insertions or a combination of substitutions and deletions or insertions. In some embodiments, the FG loop has up to 12 amino acid substitutions, up to 11 amino acid deletions, up to 28 amino acid insertions or a combination of substitutions and deletions or insertions.

Naturally occurring ^{10}Fn3 comprises an "arginine-glycine-aspartic acid" (RGD) integrin-binding motif in the FG loop. Preferred multimers of ^{10}Fn3 lack an RGD integrin-binding motif.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising a) an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 5, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 5, and an FG loop having the amino acid sequence set forth in amino acids 76-92 of SEQ ID NO: 5; covalently or non-covalently linked to b) an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 3, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 3, and an FG loop having the amino acid sequence set forth in amino acids 76-83 of SEQ ID NO: 3. In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, 99, or 100% identical to SEQ ID NO: 5. In some embodiments, the IGFIR binding ^{10}Fn3 has an amino acid sequence at

least 80, 90, 95, 98, 99, or 100% identical to SEQ ID NO: 3. In some embodiments, the E/I binder comprises an amino acid sequence at least 80, 85, 90, 95, 98, 99, or 100% identical to SEQ ID NOs: 20, 21, 23, 24, 90, 92, 101 or 103.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising a) an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 7, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 7, and an FG loop having the amino acid sequence set forth in amino acids 76-87 of SEQ ID NO: 7; covalently or non-covalently linked to b) an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 3, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 3, and an FG loop having the amino acid sequence set forth in amino acids 76-83 of SEQ ID NO: 3. In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 7. In some embodiments, the IGFIR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 3. In some embodiments, the E/I binder comprises an amino acid sequence at least 80, 85, 90, 95, 98, or 100% identical to SEQ ID NOs: 26, 27, 29, 30, 89, 91, 100 or 102.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising a) an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 82, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 82, and an FG loop having the amino acid sequence set forth in amino acids 76-87 of SEQ ID NO: 82; covalently or non-covalently linked to b) an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 3, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 3, and an FG loop having the amino acid sequence set forth in amino acids 76-83 of SEQ ID NO: 3. In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 82. In some embodiments, the IGFIR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 3. In some embodiments, the E/I

binder comprises an amino acid sequence at least 80, 85, 90, 95, 98, or 100% identical to SEQ ID NOs: 53, 54, 87, 88, 98, 99, 104 or 105.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising a) an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 106, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 106, and an FG loop having the amino acid sequence set forth in amino acids 76-92 of SEQ ID NO: 106; covalently or non-covalently linked to b) an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 3, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 3, and an FG loop having the amino acid sequence set forth in amino acids 76-83 of SEQ ID NO: 3. In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 106. In some embodiments, the IGFIR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 3. In some embodiments, the E/I binder comprises an amino acid sequence at least 80, 85, 90, 95, 98, or 100% identical to SEQ ID NOs: 118-125.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising a) an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 112, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 112, and an FG loop having the amino acid sequence set forth in amino acids 76-92 of SEQ ID NO: 112; covalently or non-covalently linked to b) an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 3, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 3, and an FG loop having the amino acid sequence set forth in amino acids 76-83 of SEQ ID NO: 3. In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 112. In some embodiments, the IGFIR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 3. In some embodiments, the E/I binder comprises an amino acid sequence at least 80, 85, 90, 95, 98, or 100% identical to SEQ ID NOs: 126-133.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising a) an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 13-22 of SEQ ID NO: 141, a DE loop having the amino acid sequence set forth in amino acids 43-48 of SEQ ID NO: 141, and an FG loop having the amino acid sequence set forth in amino acids 68-84 of SEQ ID NO: 141; covalently or non-covalently linked to b) an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 3, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 3, and an FG loop having the amino acid sequence set forth in amino acids 76-83 of SEQ ID NO: 3. In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 140, 141, 142 or 300. In some embodiments, the IGFIR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 3. In some embodiments, the E/I binder comprises an amino acid sequence at least 80, 85, 90, 95, 98, or 100% identical to SEQ ID NOs: 149-154.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising a) an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 13-22 of SEQ ID NO: 156, a DE loop having the amino acid sequence set forth in amino acids 43-48 of SEQ ID NO: 156, and an FG loop having the amino acid sequence set forth in amino acids 68-84 of SEQ ID NO: 156; covalently or non-covalently linked to b) an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 3, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 3, and an FG loop having the amino acid sequence set forth in amino acids 76-83 of SEQ ID NO: 3. In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 155, 156, 157 or 305. In some embodiments, the IGFIR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 3. In some embodiments, the E/I binder comprises an amino acid sequence at least 80, 85, 90, 95, 98, or 100% identical to SEQ ID NOs: 158-166.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising a) an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid

sequence set forth in amino acids 13-22 of SEQ ID NO: 171, a DE loop having the amino acid sequence set forth in amino acids 43-48 of SEQ ID NO: 171, and an FG loop having the amino acid sequence set forth in amino acids 68-84 of SEQ ID NO: 171; covalently or non-covalently linked to b) an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 3, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 3, and an FG loop having the amino acid sequence set forth in amino acids 76-83 of SEQ ID NO: 3. In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 170, 171, 172 or 311. In some embodiments, the IGFIR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 3. In some embodiments, the E/I binder comprises an amino acid sequence at least 80, 85, 90, 95, 98, or 100% identical to SEQ ID NOs: 179-184.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising a) an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 13-22 of SEQ ID NO: 186, a DE loop having the amino acid sequence set forth in amino acids 43-48 of SEQ ID NO: 186, and an FG loop having the amino acid sequence set forth in amino acids 68-84 of SEQ ID NO: 186; covalently or non-covalently linked to b) an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 3, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 3, and an FG loop having the amino acid sequence set forth in amino acids 76-83 of SEQ ID NO: 3. In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 185, 186, 187 or 320. In some embodiments, the IGFIR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 3. In some embodiments, the E/I binder comprises an amino acid sequence at least 80, 85, 90, 95, 98, or 100% identical to SEQ ID NOs: 192-197.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising a) an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 13-22 of SEQ ID NO: 199, a DE loop having the amino acid sequence set forth in amino acids 43-48 of SEQ ID NO: 199, and an FG

loop having the amino acid sequence set forth in amino acids 68-84 of SEQ ID NO: 199; covalently or non-covalently linked to b) an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 3, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 3, and an FG loop having the amino acid sequence set forth in amino acids 76-83 of SEQ ID NO: 3. In some embodiments, the EGFR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 198, 199, 200 or 327. In some embodiments, the IGFIR binding ^{10}Fn3 has an amino acid sequence at least 80, 90, 95, 98, or 100% identical to SEQ ID NO: 3. In some embodiments, the E/I binder comprises an amino acid sequence at least 80, 85, 90, 95, 98, or 100% identical to SEQ ID NOs: 205-210.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence X_aSARLKVAX_b (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX_d (SEQ ID NO: 48), and an FG loop having the amino acid sequence X_eRFRDYQX_f (SEQ ID NO: 50); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence X_gDSGRGSYQX_h (SEQ ID NO: 40), a DE loop having the amino acid sequence X_iGPVHX_j (SEQ ID NO: 42), and an FG loop having the amino acid sequence X_kDHKPHADGPHTYHEX_l (SEQ ID NO: 44); wherein X is any amino acid and a, b, c, d, e, f, g, h, i, j, k, and l are integers independently selected from 0 to 5. In some embodiments, a, g, and l are 2; b-f and i-k are 1; and h is zero. In some embodiments, a-l are zero.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWDSGRGSYQ (SEQ ID NO: 39), a DE loop having the amino acid sequence PGPVHT (SEQ ID NO: 41), and an FG loop having the amino acid sequence TDHKPHADGPHTYHESP (SEQ ID NO: 43).

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence $X_aSARLKVAX_b$ (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX_d (SEQ ID NO: 48), and an FG loop having the amino acid sequence $X_eRFRDYQX_f$ (SEQ ID NO: 50); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence $X_mVAGAEDYQX_n$ (SEQ ID NO: 34), a DE loop having the amino acid sequence X_oHDLVX_p (SEQ ID NO: 36), and an FG loop having the amino acid sequence $X_qDMMHVEYTEHX_r$ (SEQ ID NO: 38); wherein X is any amino acid and a, b, c, d, e, f, m, n, o, p, q, and r are integers from 0 to 5, independently. In some embodiments, a and m are 2; b-f and o-r are 1; and n is zero. In some embodiments, a-f and m-r are zero.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWVAGAEDYQ (SEQ ID NO: 33), a DE loop having the amino acid sequence PHDLVT (SEQ ID NO: 35), and an FG loop having the amino acid sequence TDMMHVEYTEHP (SEQ ID NO: 37).

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence $X_aSARLKVAX_b$ (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX_d (SEQ ID NO: 48), and an FG loop having the amino acid sequence $X_eRFRDYQX_f$ (SEQ ID NO: 50); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence $X_sLPGKLRYQX_t$ (SEQ ID NO: 60), a DE loop having the amino acid sequence X_uHDLRX_w (SEQ ID NO: 62), and an FG loop having the amino acid sequence $X_yNMMHVEYSEYX_z$ (SEQ ID NO: 64); wherein X is any amino acid and a, b, c, d, e, f, s, t, u, w, y, and z are integers from 0 to 5, independently. In some

embodiments, a and s are 2; b-f, u, w, y and z are 1; and t is zero. In some embodiments, a-f, s-u, w, y and z are zero.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWLPGKLRYQ (SEQ ID NO: 59), a DE loop having the amino acid sequence PHDLRT (SEQ ID NO: 61), and an FG loop having the amino acid sequence TNMMHVEYSEYP (SEQ ID NO: 63).

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence X_aSARLKVAX$_b$ (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX$_d$ (SEQ ID NO: 48), and an FG loop having the amino acid sequence X_eRFRDYQX$_f$ (SEQ ID NO: 50); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence X_gHERDGSRQX$_h$ (SEQ ID NO: 134), a DE loop having the amino acid sequence X_iGGVRX$_j$ (SEQ ID NO: 135), and an FG loop having the amino acid sequence X_kDYFNPTTHEYIYQTTX$_l$ (SEQ ID NO: 136); wherein X is any amino acid and a, b, c, d, e, f, g, h, i, j, k and l are integers from 0 to 5, independently. In some embodiments, a and g are 2; b-f and i-l are 1; and h is zero. In some embodiments, a-l are zero.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWHERDGSRQ (SEQ ID NO: 109), a DE loop having the amino acid sequence PGGVRT (SEQ ID NO: 110), and an FG loop having the amino acid sequence TDYFNPTTHEYIYQTTP (SEQ ID NO: 111).

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence $X_aSARLKVAX_b$ (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX_d (SEQ ID NO: 48), and an FG loop having the amino acid sequence $X_eRFRDYQX_f$ (SEQ ID NO: 50); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence $X_gWAPVDRYQX_h$ (SEQ ID NO: 137), a DE loop having the amino acid sequence X_iRDVYX_j (SEQ ID NO: 138), and an FG loop having the amino acid sequence $X_kDYKPHADGPHTYHESX_l$ (SEQ ID NO: 139); wherein X is any amino acid and a, b, c, d, e, f, g, h, i, j, k and l are integers from 0 to 5, independently. In some embodiments, a and g are 2; b-f and i-l are 1; and h is zero. In some embodiments, a-l are zero.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWWAPVDRYQ (SEQ ID NO: 115), a DE loop having the amino acid sequence PRDVYT (SEQ ID NO: 116), and an FG loop having the amino acid sequence TDYKPHADGPHTYHESP (SEQ ID NO: 117).

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence $X_aSARLKVAX_b$ (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX_d (SEQ ID NO: 48), and an FG loop having the amino acid sequence $X_eRFRDYQX_f$ (SEQ ID NO: 50); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence $X_gTQGSTHYQX_h$ (SEQ ID NO: 146), a DE loop having the amino acid sequence X_iGMVYX_j (SEQ ID NO: 147), and an FG loop having the amino acid sequence $X_kDYFDRSTHEYKYRTTX_l$ (SEQ ID NO: 148); wherein X is any amino acid and a, b, c, d, e, f, g, h, i, j, k and l are integers from 0 to 5, independently. In some

embodiments, a and g are 2; b-f and i-l are 1; and h is zero. In some embodiments, a-l are zero.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWTQGSTHYQ (SEQ ID NO: 143), a DE loop having the amino acid sequence PGMVYT (SEQ ID NO: 144), and an FG loop having the amino acid sequence TDYFDRSTHEYKYRTTP (SEQ ID NO: 145).

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence X_aSARLKVAX_b (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX_d (SEQ ID NO: 48), and an FG loop having the amino acid sequence X_eRFRDYQX_f (SEQ ID NO: 50); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence X_gYWEGLPYQX_h (SEQ ID NO: 161), a DE loop having the amino acid sequence X_iRDVNX_j (SEQ ID NO: 162), and an FG loop having the amino acid sequence X_kDWYNPDTHEYIYHTIX_l (SEQ ID NO: 163); wherein X is any amino acid and a, b, c, d, e, f, g, h, i, j, k and l are integers from 0 to 5, independently. In some embodiments, a and g are 2; b-f and i-l are 1; and h is zero. In some embodiments, a-l are zero.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWYWEGLPYQ (SEQ ID NO: 158), a DE loop having the amino acid sequence PRDVNT (SEQ ID NO: 159), and an FG loop having the amino acid sequence TDWYNPDTHEYIYHTIP (SEQ ID NO: 160).

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence $X_aSARLKVAX_b$ (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX_d (SEQ ID NO: 48), and an FG loop having the amino acid sequence $X_eRFRDYQX_f$ (SEQ ID NO: 50); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence $X_gASNRGTYQX_h$ (SEQ ID NO: 176), a DE loop having the amino acid sequence X_iGGVSX_j (SEQ ID NO: 177), and an FG loop having the amino acid sequence $X_kDAFNPTTHEYNYFTTX_l$ (SEQ ID NO: 178); wherein X is any amino acid and a, b, c, d, e, f, g, h, i, j, k and l are integers from 0 to 5, independently. In some embodiments, a and g are 2; b-f and i-l are 1; and h is zero. In some embodiments, a-l are zero.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWASNRGTYQ (SEQ ID NO: 173), a DE loop having the amino acid sequence PGGVST (SEQ ID NO: 174), and an FG loop having the amino acid sequence TDAFNPTTHEYNYFTTTP (SEQ ID NO: 175).

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence $X_aSARLKVAX_b$ (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX_d (SEQ ID NO: 48), and an FG loop having the amino acid sequence $X_eRFRDYQX_f$ (SEQ ID NO: 50); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence $X_gDAPTSRYQX_h$ (SEQ ID NO: 190), a DE loop having the amino acid sequence X_iGGLSX_j (SEQ ID NO: 191), and an FG loop having the amino acid sequence $X_kDYKPHADGPHTYHESX_l$ (SEQ ID NO: 139); wherein X is any amino acid and a, b, c, d, e, f, g, h, i, j, k and l are integers from 0 to 5, independently. In some

embodiments, a and g are 2; b-f and i-l are 1; and h is zero. In some embodiments, a-l are zero.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWDAPTSRYQ (SEQ ID NO: 188), a DE loop having the amino acid sequence PGGLST (SEQ ID NO: 189), and an FG loop having the amino acid sequence TDYKPHADGPHTYHESP (SEQ ID NO: 117).

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence X_aSARLKVAX$_b$ (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX$_d$ (SEQ ID NO: 48), and an FG loop having the amino acid sequence X_eRFRDYQX$_f$ (SEQ ID NO: 50); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence X_gDAGAVTYQX$_h$ (SEQ ID NO: 203), a DE loop having the amino acid sequence X_iGGVRX$_j$ (SEQ ID NO: 135), and an FG loop having the amino acid sequence X_kDYKPHADGPHTYHEYX$_l$ (SEQ ID NO: 204); wherein X is any amino acid and a, b, c, d, e, f, g, h, i, j, k and l are integers from 0 to 5, independently. In some embodiments, a and g are 2; b-f and i-l are 1; and h is zero. In some embodiments, a-l are zero.

In some embodiments, an E/I binder is an antibody-like protein dimer comprising an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49); covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWDAGAVTYQ (SEQ ID NO: 201), a DE loop having the amino acid sequence PGGVRT (SEQ ID NO: 110), and an FG loop having the amino acid sequence TDYKPHADGPHTYHEYP (SEQ ID NO: 202).

In some embodiments, an E/I binder is an antibody-like protein dimer comprising a) an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 23-29 of SEQ ID NO: 3, a DE loop having the amino acid sequence set forth in amino acids 52-55 of SEQ ID NO: 3, and an FG loop having the amino acid sequence set forth in amino acids 77-82 of SEQ ID NO: 3; covalently or non-covalently linked to b) an EGFR binding ^{10}Fn3 comprising a BC, DE and FG loop as set forth in any one of SEQ ID NOs: 219-327 (see e.g., Figure 45 wherein the BC, DE and FG loop sequences for each EGFR binding ^{10}Fn3 are underlined). In some embodiments, an E/I binder is an antibody-like protein dimer comprising a) an IGFIR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids 23-29 of SEQ ID NO: 3, a DE loop having the amino acid sequence set forth in amino acids 52-55 of SEQ ID NO: 3, and an FG loop having the amino acid sequence set forth in amino acids 77-82 of SEQ ID NO: 3; covalently or non-covalently linked to b) an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence set forth in amino acids corresponding to amino acid residues 23-30 of SEQ ID NO: 1 of any one of SEQ ID NOs: 5-8, 52, 66-68, 106-108, 112-114, 140-142, 155-157, 170-172, 182, 185-187, 198-200, or 219-327, a DE loop having the amino acid sequence set forth in amino acids corresponding to amino acid residues 52-55 of SEQ ID NO: 1 of any one of SEQ ID NOs: 5-8, 52, 66-68, 106-108, 112-114, 140-142, 155-157, 170-172, 182, 185-187, 198-200, or 219-327, and an FG loop having the amino acid sequence set forth in amino acids corresponding to amino acid residues 77-86 of SEQ ID NO: 15-8, 52, 66-68, 106-108, 112-114, 140-142, 155-157, 170-172, 182, 185-187, 198-200, or 219-327. In some embodiments, the EGFR binding ^{10}Fn3 of the antibody-like protein dimer comprises an amino acid sequence at least 80, 90, 95, or 100% identical to the amino acid sequence of amino acid residues corresponding to E9 of SEQ ID NO: 1 through T94 of SEQ ID NO: 1 of any one of SEQ ID NOs: 5-8, 52, 66-68, 106-108, 112-114, 140-142, 155-157, 170-172, 182, 185-187, 198-200, or 219-327. In some embodiments, the IGFIR binding ^{10}Fn3 of the antibody-like protein dimer has an amino acid sequence at least 80, 90, 95, 98, 99, or 100% identical to the amino acid sequence of amino acid residues corresponding to E9 of SEQ ID NO: 1 through T94 of SEQ ID NO: 1 of SEQ ID NO: 3. In some

embodiments, the E/I binder comprises an amino acid sequence at least 80, 85, 90, 95, 98, 99, or 100% identical to any one of SEQ ID NOs: 20-31, 53-58, 87-92, 98-105, 118-133, 149-154, 164-169, 179-184, 192-197, 205-210 and 211-216.

Preferably, X as defined herein is a naturally occurring amino acid.

In certain embodiments, the E binders, or the E and/or I monomers of the E/I binders described herein may contain a Ser to Cys amino acid substitution at a position corresponding to serine 62 or serine 91 of SEQ ID NO: 1.

In certain aspects, the disclosure provides short peptide sequences that mediate EGFR binding. Examples of such sequences include the amino acid residues that correspond to the BC, DE, and FG loops from SEQ ID NOs: 5, 7, 82, 106, 112, 141, 156, 171, 186 and 199. Other examples of such sequences include the amino acid residues that correspond to the BC, DE, and FG loops from SEQ ID NOs: 219-327. In some embodiments, the peptides bind to their respective ligand with a dissociation constant (K_D) of less than 500nM, 100nM, 50nM, 5nM or less. Such sequences may mediate ligand binding in an isolated form or when inserted into a particular protein structure, such as an immunoglobulin or immunoglobulin-like domain.

In one embodiment, an antibody-like protein dimer comprises a polypeptide having the structure A-B-C, wherein A is a polypeptide comprising, consisting essentially of, or consisting of a ^{10}Fn3 domain that binds to EGFR, B is a polypeptide linker, and C is a polypeptide comprising, consisting essentially of, or consisting of a ^{10}Fn3 domain that binds to IGF-IR. In another embodiment, a antibody-like protein dimer comprises a polypeptide having the structure A-B-C, wherein A is a polypeptide comprising, consisting essentially of, or consisting of a ^{10}Fn3 domain that binds to IGF-IR, B is a polypeptide linker, and C is a polypeptide comprising, consisting essentially of, or consisting of a ^{10}Fn3 domain that binds to EGFR. Specific examples of antibody-like protein dimers having the structure A-B-C are polypeptides comprising (i) a polypeptide having an amino acid sequence set forth in any one of SEQ ID NOs: 20-31, 53-58, 87-92, 98-105, 118-133, 149-154, 164-169, 179-184, 192-197, 205-210 and 211-216, or (ii) a polypeptide comprising an amino acid sequence at least 85%, 90%, 95%, 97%, 98%, or 99% identical to any

one of the amino acid sequences set forth in SEQ ID NOs: 20-31, 53-58, 87-92, 98-105, 118-133, 149-154, 164-169, 179-184, 192-197, 205-210 and 211-216.

In certain embodiments, the A or C region is a polypeptide comprising a ^{10}Fn3 domain that binds to EGFR; wherein the ^{10}Fn3 domain has the structure from N-terminus to C-terminus: beta strand A, loop AB, beta strand B, loop BC, beta strand C, loop CD, beta strand D, loop DE, beta strand E, loop EF, beta strand F, loop FG, beta strand G; wherein: (i) the BC loop has the amino acid sequence of SEQ ID NO: 33 or 34, the DE loop has the amino acid sequence of SEQ ID NO: 35 or 36, and the FG loop has the amino acid sequence of SEQ ID NO: 37 or 38, (ii) the BC loop has the amino acid sequence of SEQ ID NO: 39 or 40, the DE loop has the amino acid sequence of SEQ ID NO: 41 or 42, and the FG loop has the amino acid sequence of SEQ ID NO: 43 or 44, (iii) the BC loop has the amino acid sequence of SEQ ID NO: 59 or 60, the DE loop has the amino acid sequence of SEQ ID NO: 61 or 62, and the FG loop has the amino acid sequence of SEQ ID NO: 63 or 64, (iv) the BC loop has the amino acid sequence of SEQ ID NO: 109 or 134, the DE loop has the amino acid sequence of SEQ ID NO: 110 or 135, and the FG loop has the amino acid sequence of SEQ ID NO: 111 or 136, (v) the BC loop has the amino acid sequence of SEQ ID NO: 115 or 137, the DE loop has the amino acid sequence of SEQ ID NO: 116 or 138, and the FG loop has the amino acid sequence of SEQ ID NO: 117 or 139, (vi) the BC loop has the amino acid sequence of SEQ ID NO: 143 or 146, the DE loop has the amino acid sequence of SEQ ID NO: 144 or 147, and the FG loop has the amino acid sequence of SEQ ID NO: 145 or 148, (vii) the BC loop has the amino acid sequence of SEQ ID NO: 158 or 161, the DE loop has the amino acid sequence of SEQ ID NO: 159 or 162, and the FG loop has the amino acid sequence of SEQ ID NO: 160 or 163, (viii) the BC loop has the amino acid sequence of SEQ ID NO: 173 or 176, the DE loop has the amino acid sequence of SEQ ID NO: 174 or 177, and the FG loop has the amino acid sequence of SEQ ID NO: 175 or 178, (ix) the BC loop has the amino acid sequence of SEQ ID NO: 188 or 190, the DE loop has the amino acid sequence of SEQ ID NO: 189 or 191, and the FG loop has the amino acid sequence of SEQ ID NO: 117 or 139, (x) the BC loop has the amino acid sequence of SEQ ID NO: 201 or 203, the DE loop has the amino acid sequence of SEQ ID NO: 110 or 135, and the FG loop has the amino

acid sequence of SEQ ID NO: 202 or 204, or (xi) the BC, DE and FG loops have the amino acid sequences as set forth in any one of SEQ ID NOs: 219-327 (see e.g., Figure 45 wherein the BC, DE and FG loops for each of SEQ ID NOs: 219-327 are underlined); wherein the ^{10}Fn3 domain folds into an antibody heavy chain variable region-like structure; and wherein the polypeptide binds to EGFR with a K_D of less than 100 nM. The ^{10}Fn3 domain that binds to EGFR preferably folds into a structure wherein the 7 beta strands are distributed between two beta sheets that pack against each other forming a stable core and wherein the beta strands are connected by the six loops which are solvent exposed. In exemplary embodiments, the ^{10}Fn3 domain is from 80-150 amino acids in length.

In exemplary embodiments, the A or C region is a ^{10}Fn3 domain that binds to EGFR with a K_D of less than 100 nM having a sequence selected from the group consisting of SEQ ID NO: 83-85 and 466-472 as set forth below:

EVVAATX$_{n1}$SLLIX$_{a1}$**SWVAGAEDYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PHDLVTX**$_{a4}$ATIX$_{n3}$DYTITVYAVX$_{a5}$**TDMMHVEYTEHP**X$_{a6}$ISINYRT (SEQ ID NO: 83);

EVVAATX$_{n1}$SLLIX$_{a1}$**SWDSGRGSYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PGPVHTX**$_{a4}$ATIX$_{n3}$DYTITVYAVX$_{a5}$**TDHKPHADGPHTYHESP**X$_{a6}$ISINYRT (SEQ ID NO: 84); or

EVVAATX$_{n1}$SLLIX$_{a1}$**SWLPGKLRYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PHDLRTX**$_{a4}$ATIX$_{n3}$DYTITVYAVX$_{a5}$**TNMMHVEYSEYP**X$_{a6}$ISINYRT (SEQ ID NO: 85).

EVVAATX$_{n1}$SLLIX$_{a1}$**SWHERDGSRQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PGGVRTX**$_{a4}$ATIX$_{n3}$DYTITVYAVX$_{a5}$**TDYFNPTTHEYIYQTTP**X$_{a6}$ISINYRT (SEQ ID NO: 466).

EVVAATX$_{n1}$SLLIX$_{a1}$**SWWAPVDRYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PRDVYTX**$_{a4}$ATIX$_{n3}$DYTITVYAVX$_{a5}$**TDYKPHADGPHTYHESP**X$_{a6}$ISINYRT (SEQ ID NO: 467).

EVVAATX$_{n1}$SLLIX$_{a1}$**SWTQGSTHYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PGMVYT**X$_{a4}$ATIX$_{n3}$DYTITVYAVX$_{a5}$**TDYFDRSTHEYKYRTTPX**$_{a6}$ISINYRT (SEQ ID NO: 468).

EVVAATX$_{n1}$SLLIX$_{a1}$**SWYWEGLPYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PRDVNT**X$_{a4}$ATIX$_{n3}$DYTITVYAVX$_{a5}$**TDWYNPDTHEYIYHTIPX**$_{a6}$ISINYRT (SEQ ID NO: 469).

EVVAATX$_{n1}$SLLIX$_{a1}$**SWASNRGTYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PGGVST**X$_{a4}$ATIX$_{n3}$DYTITVYAVX$_{a5}$**TDAFNPTTHEYNYFTTPX**$_{a6}$ISINYRT (SEQ ID NO: 470).

EVVAATX$_{n1}$SLLIX$_{a1}$**SWDAPTSRYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PGGLST**X$_{a4}$ATIX$_{n3}$DYTITVYAVX$_{a5}$**TDYKPHADGPHTYHESPX**$_{a6}$ISINYRT (SEQ ID NO: 471).

EVVAATX$_{n1}$SLLIX$_{a1}$**SWDAGAVTYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PGGVRT**X$_{a4}$ATIX$_{n3}$DYTITVYAVX$_{a5}$**TDYKPHADGPHTYHEYPX**$_{a6}$ISINYRT (SEQ ID NO: 472).

In SEQ ID NOs: 83-85 and 466-472, the BC, DE and FG loops have a fixed sequence as shown in bold, or a sequence at least 75%, 80%, 85%, 90%, 95%, 97%, 98%, or 99% identical to the sequences shown in bold, the AB loop is represented by X_{n1}, the CD is represented by X_{n2}, and EF loop is represented by X_{n3}, and the beta strands A-G are underlined. X represents any amino acid and the subscript following the X represents an integer of the number of amino acids. In particular, n1 may be anywhere from 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3, or 1-2 amino acids; n2 and n3 may each independently be anywhere from 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7, or 6-7 amino acids; and a1-a6 may each independently comprise from 0-10, 0-5, 1-10, 1-5, or 2-5 amino acids. In preferred embodiments, n1 is 2 amino acids, n2 is 7 amino acids, n3 is 7 amino acids, and a1-a6 is 0 amino acids. The sequences of the beta strands may

have anywhere from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 substitutions, deletions or additions across all 7 scaffold regions relative to the corresponding amino acids shown in SEQ ID NO: 1. In an exemplary embodiment, the sequences of the beta strands may have anywhere from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 conservative substitutions across all 7 scaffold regions relative to the corresponding amino acids shown in SEQ ID NO: 1. In certain embodiments, the core amino acid residues are fixed and any substitutions, conservative substitutions, deletions or additions occur at residues other than the core amino acid residues. In certain embodiments, the EGFR binder is represented by one of the following amino acid sequences:

EVVAATPTSLLISW**VAGAEDYQ**YYRITYGETGGNSPVQEFTVP**HDLV**TATIS GLKPGVDYTITVYAVT**DMMHVEYTEH**PISINYRT (SEQ ID NO: 66);

EVVAATPTSLLISW**DSGRGSYQ**YYRITYGETGGNSPVQEFTVP**GPVH**TATIS GLKPGVDYTITVYAVT**DHKPHADGPHTYHES**PISINYRT (SEQ ID NO: 67);

EVVAATPTSLLISW**LPGKLRYQ**YYRITYGETGGNSPVQEFTVP**HDLR**TATIS GLKPGVDYTITVYAVT**NMMHVEYSEY**PISINYRT (SEQ ID NO: 68);

EVVAATPTSLLISW**HERDGSRQ**YYRITYGETGGNSPVQEFTVP**GGVR**TATIS GLKPGVDYTITVYAVT**DYFNPTTHEYIYQTT**PISINYRT (SEQ ID NO: 108); or

EVVAATPTSLLISW**WAPVDRYQ**YYRITYGETGGNSPVQEFTVP**RDVY**TATI SGLKPGVDYTITVYAVT**DYKPHADGPHTYHES**PISINYRT (SEQ ID NO: 114).

EVVAATPTSLLISW**TQGSTHYQ**YYRITYGETGGNSPVQEFTVP**GMVY**TATI SGLKPGVDYTITVYAVT**DYFDRSTHEYKYRTT**PISINYRT (SEQ ID NO: 141)

EVVAATPTSLLISW**YWEGLPYQ**YYRITYGETGGNSPVQEFTV**PRDVN**TATI SGLKPGVDYTITVYAVT**DWYNPDTHEYIYHTI**PISINYRT (SEQ ID NO: 156)

EVVAATPTSLLISW**ASNRGTYQ**YYRITYGETGGNSPVQEFTVP**GGVS**TATIS GLKPGVDYTITVYAVT**DAFNPTTHEYNYFTT**PISINYRT (SEQ ID NO: 171)

EVVAATPTSLLISW**DAPTSRYQ**YYRITYGETGGNSPVQEFTVP**GGLS**TATIS GLKPGVDYTITVYAVT**DYKPHADGPHTYHES**PISINYRT (SEQ ID NO: 186)

E112

EVVAATPTSLLISW**DAGAVTYQ**YYRITYGETGGNSPVQEFTVP**GGVR**TATI SGLKPGVDYTITVYAVT**DYKPHADGPHTYHEY**PISINYRT (SEQ ID NO: 199)

In SEQ ID NOs: 66-68, 108, 114, 141, 156, 171, 186 and 199, the sequence of the BC, DE and FG loops have a fixed sequence as shown in bold, or a sequence at least 75%, 80%, 85%, 90%, 95%, 97%, 98%, or 99% identical to the sequences shown in bold, and the remaining sequence which is underlined (e.g., the sequence of the 7 beta strands and the AB, CD and EF loops) has anywhere from 0 to 20, from 0 to 15, from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 substitutions, conservative substitutions, deletions or additions relative to the corresponding amino acids shown in SEQ ID NO: 66-68, 108, 114, 141, 156, 171, 186 and 199. In certain embodiments, the core amino acid residues are fixed and any substitutions, conservative substitutions, deletions or additions occur at residues other than the core amino acid residues. The ^{10}Fn3 domain that binds to EGFR may optionally comprise an N-terminal extension of from 1-20, 1-15, 1-10, 1-8, 1-5, 1-4, 1-3, 1-2, or 1 amino acids in length. Exemplary N-terminal extensions include (represented by the single letter amino acid code) M, MG, G, MGVSDVPRDL (SEQ ID NO: 69), GVSDVPRDL (SEQ ID NO: 70), and VSDVPRDL (SEQ ID NO: 71), or N-terminal truncations of any one of SEQ ID NOs: 69, 70, or 71. Other suitable N-terminal extensions include, for example, X_nSDVPRDL (SEQ ID NO: 72), X_nDVPRDL (SEQ ID NO: 73), X_nVPRDL (SEQ ID NO: 74), X_nPRDL (SEQ ID NO: 75), X_nRDL (SEQ ID NO: 76), X_nDL (SEQ ID

NO: 77), or X_nL, wherein n = 0, 1 or 2 amino acids, wherein when n = 1, X is Met or Gly, and when n = 2, X is Met-Gly. The ^{10}Fn3 domain that binds to EGFR may optionally comprise a C-terminal tail. Exemplary C-terminal tails include polypeptides that are from 1-20, 1-15, 1-10, 1-8, 1-5, 1-4, 1-3, 1-2, or 1 amino acids in length. Specific examples of C-terminal tails include EIDKPSQ (SEQ ID NO: 9), EIDKPCQ (SEQ ID NO: 10), and EIDK (SEQ ID NO: 78). In other embodiments, suitable C-terminal tails may be a C-terminally truncated fragment of SEQ ID NOs: 9, 10 or 78, including, for example, one of the following amino acid sequences (represented by the single letter amino acid code): E, EI, EID, EIDKP (SEQ ID NO: 79), EIDKPS (SEQ ID NO: 80), or EIDKPC (SEQ ID NO: 81). Other suitable C-terminal tails include, for example, ES, EC, EGS, EGC, EGSGS (SEQ ID NO: 96), EGSGC (SEQ ID NO: 97), or EIEK (SEQ ID NO: 217). In certain embodiments, the ^{10}Fn3 domain that binds to EGFR comprises both an N-terminal extension and a C-terminal tail. In exemplary embodiments, the A region comprises an N-terminal extension beginning with Gly or Met-Gly and a C-terminal extension that does not contain a cysteine residue and the B region comprises an N-terminal extension that does not start with a Met and a C-terminal extension that comprises a cysteine residue. Specific examples of ^{10}Fn3 domains that bind to EGFR are polypeptides comprising (i) a polypeptide having an amino acid sequence set forth in any one of SEQ ID NOs: 5-8, 52, 66-68, 82-85, 106-108, 112-114, 140-142, 155-157, 170-172, 185-187, 198-200, and 219-327, or (ii) a polypeptide comprising an amino acid sequence at least 85%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 5-8, 52, 66-68, 82-85, 106-108, 112-114, 140-142, 155-157, 170-172, 185-187, 198-200, and 219-327.

In certain embodiments, the A or C region is a polypeptide comprising a ^{10}Fn3 domain that binds to IGF-IR, wherein the ^{10}Fn3 domain has the structure from N-terminus to C-terminus: beta strand A, loop AB, beta strand B, loop BC, beta strand C, loop CD, beta strand D, loop DE, beta strand E, loop EF, beta strand F, loop FG, beta strand G, wherein the BC loop has the amino acid sequence of SEQ ID NO: 45 or 46, the DE loop has the amino acid sequence of SEQ ID NO: 47 or 48, and the FG loop has the amino acid sequence of SEQ ID NO: 49 or 50, wherein the ^{10}Fn3 domain folds into an antibody heavy chain variable region-like structure, and

wherein the polypeptide binds to IGF-IR with a K_D of less than 100 nM. The ^{10}Fn3 domain that binds to IGF-IR preferably folds into a structure wherein the 7 beta strands are distributed between two beta sheets that pack against each other forming a stable core and wherein the beta strands are connected by the six loops which are solvent exposed. In exemplary embodiments, the ^{10}Fn3 domain is from 80-150 amino acids in length.

In exemplary embodiments, the A or C region is a ^{10}Fn3 domain that binds to IGF-IR with a K_D of less than 100 nM having the sequence set forth below:

EVVAATX$_{n1}$SLLIX$_{a1}$**SWSARLKVAR**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PKNVYT**X$_{a4}$ATIX$_{n3}$DYTITVYAVX$_{a5}$**TRFRDYQP**X$_{a6}$ISINYRT (SEQ ID NO: 86).

In SEQ ID NO: 86, the BC, DE and FG loops have a fixed sequence as shown in bold, or a sequence at least 75%, 80%, 85%, 90%, 95%, 97%, 98%, or 99% identical to the sequences shown in bold, the AB loop is represented by X_{n1}, the CD loop is represented by X_{n2}, and the EF loop is represented by X_{n3}, and the beta strands A-G are underlined. X represents any amino acid and the subscript following the X represents an integer of the number of amino acids. In particular, n1 may be anywhere from 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3, or 1-2 amino acids; n2 and n3 may each independently be anywhere from 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7, or 6-7 amino acids; and a1-a6 may each independently comprise from 0-10, 0-5, 1-10, 1-5, or 2-5 amino acids. In preferred embodiments, n1 is 2 amino acids, n2 is 7 amino acids, n3 is 7 amino acids, and a1-a6 is 0 amino acids. The sequences of the beta strands may have anywhere from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 substitutions, deletions or additions across all 7 scaffold regions relative to the corresponding amino acids shown in SEQ ID NO: 1. In an exemplary embodiment, the sequences of the beta strands may have anywhere from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 conservative substitutions across all 7 scaffold regions relative to the corresponding amino acids shown in SEQ ID NO: 1. In certain embodiments, the core amino acid residues are fixed and any substitutions, conservative

substitutions, deletions or additions occur at residues other than the core amino acid residues. In certain embodiments, the IGF-IR binder is represented by the following amino acid sequence:

EVVAATPTSLLISW**SARLKVA**RYYRITYGETGGNSPVQEFTVP**KNVY**TATIS GLKPGVDYTITVYAVT**RFRDYQ**PISINYRT (SEQ ID NO: 65).

In SEQ ID NO: 65, the sequence of the BC, DE and FG loops have a fixed sequence as shown in bold, or a sequence at least 75%, 80%, 85%, 90%, 95%, 97%, 98%, or 99% identical to the sequences shown in bold, and the remaining sequence which is underlined (e.g., the sequence of the 7 beta strands and the AB, CD and EF loops) has anywhere from 0 to 20, from 0 to 15, from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 substitutions, conservative substitutions, deletions or additions relative to the corresponding amino acids shown in SEQ ID NO: 65. In certain embodiments, the core amino acid residues are fixed and any substitutions, conservative substitutions, deletions or additions occur at residues other than the core amino acid residues. The ^{10}Fn3 domain that binds to IGF-IR may optionally comprise an N-terminal extension of from 1-20, 1-15, 1-10, 1-8, 1-5, 1-4, 1-3, 1-2, or 1 amino acids in length. Exemplary N-terminal extensions include (represented by the single letter amino acid code) M, MG, G, MGVSDVPRDL (SEQ ID NO: 69), GVSDVPRDL (SEQ ID NO: 70), and VSDVPRDL (SEQ ID NO: 71), or N-terminal truncations of any one of SEQ ID NOs: 69, 70, or 71. Other suitable N-terminal extensions include, for example, X_nSDVPRDL (SEQ ID NO: 72), X_nDVPRDL (SEQ ID NO: 73), X_nVPRDL (SEQ ID NO: 74), X_nPRDL (SEQ ID NO: 75), X_nRDL (SEQ ID NO: 76), X_nDL (SEQ ID NO: 77), or X_nL, wherein n = 0, 1 or 2 amino acids, wherein when n = 1, X is Met or Gly, and when n = 2, X is Met-Gly. The ^{10}Fn3 domain that binds to IGF-IR may optionally comprise a C-terminal tail. Exemplary C-terminal tails include polypeptides that are from 1-20, 1-15, 1-10, 1-8, 1-5, 1-4, 1-3, 1-2, or 1 amino acids in length. Specific examples of C-terminal tails include EIDKPSQ (SEQ ID NO: 9), EIDKPCQ (SEQ ID NO: 10), and EIDK (SEQ ID NO: 78). In other embodiments, suitable C-terminal tails may be a C-terminally truncated fragment of SEQ ID NOs:

9, 10 or 78, including, for example, one of the following amino acid sequences (represented by the single letter amino acid code): E, EI, EID, EIDKP (SEQ ID NO: 79), EIDKPS (SEQ ID NO: 80), or EIDKPC (SEQ ID NO: 81). Other suitable C-terminal tails include, for example, ES, EC, EGS, EGC, EGSGS (SEQ ID NO: 96), EGSGC (SEQ ID NO: 97), or EIEK (SEQ ID NO: 217). In certain embodiments, the ^{10}Fn3 domain that binds to IGF-IR comprises both an N-terminal extension and a C-terminal tail. In exemplary embodiments, the A region comprises an N-terminal extension beginning with Gly or Met-Gly and a C-terminal extension that does not contain a cysteine residue and the B region comprises an N-terminal extension that does not start with a Met and a C-terminal extension that comprises a cysteine residue. Specific examples of ^{10}Fn3 domains that bind to IGF-IR are polypeptides comprising (i) a polypeptide having an amino acid sequence set forth in any one of SEQ ID NOs: 3, 4, 65 or 86, or (ii) a polypeptide comprising an amino acid sequence at least 85%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 3, 4, 65 or 86.

The B region is a linker as described further herein. In exemplary embodiments, the B region is a polypeptide linker. Exemplary polypeptide linkers include polypeptides having from 1-20, 1-15, 1-10, 1-8, 1-5, 1-4, 1-3, or 1-2 amino acids. Specific examples of suitable polypeptide linkers are described further herein and include, for example, linkers having a sequence selected from the group consisting of SEQ ID NOs: 11-19, 51, 93-95 and 218. In certain embodiments, the linker may be a C-terminal tail polypeptide as described herein, an N-terminal extension polypeptide as described herein, or a combination thereof.

In one embodiment, an antibody-like protein dimer comprises a polypeptide having the structure X_1-A-X_2-B-X_3-C-X_4, wherein X_1 is an optional N-terminal extension, A is a ^{10}Fn3 domain that binds to EGFR, X_2 is an optional C-terminal tail, B is a polypeptide linker, X_3 is an optional N-terminal extension, C is a ^{10}Fn3 domain that binds to IGF-IR, and X_4 is an optional C-terminal tail. In another embodiment, an antibody-like protein dimer comprises a polypeptide having the structure X_1-A-X_2-B-X_3-C-X_4, wherein X_1 is an optional N-terminal extension, A is a ^{10}Fn3 domain that binds to IGF-IR, X_2 is an optional C-terminal tail, B is a polypeptide linker, X_3 is an optional N-terminal extension, C is a ^{10}Fn3 domain that

binds to EGFR, and X_4 is an optional C-terminal tail. Specific examples of suitable N-terminal extensions and C-terminal tails are described above. In certain embodiments, one or more of X_1, X_2, B, X_3 or X_4 may comprise an amino acid residue suitable for pegylation, such as a cysteine or lysine residue. In exemplary embodiments, X_4 comprises at least one amino acid suitable for pegylation, such as a cysteine or lysine residue. Specific examples of suitable polypeptide linkers are described further below. Specific examples of antibody-like protein dimers having the structure X_1-A-X_2-B-X_3-C-X_4 are polypeptides comprising (i) a polypeptide having the amino acid sequence set forth in any one of SEQ ID NOs: 20-31, 53-58, 87-92, 98-105, 118-133, 149-154, 164-169, 179-184, 192-197, 205-210 and 211-216, or (ii) a polypeptide comprising an amino acid sequence at least 85%, 90%, 95%, 97%, 98%, or 99% identical to the amino acid sequence set forth in any one of SEQ ID NOs: 20-31, 53-58, 87-92, 98-105, 118-133, 149-154, 164-169, 179-184, 192-197, 205-210 and 211-216.

In certain embodiments, it may be desirable to tune the potency of one ^{10}Fn3 binding domain relative to the other ^{10}Fn3 binding domain in the antibody-like protein dimers described herein. For example, if the binding affinity of the first ^{10}Fn3 domain is significantly higher than the binding affinity of the second ^{10}Fn3 domain, the biological effect of the first ^{10}Fn3 domain could overwhelm the effects of the second of second ^{10}Fn3 domain. Accordingly, in certain embodiments, it may be desirable for the binding affinities of the first and second ^{10}Fn3 domains of an antibody-like protein dimer to be similar to each other, e.g., binding affinities within 100-fold, 30-fold, 10-fold, 3-fold, 1-fold, 0.3-fold or 0.1-fold, of each other, or binding affinities within 0.1-fold to 10-fold, within 0.3-fold to 10-fold, within 0.1-fold to 3-fold, within 0.3-fold to 3-fold, within 0.1-fold to 1-fold, within 0.3-fold to 1-fold, within 1-fold to 10-fold, within 3-fold to 10-fold, within 3-fold to 30-fold, or within 1-fold to 3-fold of each other.

Conjugation

Multimers of antibody-like proteins may be covalently or non-covalently linked. In some embodiments, an EGFR binding ^{10}Fn3 may be directly or indirectly linked to an IGFIR binding ^{10}Fn3 via a polypeptide linker. Suitable linkers for joining Fn3 are those which allow the separate domains to fold independently of

each other forming a three dimensional structure that permits high affinity binding to a target molecule.

The disclosure provides a number of suitable linkers that meet these requirements, including glycine-serine based linkers, glycine-proline based linkers, as well as the linker having the amino acid sequence PSTSTST (SEQ ID NO: 12). The Examples described herein demonstrate that Fn3 domains joined via polypeptide linkers retain their target binding function. In some embodiments, the linker is a glycine-serine based linker. These linkers comprise glycine and serine residues and may be between 8 and 50, 10 and 30, and 10 and 20 amino acids in length. Examples include linkers having an amino acid sequence GSGSGSGSGSGSGSGSGS (SEQ ID NO: 11), GSGSGSGSGS (SEQ ID NO: 13), GGGGS GGGGS GGGGS (SEQ ID NO: 14), GGGGS GGGGS GGGGS GGGGS (SEQ ID NO: 15), GGGGS GGGGS GGGGS GGGGS GGGGS (SEQ ID NO: 16), or GGGGSGGGGSGGGGSG (SEQ ID NO: 17). In some embodiments, the linker is a glycine-proline based linker. These linkers comprise glycine and proline residues and may be between 3 and 30, 10 and 30, and 3 and 20 amino acids in length. Examples include linkers having an amino acid sequence GPGPGPG (SEQ ID NO: 18), GPGPGPGPGPG (SEQ ID NO: 19), and GPG (SEQ ID NO: 51). In some embodiments, the linker is a proline-alanine based linker. These linkers comprise proline and alanine residues and may be between 3 and 30, 10 and 30, 3 and 20 and 6 and 18 amino acids in length. Examples of such linkers include SEQ ID NOs: 93, 94 and 95. It is contemplated, that the optimal linker length and amino acid composition may be determined by routine experimentation by methods well known in the art.

In some embodiments, multimers of antibody-like proteins are linked via a polypeptide linker having a protease site that is cleavable by a protease in the blood or target tissue. Such embodiments can be used to release two or more therapeutic proteins for better delivery or therapeutic properties or more efficient production compared to separately producing such proteins.

Additional linkers or spacers, e.g., SEQ ID NOs: 9 and 10, may be introduced at the C-terminus of a Fn3 domain between the Fn3 domain and the

polypeptide linker. Additional linkers or spacers may be introduced at the N-terminus of a Fn3 domain between the Fn3 domain and the polypeptide linker.

In some embodiments, multimers of antibody-like proteins may be directly or indirectly linked via a polymeric linker. Polymeric linkers can be used to optimally vary the distance between each protein moiety to create a protein with one or more of the following characteristics: 1) reduced or increased steric hindrance of binding of one or more protein domain when binding to a protein of interest, 2) increased protein stability or solubility, 3) decreased protein aggregation, and 4) increased overall avidity or affinity of the protein.

In some embodiments, multimers of antibody-like proteins are linked via a biocompatible polymer such as a polymeric sugar. The polymeric sugar can include an enzymatic cleavage site that is cleavable by an enzyme in the blood or target tissue. Such embodiments can be used to release two or more therapeutic proteins for better delivery or therapeutic properties or more efficient production compared to separately producing such proteins

In some embodiments, multimers of antibody-like proteins are linked via a polyoxyalkylene, in particular a polyethylene glycol (PEG) moiety. Antibody-like proteins may comprise a cysteine containing linker, such as the linker set forth in SEQ ID NO: 10, 81, 97 or 218. PEG may be conjugated to the cysteine moiety in the linker sequence and may operably link the two domains.

Pharmacokinetic moieties

In one aspect, the disclosure provides E binders and E/I binders further comprising a pharmacokinetic (PK) moiety. In some embodiments, the E/I binder is a multimer of antibody-like proteins, in particular, a dimer of an EGFR binding ^{10}Fn3 and an IGFIR binding ^{10}Fn3. Improved pharmacokinetics may be assessed according to the perceived therapeutic need. Often it is desirable to increase bioavailability and/or increase the time between doses, possibly by increasing the time that a protein remains available in the serum after dosing. In some instances, it is desirable to improve the continuity of the serum concentration of the protein over time (e.g., decrease the difference in serum concentration of the protein shortly after administration and shortly before the next administration). E binders and E/I binders may be attached to a moiety that reduces the clearance rate of the polypeptide in a

mammal (e.g., mouse, rat, or human) by greater than three-fold relative to the unmodified polypeptide. Other measures of improved pharmacokinetics may include serum half-life, which is often divided into an alpha phase and a beta phase. Either or both phases may be improved significantly by addition of an appropriate moiety.

Moieties that tend to slow clearance of a protein from the blood include polyoxyalkylene moieties (e.g., polyethylene glycol); sugars (e.g., sialic acid); and well-tolerated protein moieties (e.g., Fc, Fc fragments, transferrin, or serum albumin).

In some embodiments, the PK moiety is a serum albumin binding protein such as those described in U.S. Publication Nos. 2007/0178082 and 2007/0269422.

In some embodiments, the PK moiety is a serum immunoglobulin binding protein such as those described in U.S. Publication No. 2007/0178082.

In some embodiments, the PK moiety is polyethylene glycol (PEG).

The serum clearance rate of a PK-modified antibody-like protein multimer may be decreased by about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or even 90%, relative to the clearance rate of the unmodified E/I binders. The PK-modified multimer may have a half-life ($t_{1/2}$) which is enhanced relative to the half-life of the unmodified multimer. The half-life of PK- binding polypeptide may be enhanced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400% or 500%, or even by 1000% relative to the half-life of the unmodified multimer. In some embodiments, the multimer half-life is determined in vitro, such as in a buffered saline solution or in serum. In other embodiments, the multimer half-life is an in vivo half life, such as the half-life of the multimer in the serum or other bodily fluid of an animal.

In some embodiments, a PK moiety is linked to an antibody-like protein multimer via at least one disulfide bond, a peptide bond, a polypeptide, a polymeric sugar, or a polyethylene glycol moiety. Exemplary polypeptide linkers include PSTSTST (SEQ ID NO: 12), EIDKPSQ (SEQ ID NO: 9), and GS linkers, such as GSGSGSGSGS (SEQ ID NO: 13) and multimers thereof.

Binding/Screening

The disclosure provides E binders and E/I binders, in particular, antibody-like protein multimers such as a dimer of an EGFR binding ^{10}Fn3 and an IGFIR binding ^{10}Fn3. Binding to EGFR or IGFIR may be assessed in terms of equilibrium constants (e.g., dissociation, K_D) and in terms of kinetic constants (e.g., on rate constant, k_{on} and off rate constant, k_{off}). In some embodiments, an antibody-like protein monomer or multimer will bind to EGFR with a K_D of less than 500nM, 100nM, 50nM, 5nM or less. In some embodiments, an antibody-like protein multimer will bind to IGFIR with a K_D of less than 500nM, 100nM, 50nM, 5nM or less. Higher K_D values may be tolerated where the k_{off} is sufficiently low or the k_{on} is sufficiently high.

E binders and E/I binders may bind to any part of EGFR, including the extracellular domain of a EGFR, in particular the ligand binding domain of EGFR. Binding of E binders and E/I binders to EGFR may disrupt the interaction of EGFR with one or more ligands, including TGF-alpha and EGF, and/or disrupt receptor dimerization. In some embodiments, E binders and E/I binders compete with an anti-EGFR antibody for binding to EGFR. The anti-EGFR antibody may be selected from any known anti-EGFR antibody including panitumumab (Amgen), nimotuzumab (YM Biosciences), zalutumumab (Genmab), EMD72000 (Merck KGaA), and cetuximab (ImClone Systems).

In some embodiments, E binders and E/I binders inhibit downstream signaling of EGFR. EGFR ligand binding leads to homo- or heterodimeric receptor dimerization with EGFR or another HER family member. Dimerization promotes receptor autophosphorylation, which in turn leads to the activation of several signaling pathways.

E/I binders may bind to any part of IGFIR, including the extracellular domain of a IGFIR, in particular the ligand binding domain of IGFIR. Binding of E/I binders to IGFIR may disrupt the interaction of IGFIR with one or more ligands, e.g., IGF-I and IGF-II; and/or disrupt assembly of receptor heterotetramers. In some embodiments, E/I binders compete with an anti-IGFIR antibody for binding to IGFIR. The anti-IGFIR antibody may be selected from any known anti-IGFIR antibody.

In some embodiments, E/I binders inhibit downstream signaling of IGFIR. The IGF-I receptor is composed of two types of subunits: an alpha subunit (a 130-135 kDa protein that is entirely extracellular and functions in ligand binding) and a beta subunit (a 95-kDa transmembrane protein, with transmembrane and cytoplasmic domains). IGFIR is initially synthesized as a single chain proreceptor polypeptide that is processed by glycosylation, proteolytic cleavage, and covalent bonding to assemble into a mature 460-kDa heterotetramer comprising two alpha-subunits and two beta-subunits. The beta subunit(s) possesses ligand-activated tyrosine kinase activity.

EGFR and IGFIR receptor signaling independently activates the MAPK pathway, including the phosphorylation of MEK. Another activated pathway is the phosphatidylinositol 3-kinase (PI3K) pathway, including phosphorylation of AKT. Receptor signaling is transduced to the nucleus, resulting in the activation of various transcription factors.

Screening assays may be designed to identify and characterize E binders and E/I binders. Binding assays, such as surface plasmon resonance and ELISA, and assays that detect activated signaling pathways are well-known in the art, see e.g., Example 5. Various antibodies, including many that are commercially available, have been produced which specifically bind to phosphorylated, activated isoforms of EGFR and IGFIR, see e.g., Examples 6 and 7. Downstream signaling events may also be used as an indicator of receptor inhibition, such as by measuring levels of AKT phosphorylation, see e.g., Example 8. Cell proliferation assays are also a useful method for characterizing the ability of candidate E/I binders to bind and inhibit EGFR and IGFIR signaling, see e.g., Example 9.

Polymer conjugation

Conjugation to a biocompatible polymer may be used to link antibody-like protein multimers and/or to improve the pharmacokinetics of the proteins. The identity, size and structure of the polymer is selected so as to improve the circulation half-life of the multimer or decrease the antigenicity of the multimer without an unacceptable decrease in activity.

Examples of polymers useful in the invention include, but are not limited to, poly(alkylene glycols) such as polyethylene glycol (PEG). The polymer is not

limited to a particular structure and can be linear (e.g., alkoxy PEG or bifunctional PEG), or non-linear such as branched, forked, multi-armed (e.g., PEGs attached to a polyol core), and dendritic.

Typically, PEG and other water-soluble polymers (i.e., polymeric reagents) are activated with a suitable activating group appropriate for coupling to a desired site on the polypeptide. Thus, a polymeric reagent will possess a reactive group for reaction with the polypeptide. Representative polymeric reagents and methods for conjugating these polymers to an active moiety are well-known in the art and further described in Zalipsky, S., et al., "Use of Functionalized Poly(Ethylene Glycols) for Modification of Polypeptides" in Polyethylene Glycol Chemistry: Biotechnical and Biomedical Applications, J. M. Harris, Plenus Press, New York (1992), and in Zalipsky (1995) Advanced Drug Reviews 16: 157-182.

Typically, the weight-average molecular weight of the polymer is from about 100 Daltons to about 150,000 Daltons. Exemplary weight-average molecular weights for the biocompatible polymer include about 20,000 Daltons, about 40,000 Daltons, about 60,000 Daltons and about 80,000 Daltons. Branched versions of the biocompatible polymer having a total molecular weight of any of the foregoing can also be used.

In some embodiments, the polymer is PEG. PEG is a well-known, water soluble polymer that is commercially available or can be prepared by ring-opening polymerization of ethylene glycol according to methods well known in the art (Sandler and Karo, Polymer Synthesis, Academic Press, New York, Vol. 3, pages 138-161). The term "PEG" is used broadly to encompass any polyethylene glycol molecule, without regard to size or to modification at an end of the PEG, and can be represented by the formula: $X—O(CH_2CH_2O)_{n-1}CH_2CH_2OH$, where n is 20 to 2300 and X is H or a terminal modification, e.g., a C_{1-4} alkyl. PEG can contain further chemical groups which are necessary for binding reactions, which result from the chemical synthesis of the molecule; or which act as a spacer for optimal distance of parts of the molecule. In addition, such a PEG can consist of one or more PEG side-chains which are linked together. PEGs with more than one PEG chain are called multiarmed or branched PEGs. Branched PEG are described in, for example, European Published Application No. 473084A and U.S. Patent No. 5,932,462.

To effect covalent attachment of the polymer molecule(s) to a polypeptide, the hydroxyl end groups of the polymer molecule must be provided in activated form, i.e. with reactive functional groups. Suitably activated polymer molecules are commercially available, e.g. from Nektar Therapeutics, Inc., Huntsville, Ala., USA; PolyMASC Pharmaceuticals plc, UK; or SunBio Corporation, Anyang City, South Korea. Alternatively, the polymer molecules can be activated by conventional methods known in the art, e.g. as disclosed in WO 90/13540. Specific examples of activated PEG polymers include the following linear PEGs: NHS-PEG, SPA-PEG, SSPA-PEG, SBA-PEG, SS-PEG, SSA-PEG, SC-PEG, SG-PEG, SCM-PEG, NOR-PEG, BTC-PEG, EPOX-PEG, NCO-PEG, NPC-PEG, CDI-PEG, ALD-PEG, TRES-PEG, VS-PEG, OPSS-PEG, IODO-PEG, and MAL-PEG, and branched PEGs, such as PEG2-NHS, PEG2-MAL, and those disclosed in U.S. Pat. No. 5,932,462 and U.S. Pat. No. 5,643,575, both of which are incorporated herein by reference.

In some embodiments where PEG molecules are conjugated to cysteine residues on an antibody-like protein multimer, the cysteine residues are native to the protein, whereas in other embodiments, one or more cysteine residues are engineered into the protein. Mutations may be introduced into a protein coding sequence to generate cysteine residues. This might be achieved, for example, by mutating one or more amino acid residues to cysteine. Preferred amino acids for mutating to a cysteine residue include serine, threonine, alanine and other hydrophilic residues. Preferably, the residue to be mutated to cysteine is a surface-exposed residue. Algorithms are well-known in the art for predicting surface accessibility of residues based on primary sequence or a protein. Alternatively, surface residues may be predicted by comparing the amino acid sequences of binding polypeptides, given that the crystal structure of the framework based on which binding polypeptides are designed and evolved has been solved (see Himanen et al., Nature. (2001) 20-27;414(6866):933-8) and thus the surface-exposed residues identified. In some embodiments, cysteine residues are introduced into antibody-like protein multimers at or near the N- and/or C-terminus, or within loop regions. Pegylation of cysteine residues may be carried out using, for example, PEG-maleiminde, PEG-vinylsulfone, PEG-iodoacetamide, or PEG-orthopyridyl disulfide.

In some embodiments, the pegylated antibody-like protein multimer

comprises a PEG molecule covalently attached to the alpha amino group of the N-terminal amino acid. Site specific N-terminal reductive amination is described in Pepinsky et al., (2001) JPET, 297,1059, and U.S. Patent No. 5,824,784. The use of a PEG-aldehyde for the reductive amination of a protein utilizing other available nucleophilic amino groups is described in U.S. Patent No. 4,002,531, in Wieder et al., (1979) J. Biol. Chem. 254,12579, and in Chamow et al., (1994) Bioconjugate Chem. 5, 133.

In another embodiment, pegylated antibody-like protein multimer comprises one or more PEG molecules covalently attached to a linker, which in turn is attached to the alpha amino group of the amino acid residue at the N-terminus of the binding polypeptide. Such an approach is disclosed in U.S. Publication No. 2002/0044921 and PCT Publication No. WO 94/01451.

In some embodiments, an antibody-like protein multimer is pegylated at the C-terminus. A protein may be pegylated at the C-terminus by the introduction of C-terminal azido-methionine and the subsequent conjugation of a methyl-PEG-triarylphosphine compound via the Staudinger reaction. This C-terminal conjugation method is described in Cazalis et al., C-Terminal Site-Specific PEGylation of a Truncated Thrombomodulin Mutant with Retention of Full Bioactivity, *Bioconjug Chem.* 2004;15(5):1005-1009.

Conventional separation and purification techniques known in the art can be used to purify PEGylated antibody-like protein multimers, such as size exclusion (e.g., gel filtration) and ion exchange chromatography. Products may also be separated using SDS-PAGE. Products that may be separated include mono-, di-, tri-, poly- and un- pegylated binding polypeptide, as well as free PEG. The percentage of mono-PEG conjugates can be controlled by pooling broader fractions around the elution peak to increase the percentage of mono-PEG in the composition. About ninety percent mono-PEG conjugates represents a good balance of yield and activity.

In some embodiments, the pegylated antibody-like protein multimers will preferably retain at least about 25%, 50%, 60%, 70%, 80%, 85%, 90%, 95% or 100% of the biological activity associated with the unmodified protein. In some embodiments, biological activity refers to its ability to bind to EGFR and IGFIR, as

assessed by K_D, k_{on} or k_{off}. In some embodiments, the pegylated antibody-like protein multimer shows an increase in binding to EGFR and/or IGFIR relative to unpegylated protein.

Deimmunization of binding polypeptides

The amino acid sequences of E binders and E/I binders, in particular, antibody-like protein multimers, such as a dimer of an EGFR binding ^{10}Fn3 and an IGFIR binding ^{10}Fn3, may be altered to eliminate one or more B- or T-cell epitopes. A protein, or a multimer of proteins, may be deimmunized to render it non-immunogenic, or less immunogenic, to a given species. Deimmunization can be achieved through structural alterations to the protein. Any deimmunization technique known to those skilled in the art can be employed, see e.g., WO 00/34317, the disclosure of which is incorporated herein in its entirety.

In one embodiment, the sequences of the E binders and E/I binders can be analyzed for the presence of MHC class II binding motifs. For example, a comparison may be made with databases of MHC-binding motifs such as, for example by searching the "motifs" database on the worldwide web at sitewehil.wehi.edu.au. Alternatively, MHC class II binding peptides may be identified using computational threading methods such as those devised by Altuvia et al. (J. Mol. Biol. 249 244-250 (1995)) whereby consecutive overlapping peptides from the polypeptide are testing for their binding energies to MHC class II proteins. Computational binding prediction algorithms include iTope™, Tepitope, SYFPEITHI, EpiMatrix (EpiVax), and MHCpred. In order to assist the identificationof MHC class II-binding peptides, associated sequence features which relate to successfully presented peptides such as amphipathicity and Rothbard motifs, and cleavage sites for cathepsin B and other processing enzymes can be searched for.

Having identified potential (e.g. human) T-cell epitopes, these epitopes are then eliminated by alteration of one or more amino acids, as required to eliminate the T-cell epitope. Usually, this will involve alteration of one or more amino acids within the T-cell epitope itself. This could involve altering an amino acid adjacent the epitope in terms of the primary structure of the protein or one which is not adjacent in the primary structure but is adjacent in the secondary structure of the

molecule. The usual alteration contemplated will be amino acid substitution, but it is possible that in certain circumstances amino acid addition or deletion will be appropriate. All alterations can be accomplished by recombinant DNA technology, so that the final molecule may be prepared by expression from a recombinant host, for example by well established methods, but the use of protein chemistry or any other means of molecular alteration may also be used.

Once identified T-cell epitopes are removed, the deimmunized sequence may be analyzed again to ensure that new T-cell epitopes have not been created and, if they have, the epitope(s) can be deleted.

Not all T-cell epitopes identified computationally need to be removed. A person skilled in the art will appreciate the significance of the "strength" or rather potential immunogenicity of particular epitopes. The various computational methods generate scores for potential epitopes. A person skilled in the art will recognize that only the high scoring epitopes may need to be removed. A skilled person will also recognize that there is a balance between removing potential epitopes and maintaining binding affinity of the protein. Therefore, one strategy is to sequentially introduce substitutions into the protein and then test for antigen binding and immunogenicity.

In one aspect, the deimmunized protein is less immunogenic (or rather, elicits a reduced HAMA response) than the original protein in a human subject. Assays to determine immunogenicity are well within the knowledge of the skilled person. Art-recognized methods of determining immune response can be performed to monitor a HAMA response in a particular subject or during clinical trials. Subjects administered deimmunized protein can be given an immunogenicity assessment at the beginning and throughout the administration of said therapy. The HAMA response is measured, for example, by detecting antibodies to the deimmunized protein in serum samples from the subject using a method known to one in the art, including surface plasmon resonance technology (BIAcore) and/or solid-phase ELISA analysis. Alternatively, in vitro assays designed to measure a T-cell activation event are also indicative of immunogenicity.

Additional Modifications

In certain embodiments, E binders and E/I binders, in particular, antibody-like protein multimers such as a dimer of an EGFR binding ^{10}Fn3 and an IGFIR binding ^{10}Fn3, may further comprise post-translational modifications. Exemplary post-translational protein modification include phosphorylation, acetylation, methylation, ADP-ribosylation, ubiquitination, glycosylation, carbonylation, sumoylation, biotinylation or addition of a polypeptide side chain or of a hydrophobic group. As a result, the modified E binders and E/I binders may contain non-amino acid elements, such as lipids, poly- or mono-saccharide, and phosphates. A preferred form of glycosylation is sialylation, which conjugates one or more sialic acid moieties to the polypeptide. Sialic acid moieties improve solubility and serum half-life while also reducing the possible immunogenicity of the protein. See, e.g., Raju et al. Biochemistry. 2001 Jul 31;40(30):8868-76. Effects of such non-amino acid elements on the functionality of an E binder or E/I binder may be tested for its antagonizing role in EGFR and IGFIR signaling function.

In some embodiments, E binders and E/I binders are modified to enhance antigen-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC). In some embodiments, the E/I binder is a dimer of an EGFR binding ^{10}Fn3 and an IGFIR binding ^{10}Fn3, further comprising an Fc region. In some embodiments, the Fc region is a variant that enhances ADCC or CDC. The Fc region variant may comprise a human Fc region sequence (e.g., a human IgG1, IgG2, IgG3 or IgG4 Fc region) comprising an amino acid modification (e.g., a substitution) at one or more amino acid positions, including positions 256, 290, 298, 312, 326, 330, 333, 334, 360, 378 or 430, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

Vectors & Polynucleotides Embodiments

Also included in the present disclosure are nucleic acid sequences encoding any of the proteins described herein. As appreciated by those skilled in the art, because of third base degeneracy, almost every amino acid can be represented by more than one triplet codon in a coding nucleotide sequence. In addition, minor base pair changes may result in a conservative substitution in the amino acid sequence encoded but are not expected to substantially alter the biological activity of

the gene product. Therefore, a nucleic acid sequence encoding a protein described herein may be modified slightly in sequence and yet still encode its respective gene product.

Exemplary nucleic acids encoding the E/I binders described herein include nucleic acids having SEQ ID NOs: 442-465 or nucleic acids having a sequence at least 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identical to any one of SEQ ID NOs: 442-465. Isolated nucleic acids which differ from the nucleic acids as set forth in SEQ ID NOs: 442-465 due to degeneracy in the genetic code are also within the scope of the invention. Also provided are E/I binders comprising an I monomer encoded by a nucleotide sequence at least 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 328 and/or E/I binders comprising an E monomer encoded by a nucleotide sequence at 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identical to any one of SEQ ID NOs: 329-441 or 495. Also provided are E binders encoded by a nucleotide sequence at 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identical to any one of SEQ ID NOs:. 329-441 or 495. In certain embodiments, the nucleotide sequences encoding the E/I binders, an E monomer, or an I monomer do not contain a sequence encoding a 6XHis tag (SEQ ID NO: 487).

Nucleic acids encoding any of the various proteins or polypeptides disclosed herein may be synthesized chemically. Codon usage may be selected so as to improve expression in a cell. Such codon usage will depend on the cell type selected. Specialized codon usage patterns have been developed for E. coli and other bacteria, as well as mammalian cells, plant cells, yeast cells and insect cells. See for example: Mayfield et al., Proc Natl Acad Sci U S A. 2003 100(2):438-42; Sinclair et al. Protein Expr Purif. 2002 (1):96-105; Connell ND. Curr Opin Biotechnol. 2001 (5):446-9; Makrides et al. Microbiol Rev. 1996 60(3):512-38; and Sharp et al. Yeast. 1991 7(7):657-78.

General techniques for nucleic acid manipulation are within the purview of one skilled in the art and are also described for example in Sambrook et al., Molecular Cloning: A Laboratory Manual, Vols. 1-3, Cold Spring Harbor Laboratory Press, 2 ed., 1989, or F. Ausubel et al., Current Protocols in Molecular Biology (Green Publishing and Wiley-Interscience: New York, 1987) and periodic updates, herein incorporated by reference. The DNA encoding a protein is operably

linked to suitable transcriptional or translational regulatory elements derived from mammalian, viral, or insect genes. Such regulatory elements include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences that control the termination of transcription and translation. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants are additionally incorporated. Suitable regulatory elements are well-known in the art.

The proteins described herein may be produced as a fusion protein with a heterologous polypeptide, which is preferably a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. The heterologous signal sequence selected preferably is one that is recognized and processed (i.e., cleaved by a signal peptidase) by the host cell. For prokaryotic host cells that do not recognize and process a native signal sequence, the signal sequence is substituted by a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion, the native signal sequence may be substituted by, e.g., the yeast invertase leader, a factor leader (including Saccharomyces and Kluyveromyces alpha-factor leaders), or acid phosphatase leader, the C. albicans glucoamylase leader, or the signal described in PCT Publication No. WO 90/13646. In mammalian cell expression, mammalian signal sequences as well as viral secretory leaders, for example, the herpes simplex gD signal, are available. The DNA for such precursor regions may be ligated in reading frame to DNA encoding the protein.

Expression vectors used in eukaryotic host cells (e.g., yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding the multivalent antibody. One useful transcription termination component is the bovine growth hormone polyadenylation

region. See PCT Publication No. WO 94/11026 and the expression vector disclosed therein.

The recombinant DNA can also include any type of protein tag sequence that may be useful for purifying the protein. Examples of protein tags include but are not limited to a histidine tag, a FLAG tag, a myc tag, an HA tag, or a GST tag. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts can be found in Cloning Vectors: A Laboratory Manual, (Elsevier, New York, 1985), the relevant disclosure of which is hereby incorporated by reference.

The expression construct is introduced into the host cell using a method appropriate to the host cell, as will be apparent to one of skill in the art. A variety of methods for introducing nucleic acids into host cells are known in the art, including, but not limited to, electroporation; transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; and infection (where the vector is an infectious agent).

Suitable host cells include prokaryotes, yeast, mammalian cells, or bacterial cells. Suitable bacteria include gram negative or gram positive organisms, for example, E. coli or Bacillus spp. Yeast, preferably from the Saccharomyces species, such as S. cerevisiae, may also be used for production of polypeptides. Various mammalian or insect cell culture systems can also be employed to express recombinant proteins. Baculovirus systems for production of heterologous proteins in insect cells are reviewed by Luckow and Summers, (Bio/Technology, 6:47, 1988). In some instance it will be desired to produce proteins in vertebrate cells, such as for glycosylation, and the propagation of vertebrate cells in culture (tissue culture) has become a routine procedure. Examples of suitable mammalian host cell lines include endothelial cells, COS-7 monkey kidney cells, CV-1, L cells, C127, 3T3, Chinese hamster ovary (CHO), human embryonic kidney cells, HeLa, 293, 293T, and BHK cell lines. For many applications, the small size of the protein multimers described herein would make E. coli the preferred method for expression.

Protein Production

Host cells are transformed with the herein-described expression or cloning vectors for protein production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences.

The host cells used to produce the proteins of this invention may be cultured in a variety of media. Commercially available media such as Ham's F10 (Sigma), Minimal Essential Medium ((MEM), Sigma), RPMI-1640 (Sigma), and Dulbecco's Modified Eagle's Medium ((DMEM), Sigma) are suitable for culturing the host cells. In addition, any of the media described in Ham et al., Meth. Enz. 58:44 (1979), Barnes et al., Anal. Biochem.102:255 (1980), U.S. Patent Nos. 4,767,704; 4,657,866; 4,927,762; 4,560,655; or 5,122,469; WO 90/03430; WO 87/00195; or U.S. Patent No. Re. 30,985 may be used as culture media for the host cells. Any of these media may be supplemented as necessary with hormones and/or other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics (such as GENTAMYCIN™ drug), trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

Proteins disclosed herein can also be produced using cell-translation systems. For such purposes, the nucleic acids encoding the proteins must be modified to allow in vitro transcription to produce mRNA and to allow cell-free translation of the mRNA in the particular cell-free system being utilized. Exemplary eukaryotic cell-free translation systems include, for example, mammalian or yeast cell-free translation systems, and exemplary prokaryotic cell-free translation systems include, for example, bacterial cell-free translation systems.

Proteins disclosed herein can also be produced by chemical synthesis (e.g., by the methods described in Solid Phase Peptide Synthesis, 2nd ed., 1984, The Pierce Chemical Co., Rockford, IL). Modifications to the protein can also be produced by chemical synthesis.

The proteins disclosed herein can be purified by isolation/purification methods for proteins generally known in the field of protein chemistry. Non-limiting examples include extraction, recrystallization, salting out (e.g., with ammonium sulfate or sodium sulfate), centrifugation, dialysis, ultrafiltration, adsorption chromatography, ion exchange chromatography, hydrophobic chromatography, normal phase chromatography, reversed-phase chromatography, gel filtration, gel permeation chromatography, affinity chromatography, electrophoresis, countercurrent distribution or any combinations of these. After purification, proteins may be exchanged into different buffers and/or concentrated by any of a variety of methods known to the art, including, but not limited to, filtration and dialysis.

The purified proteins are preferably at least 85% pure, more preferably at least 95% pure, and most preferably at least 98% pure. Regardless of the exact numerical value of the purity, the proteins are sufficiently pure for use as a pharmaceutical product.

Imaging, Diagnostic and Other Applications

The E binders described herein can be detectably labeled and used to contact cells expressing EGFR for imaging or diagnostic applications. The E/I binders described herein can be detectably labeled and used to contact cells expressing EGFR and/or IGFIR for imaging or diagnostic applications. Any method known in the art for conjugating a protein to the detectable moiety may be employed, including those methods described by Hunter, et al., Nature 144:945 (1962); David, et al., Biochemistry 13:1014 (1974); Pain, et al., J. Immunol. Meth. 40:219 (1981); and Nygren, J. Histochem. and Cytochem. 30:407 (1982).

In certain embodiments, the E binders and E/I binders described herein are further attached to a label that is able to be detected (e.g., the label can be a radioisotope, fluorescent compound, enzyme or enzyme co-factor). The label may be a radioactive agent, such as: radioactive heavy metals such as iron chelates,

radioactive chelates of gadolinium or manganese, positron emitters of oxygen, nitrogen, iron, carbon, or gallium, ^{43}K, ^{52}Fe, ^{57}Co, ^{67}Cu, ^{67}Ga, ^{68}Ga, ^{123}I, ^{125}I, ^{131}I, ^{132}I, or ^{99}Tc. An E binder or E/I binder affixed to such a moiety may be used as an imaging agent and is administered in an amount effective for diagnostic use in a mammal such as a human and the localization and accumulation of the imaging agent is then detected. The localization and accumulation of the imaging agent may be detected by radioscintigraphy, nuclear magnetic resonance imaging, computed tomography or positron emission tomography. As will be evident to the skilled artisan, the amount of radioisotope to be administered is dependent upon the radioisotope. Those having ordinary skill in the art can readily formulate the amount of the imaging agent to be administered based upon the specific activity and energy of a given radionuclide used as the active moiety.

E binders and E/I binders also are useful as affinity purification agents. In this process, the proteins are immobilized on a suitable support, such a Sephadex resin or filter paper, using methods well known in the art. The proteins can be employed in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays (Zola, Monoclonal Antibodies: A Manual of Techniques, pp. 147-158 (CRC Press, Inc., 1987)).

E binders are useful in methods for detecting EGFR in a sample. E/I binders also are useful in methods for detecting EGFR and/or IGFIR in a sample. The sample will often by a biological sample, such as a biopsy, and particularly a biopsy of a tumor, a suspected tumor. The sample may be from a human or other mammal. The E binder or E/I binder may be labeled with a labeling moiety, such as a radioactive moiety, a fluorescent moiety, a chromogenic moiety, a chemiluminescent moiety, or a hapten moiety; and may be immobilized on a solid support. Detection may be carried out using any technique known in the art, such as, for example, radiography, immunological assay, fluorescence detection, mass spectroscopy, or surface plasmon resonance.

Therapeutic/in vivo uses

The E binders described herein are also useful in methods for treating conditions which respond to an inhibition of EGFR biological activity. The E/I binders described herein are also useful in methods for treating conditions which

respond to an inhibition of EGFR and/or IGFIR biological activity. EGFR and IGFIR are involved either directly or indirectly in the signal transduction pathways of various cell activities, including proliferation, adhesion and migration, as well as differentiation.

In one aspect, the application provides methods for treating a subject afflicted with a hyperproliferative disorder with a therapeutically effective amount of an E binder or an E/I binder. In particular, E binders and E/I binders are useful for the treatment and/or prophylaxis of tumors and/or tumor metastases. In exemplary embodiments, the E/I binder is an antibody-like protein multimer such as a dimer of an EGFR binding ^{10}Fn3 and an IGFIR binding ^{10}Fn3.

In some embodiments, pharmaceutical compositions comprising E binders or E/I binders are administered to a subject afflicted with a tumor, including but not limited to, a brain tumor, tumor of the urogenital tract, tumor of the lymphatic system, stomach tumor, laryngeal tumor, monocytic leukemia, lung adenocarcinoma, small-cell lung carcinoma, pancreatic cancer, glioblastoma and breast carcinoma; or a cancerous disease, including but not limited to, squamous cell carcinoma, bladder cancer, stomach cancer, liver cancer, kidney cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynecological cancer, thyroid cancer, lymphoma, chronic leukemia and acute leukemia.

An E binder or an E/I binder can be administered alone or in combination with one or more additional therapies such as chemotherapy radiotherapy, immunotherapy, surgical intervention, or any combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described herein. Techniques and dosages for administration vary depending on the type of specific polypeptide and the specific condition being treated but can be readily determined by the skilled artisan.

Additional Agents That May be Used with E/I Binders

One aspect of the application provides combinations of E binder or E/I binders and an additional therapeutic agent, such as a cytotoxic agent. In some embodiments, an E binder or E/I binder is linked to a cytotoxic agent. Such embodiments can be prepared by in vitro or in vivo methods as appropriate. In vitro methods include conjugation chemistry well know in the art, such as conjugation to

cysteine and lysine residues. In order to link a cytotoxic agent to a polypeptide, a linking group or reactive group is used. Suitable linking groups are well known in the art and include disulfide groups, thioether groups, acid labile groups, photolabile groups, peptidase labile groups and esterase labile groups. Cytotoxic agents can also be linked to E binders or E/I binders through an intermediary carrier molecule such as serum albumin

Exemplary cytotoxic agents that may be linked to E binders or E/I binders, include maytansinoids, taxanes, analogs of CC-1065, bacterial toxin, plant toxin, ricin, abrin, a ribonuclease (RNase), DNase I, a protease, Staphylococcal enterotoxin-A, pokeweed antiviral protein, gelonin, diphtherin toxin, Pseudomonas exotoxin, Pseudomonas endotoxin, Ranpimase (Rap), Rap (N69Q), methotrexate, daunorubicin, doxorubicin, vincristine, vinblastine, melphalan, mitomycin C, chlorambucil, and calicheamicin.

In other therapeutic treatments or compositions, E binders or E/I binders are co-administered, or administered sequentially, with one or more additional therapeutic agents. Suitable therapeutic agents include, but are not limited to, cytotoxic or cytostatic agents, such as cancer therapeutic agents.

Cancer therapeutic agents are those agents that seek to kill or limit the growth of cancer cells while having minimal effects on the patient. Thus, such agents may exploit any difference in cancer cell properties (e.g., metabolism, vascularization or cell-surface antigen presentation) from healthy host cells. Therapeutic agents that can be combined with E/I binders for improved anti-cancer efficacy include diverse agents used in oncology practice (Reference: Cancer, Principles & Practice of Oncology, DeVita, V. T., Hellman, S., Rosenberg, S. A., 6th edition, Lippincott-Raven, Philadelphia, 2001), such as doxorubicin, epirubicin, cyclophosphamide, trastuzumab, capecitabine, tamoxifen, toremifene, letrozole, anastrozole, fulvestrant, exemestane, goserelin, oxaliplatin, carboplatin, cisplatin, dexamethasone, antide, bevacizumab, 5-fluorouracil, leucovorin, levamisole, irinotecan, etoposide, topotecan, gemcitabine, vinorelbine, estramustine, mitoxantrone, abarelix, zoledronate, streptozocin, rituximab, idarubicin, busulfan, chlorambucil, fludarabine, imatinib, cytarabine, ibritumomab, tositumomab, interferon alpha-2b, melphalam, bortezomib, altretamine, asparaginase, gefitinib,

erlonitib, anti-EGF receptor antibody (e.g., cetuximab or panitumab), ixabepilone, epothilones or derivatives thereof, platinum agents (such as carboplatin, oxaliplatin, cisplatin), taxanes (such as paclitaxel, docetaxel), and camptothecin.

Therapeutic Formulations and Modes of Administration

The present application provides methods for treating conditions which respond to an inhibition of EGFR and/or IGFIR biological activity. Techniques and dosages for administration vary depending on the type of specific polypeptide and the specific condition being treated but can be readily determined by the skilled artisan. In general, regulatory agencies require that a protein reagent to be used as a therapeutic is formulated so as to have acceptably low levels of pyrogens. Accordingly, therapeutic formulations will generally be distinguished from other formulations in that they are substantially pyrogen free, or at least contain no more than acceptable levels of pyrogen as determined by the appropriate regulatory agency (e.g., FDA).

In some embodiments, the E binders and E/I binders are are pharmaceutically acceptable to a mammal, in particular a human. A "pharmaceutically acceptable" polypeptide refers to a polypeptide that is administered to an animal without significant adverse medical consequences. Examples of pharmaceutically acceptable E binders and E/I binders include ^{10}Fn3 domains that lack the integrin-binding domain (RGD) and ^{10}Fn3 domains that are essentially endotoxin free or have very low endotoxin levels.

Therapeutic compositions may be administered with a pharmaceutically acceptable diluent, carrier, or excipient, in unit dosage form. Administration may be parenteral (e.g., intravenous, subcutaneous), oral, or topical, as non-limiting examples. In addition, any gene therapy technique using nucleic acids encoding E binders or E/I binders, may be employed, such as naked DNA delivery, recombinant genes and vectors, cell-based delivery, including ex vivo manipulation of patients' cells, and the like.

The composition can be in the form of a pill, tablet, capsule, liquid, or sustained release tablet for oral administration; a liquid for intravenous, subcutaneous or parenteral administration; or a gel, lotion, ointment, cream, or a polymer or other sustained release vehicle for local administration.

Methods well known in the art for making formulations are found, for example, in "Remington: The Science and Practice of Pharmacy" (20th ed., ed. A.R. Gennaro AR., 2000, Lippincott Williams & Wilkins, Philadelphia, PA). Formulations for parenteral administration may, for example, contain excipients, sterile water, saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated napthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Nanoparticulate formulations (e.g., biodegradable nanoparticles, solid lipid nanoparticles, liposomes) may be used to control the biodistribution of the compounds. Other potentially useful parenteral delivery systems include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. The concentration of the compound in the formulation varies depending upon a number of factors, including the dosage of the drug to be administered, and the route of administration.

The polypeptide may be optionally administered as a pharmaceutically acceptable salt, such as non-toxic acid addition salts or metal complexes that are commonly used in the pharmaceutical industry. Examples of acid addition salts include organic acids such as acetic, lactic, pamoic, maleic, citric, malic, ascorbic, succinic, benzoic, palmitic, suberic, salicylic, tartaric, methanesulfonic, toluenesulfonic, or trifluoroacetic acids or the like; polymeric acids such as tannic acid, carboxymethyl cellulose, or the like; and inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid phosphoric acid, or the like. Metal complexes include zinc, iron, and the like. In one example, the polypeptide is formulated in the presence of sodium acetate to increase thermal stability.

Formulations for oral use include tablets containing the active ingredient(s) in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents or fillers (e.g., sucrose and sorbitol), lubricating agents, glidants, and anti-adhesives (e.g., magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc).

Formulations for oral use may also be provided as chewable tablets, or as hard gelatin capsules wherein the active ingredient is mixed with an inert solid

diluent, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium.

A therapeutically effective dose refers to a dose that produces the therapeutic effects for which it is administered. The exact dose will depend on the disorder to be treated, and may be ascertained by one skilled in the art using known techniques. In general, the E binder or E/I binder is administered at about 0.01 μg/kg to about 50 mg/kg per day, preferably 0.01 mg/kg to about 30 mg/kg per day, most preferably 0.1 mg/kg to about 20 mg/kg per day. The polypeptide may be given daily (e.g., once, twice, three times, or four times daily) or less frequently (e.g., once every other day, once or twice weekly, or monthly). In addition, as is known in the art, adjustments for age as well as the body weight, general health, sex, diet, time of administration, drug interaction, and the severity of the disease may be necessary, and will be ascertainable with routine experimentation by those skilled in the art.

EXEMPLIFICATION

The invention now being generally described will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention in any way.

Summary of Sequences

Many of the sequences referenced in this application are summarized in the table below. Unless otherwise specified, N-terminal extensions are indicated with a single underline, C-terminal tails are indicated with a double underline, and linker sequences are indicated in bold.

SEQ ID NO:	Description	Sequence
1	WT human ^{10}Fn3 domain	VSDVPRDLEVVAATPTSLLISWDAPAVT VRYYRITYGETGGNSPVQEFTVPGSKST ATISGLKPGVDYTITVYAVTGRGDSPAS SKPISINYRT
2	Variant human ^{10}Fn3 with the integrin binding motif removed (RGD changed to SGE; changes from SEQ ID NO: 1 are	VSDVPRDLEVVAATPTSLLISWDAPAVT VRYYRITYGETGGNSPVQEFTVPGSKST ATISGLKPGVDYTITVYAVTGSGESPASS

SEQ ID NO:	Description	Sequence
	underlined)	KPISINYRT
3	I1 IGF-IR monomer with N-terminal extension (N+8) and no tail	VSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI SINYRT
4	I1 IGF-IR monomer with N-terminal extension (N+10) and Ser tail with His tag	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIDKPSQHHHHHH
5	E2 EGFR monomer with N-terminal extension (N+8) and no tail	VSDVPRDLEVVAATPTSLLISWDSGRGS YQYYRITYGETGGNSPVQEFTVPGPVHT ATISGLKPGVDYTITVYAVTDHKPHAD GPHTYHESPISINYRT
6	E2 EGFR monomer with N-terminal extension (N+10) and Ser tail with his tag	MGVSDVPRDLEVVAATPTSLLISWDSG RGSYQYYRITYGETGGNSPVQEFTVPGP VHTATISGLKPGVDYTITVYAVTDHKPH ADGPHTYHESPISINYRTEIDKPSQHHHH HH
7	E1 EGFR monomer with N-terminal extension (N+8) and no tail	VSDVPRDLEVVAATPTSLLISWVAGAE DYQYYRITYGETGGNSPVQEFTVPHDL VTATISGLKPGVDYTITVYAVTDMMHV EYTEHPISINYRT
8	E1 EGFR monomer with N-terminal extension (N+10) and Ser tail with his tag	MGVSDVPRDLEVVAATPTSLLISWVAG AEDYQYYRITYGETGGNSPVQEFTVPH DLVTATISGLKPGVDYTITVYAVTDMM HVEYTEHPISINYRTEIDKPSQHHHHHH
9	Ser tail	EIDKPSQ
10	Cys tail	EIDKPCQ
11	$(GS)_{10}$ Linker	GSGSGSGSGSGSGSGSGS
12	Fn Based Linker	PSTSTST
13	$(GS)_5$ Linker	GSGSGSGSGS
14	$(GGGGS)_3$ Linker	GGGGS GGGGS GGGGS
15	$(GGGGS)_4$ Linker	GGGGS GGGGS GGGGS GGGGS
16	$(GGGGS)_5$ Linker	GGGGS GGGGS GGGGS GGGGS GGGGS
17	$G_4SG_4SG_3SG$ Linker	GGGGS GGGGS GGGSG
18	Linker	GPGPGPG
19	Linker	GPGPGPGPGPG
20	I1-GS10-E2: I/E tandem having I1 (with N-terminal extension (N+8) and short tail) fused via	VSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI

SEQ ID NO:	Description	Sequence
	GS_{10} linker (GS10 is SEQ ID NO: 11) to E2 (with N-terminal extension (N+8) and no tail)	SINYRTEIDK**GSGSGSGSGSGSGSGSGS GS**VSDVPRDLEVVAATPTSLLISWDSGR GSYQYYRITYGETGGNSPVQEFTVPGPV HTATISGLKPGVDYTITVYAVTDHKPHA DGPHTYHESPISINYRT
21	I1-GS10-E2: I/E tandem having I1 (with N-terminal extension (N+10) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to E2 (with N-terminal extension (N+8) and Ser tail)	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWDS GRGSYQYYRITYGETGGNSPVQEFTVPG PVHTATISGLKPGVDYTITVYAVTDHKP HADGPHTYHESPISINYRTEIDKPSQ
22	I1-GS10-E2: I/E tandem I1 (with N-terminal extension (N+10) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to E2 (with N-terminal extension (N+8) and Ser tail with his tag)	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWDS GRGSYQYYRITYGETGGNSPVQEFTVPG PVHTATISGLKPGVDYTITVYAVTDHKP HADGPHTYHESPISINYRTEIDKPSQHHH HHH
23	E2-GS10-I1: E/I tandem having E2 (with N-terminal extension (N+8) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Ser tail)	VSDVPRDLEVVAATPTSLLISWDSGRGS YQYYRITYGETGGNSPVQEFTVPGPVHT ATISGLKPGVDYTITVYAVTDHKPHAD GPHTYHESPISINYRTEIDK**GSGSGSGSG SGSGSGSGSGS**VSDVPRDLEVVAATPTS LLISWSARLKVARYYRITYGETGGNSPV QEFTVPKNVYTATISGLKPGVDYTITVY AVTRFRDYQPISINYRTEIDKPSQ
24	E2-GS10-I1: E/I tandem having E2 (with N-terminal extension (N+10) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Ser tail)	MGVSDVPRDLEVVAATPTSLLISWDSG RGSYQYYRITYGETGGNSPVQEFTVPGP VHTATISGLKPGVDYTITVYAVTDHKPH ADGPHTYHESPISINYRTEIDK**GSGSGSG SGSGSGSGSGSGS**VSDVPRDLEVVAAT PTSLLISWSARLKVARYYRITYGETGGN SPVQEFTVPKNVYTATISGLKPGVDYTI TVYAVTRFRDYQPISINYRTEIDKPSQ
25	E2-GS10-I1: E/I tandem having E2 (with N-terminal extension (N+10) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Ser tail with his tag)	MGVSDVPRDLEVVAATPTSLLISWDSG RGSYQYYRITYGETGGNSPVQEFTVPGP VHTATISGLKPGVDYTITVYAVTDHKPH ADGPHTYHESPISINYRTEIDK**GSGSGSG SGSGSGSGSGSGS**VSDVPRDLEVVAAT PTSLLISWSARLKVARYYRITYGETGGN SPVQEFTVPKNVYTATISGLKPGVDYTI TVYAVTRFRDYQPISINYRTEIDKPSQHH HHHH

SEQ ID NO:	Description	Sequence
26	I1-GS10-E1: I/E tandem having I1 (with N-terminal extension (N+8) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to E1 (with N-terminal extension (N+8) and no tail)	VSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI SINYRTEIDK**GSGSGSGSGSGSGSGSGS GS**VSDVPRDLEVVAATPTSLLISWVAG AEDYQYYRITYGETGGNSPVQEFTVPH DLVTATISGLKPGVDYTITVYAVTDMM HVEYTEHPISINYRT
27	I1-GS10-E1: I/E tandem having I1 (with N-terminal extension (N+10) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to E1 (with N-terminal extension (N+8) and Ser tail)	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWVA GAEDYQYYRITYGETGGNSPVQEFTVP HDLVTATISGLKPGVDYTITVYAVTDM MHVEYTEHPISINYRTEIDKPSQ
28	I1-GS10-E1: I/E tandem having I1 (with N-terminal extension (N+10) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to E1 (with N-terminal extension (N+8) and Ser tail with his tag)	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWVA GAEDYQYYRITYGETGGNSPVQEFTVP HDLVTATISGLKPGVDYTITVYAVTDM MHVEYTEHPISINYRTEIDKPSQHHHHH H
29	E1-GS10-I1: E/I tandem having E1 (with N-terminal extension (N+8) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and no tail)	VSDVPRDLEVVAATPTSLLISWVAGAE DYQYYRITYGETGGNSPVQEFTVPHDL VTATISGLKPGVDYTITVYAVTDMMHV EYTEHPISINYRTEIDK**GSGSGSGSGSGS GSGSGSGS**VSDVPRDLEVVAATPTSLLI SWSARLKVARYYRITYGETGGNSPVQE FTVPKNVYTATISGLKPGVDYTITVYAV TRFRDYQPISINYRT
30	E1-GS10-I1: E/I tandem having E1 (with N-terminal extension (N+10) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Ser tail)	MGVSDVPRDLEVVAATPTSLLISWVAG AEDYQYYRITYGETGGNSPVQEFTVPH DLVTATISGLKPGVDYTITVYAVTDMM HVEYTEHPISINYRTEIDK**GSGSGSGSGS GSGSGSGSGS**VSDVPRDLEVVAATPTS LLISWSARLKVARYYRITYGETGGNSPV QEFTVPKNVYTATISGLKPGVDYTITVY AVTRFRDYQPISINYRTEIDKPSQ
31	E1-GS10-I1: E/I tandem having E1 (with N-terminal extension (N+10) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Ser tail with	MGVSDVPRDLEVVAATPTSLLISWVAG AEDYQYYRITYGETGGNSPVQEFTVPH DLVTATISGLKPGVDYTITVYAVTDMM HVEYTEHPISINYRTEIDK**GSGSGSGSGS GSGSGSGSGS**VSDVPRDLEVVAATPTS LLISWSARLKVARYYRITYGETGGNSPV

SEQ ID NO:	Description	Sequence
	his tag)	QEFTVPKNVYTATISGLKPGVDYTITVY AVTRFRDYQPISINYRTEIDKPSQHHHH HH
32	^{10}Fn3 scaffold, wherein the BC, DE, and FG loops are represented by $(X)_n$, $(X)_o$, and $(X)_p$, respectively, and n is an integer from 1-20, o is an integer from 1-20, and p is an integer from 1-40	VSDVPRDLEVVAATPTSLLI $(X)_n$YYRITYGETGGNSPVQEFTV$(X)_o$ATI SGLKPGVDYTITVYAV$(X)_p$ISINYRT
33	BC loop sequence from EGFR binder E1	SWVAGAEDYQ
34	BC loop sequence from EGFR binder E1, wherein X is any amino acid and m and n are independently selected from 0 to 5 amino acids	X_mVAGAEDYQX_n
35	DE loop sequence from EGFR binder E1	PHDLVT
36	DE loop sequence from EGFR binder E1, wherein X is any amino acid and o and p are independently selected from 0 to 5 amino acids	X_oHDLVX_p
37	FG loop sequence from EGFR binder E1	TDMMHVEYTEHP
38	FG loop sequence from EGFR binder E1, wherein X is any amino acid and q and r are independently selected from 0 to 5 amino acids	X_qDMMHVEYTEHX_r
39	BC loop sequence from EGFR binder E2	SWDSGRGSYQ
40	BC loop sequence from EGFR binder E2, wherein X is any amino acid and g and h are independently selected from 0 to 5 amino acids	X_gDSGRGSYQX_h
41	DE loop sequence from EGFR binder E2	PGPVHT
42	DE loop sequence from EGFR binder E2, wherein X is any amino acid and i and j are independently selected from 0 to	X_iGPVHX_j

SEQ ID NO:	Description	Sequence
	5 amino acids	
43	FG loop sequence from EGFR binder E2	TDHKPHADGPHTYHESP
44	FG loop sequence from EGFR binder E2, wherein X is any amino acid and k and l are independently selected from 0 to 5 amino acids	X_kDHKPHADGPHTYHEX_l
45	BC loop sequence from IGF-IR binder I1	SWSARLKVAR
46	BC loop sequence from IGF-IR binder I1, wherein X is any amino acid and a and b are independently selected from 0 to 5 amino acids	X_aSARLKVAX_b
47	DE loop sequence from IGF-IR binder I1	PKNVYT
48	DE loop sequence from IGF-IR binder I1, wherein X is any amino acid and c and d are independently selected from 0 to 5 amino acids	X_cKNVYX_d
49	FG loop sequence from IGF-IR binder I1	TRFRDYQP
50	FG loop sequence from IGF-IR binder I1, wherein X is any amino acid and e and f are independently selected from 0 to 5 amino acids	X_eRFRDYQX_f
51	Linker	GPG
52	E3 EGFR monomer with N-terminal extension (N+10), Ser tail and his tag	MGVSDVPRDLEVVAATPTSLLISWLPG KLRYQYYRITYGETGGNSPVQEFTVPH DLRTATISGLKPGVDYTITVYAVTNMM HVEYSEYPISINYRTEIDKPSQHHHHHH
53	E3-GS10-I1: E/I tandem having E3 (with N-terminal extension (N+10) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Cys tail with his tag)	MGVSDVPRDLEVVAATPTSLLISWLPG KLRYQYYRITYGETGGNSPVQEFTVPH DLRTATISGLKPGVDYTITVYAVTNMM HVEYSEYPISINYRTEIDK**GSGSGSGSGS. GSGSGSGSGS**VSDVPRDLEVVAATPTS LLISWSARLKVARYYRITYGETGGNSPV QEFTVPKNVYTATISGLKPGVDYTITVY AVTRFRDYQPISINYRTEIDKPCQHHHH HH
54	I1-GS10-E3: I/E tandem having	MGVSDVPRDLEVVAATPTSLLISWSARL

SEQ ID NO:	Description	Sequence
	I1 with N-terminal extension (N+10) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to E3 (with N-terminal extension (N+8) and Cys tail with his tag)	KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWLP GKLRYQYYRITYGETGGNSPVQEFTVP HDLRTATISGLKPGVDYTITVYAVTNM MHVEYSEYPISINYRTEIDKPCQHHHHH H
55	E1-GS10-I1: E/I tandem having E1 (with N-terminal extension (N+10) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Cys tail with his tag)	MGVSDVPRDLEVVAATPTSLLISWVAG AEDYQYYRITYGETGGNSPVQEFTVPH DLVTATISGLKPGVDYTITVYAVTDMM HVEYTEHPISINYRTEIDK**GSGSGSGSGS GSGSGSGSGS**VSDVPRDLEVVAATPTS LLISWSARLKVARYYRITYGETGGNSPV QEFTVPKNVYTATISGLKPGVDYTITVY AVTRFRDYQPISINYRTEIDKPCQHHHH HH
56	E2-GS10-I1: E/I tandem having E2 (with N-terminal extension (N+10) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Cys tail with his tag)	MGVSDVPRDLEVVAATPTSLLISWDSG RGSYQYYRITYGETGGNSPVQEFTVPGP VHTATISGLKPGVDYTITVYAVTDHKPH ADGPHTYHESPISINYRTEIDK**GSGSGSG SGSGSGSGSGSGS**VSDVPRDLEVVAAT PTSLLISWSARLKVARYYRITYGETGGN SPVQEFTVPKNVYTATISGLKPGVDYTI TVYAVTRFRDYQPISINYRTEIDKPCQH HHHHH
57	I1-GS10-E1: I/E tandem having I1 (with N-terminal extension (N+10) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to E1 (with N-terminal extension (N+8) and Cys tail with his tag)	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWVA GAEDYQYYRITYGETGGNSPVQEFTVP HDLVTATISGLKPGVDYTITVYAVTDM MHVEYTEHPISINYRTEIDKPCQHHHHH H
58	I1-GS10-E2: I/E tandem having I1 (with N-terminal extension (N+10) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to E2 (with N-terminal extension (N+8) and Cys tail with his tag)	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWDS GRGSYQYYRITYGETGGNSPVQEFTVPG PVHTATISGLKPGVDYTITVYAVTDHKP HADGPHTYHESPISINYRTEIDKPCQHH HHHH
59	BC loop sequence from EGFR binder E3	SWLPGKLRYQ

SEQ ID NO:	Description	Sequence
60	BC loop sequence from EGFR binder E3, wherein X is any amino acid and s and t are independently selected from 0 to 5 amino acids	$X_sLPGKLRYQX_t$
61	DE loop sequence from EGFR binder E3	PHDLRT
62	DE loop sequence from EGFR binder E3, wherein X is any amino acid and u and w are independently selected from 0 to 5 amino acids	X_uHDLRX_w
63	FG loop sequence from EGFR binder E3	TNMMHVEYSEYP
64	DE loop sequence from EGFR binder E3, wherein X is any amino acid and y and z are independently selected from 0 to 5 amino acids	$X_yNMMHVEYSEYX_z$
65	I1 IGF-IR monomer core sequence: I1 without N-terminal extension or C-terminal tail	EVVAATPTSLLISWSARLKVARYYRITY GETGGNSPVQEFTVPKNVYTATISGLKP GVDYTITVYAVTRFRDYQPISINYRT
66	E1 EGFR monomer core sequence: E1 without N-terminal extension or C-terminal tail	EVVAATPTSLLISWVAGAEDYQYYRITY GETGGNSPVQEFTVPHDLVTATISGLKP GVDYTITVYAVTDMMHVEYTEHPISIN YRT
67	E2 EGFR monomer core sequence: E2 without N-terminal extension or C-terminal tail	EVVAATPTSLLISWDSGRGSYQYYRITY GETGGNSPVQEFTVPGPVHTATISGLKP GVDYTITVYAVTDHKPHADGPHTYHES PISINYRT
68	E3 EGFR monomer core sequence: SEQ ID NO: 82 without N-terminal extension or C-terminal tail	EVVAATPTSLLISWLPGKLRYQYYRITY GETGGNSPVQEFTVPHDLRTATISGLKP GVDYTITVYAVTNMMHVEYSEYPISINY RT
69	Exemplary N-terminal extension (N+10)	MGVSDVPRDL
70	Exemplary N-terminal extension	GVSDVPRDL
71	Exemplary N-terminal extension (N+8)	VSDVPRDL
72	Exemplary N-terminal extension, wherein X is any amino acid and n is 0, 1 or 2, preferably when n=1, X is Met or Gly and when	$X_nSDVPRDL$

SEQ ID NO:	Description	Sequence
	n=2, X is Met-Gly	
73	Exemplary N-terminal extension, wherein X is any amino acid and n is 0, 1 or 2, preferably when n=1, X is Met or Gly and when n=2, X is Met-Gly	X_nDVPRDL
74	Exemplary N-terminal extension, wherein X is any amino acid and n is 0, 1 or 2, preferably when n=1, X is Met or Gly and when n=2, X is Met-Gly	X_nVPRDL
75	Exemplary N-terminal extension, wherein X is any amino acid and n is 0, 1 or 2, preferably when n=1, X is Met or Gly and when n=2, X is Met-Gly	X_nPRDL
76	Exemplary N-terminal extension, wherein X is any amino acid and n is 0, 1 or 2, preferably when n=1, X is Met or Gly and when n=2, X is Met-Gly	X_nRDL
77	Exemplary N-terminal extension, wherein X is any amino acid and n is 0, 1 or 2, preferably when n=1, X is Met or Gly and when n=2, X is Met-Gly	X_nDL
78	Short tail	EIDK
79	Exemplary C-terminal tail	EIDKP
80	Exemplary C-terminal tail	EIDKPS
81	Exemplary C-terminal tail	EIDKPC
82	E3 EGFR monomer with N-terminal extension (N+8) and no tail	VSDVPRDLEVVAATPTSLLISWLPGKLR YQYYRITYGETGGNSPVQEFTVPHDLRT ATISGLKPGVDYTITVYAVTNMMHVEY SEYPISINYRT
87	E3-GS10-I1: E/I tandem having E3 (with N-terminal extension (N+8) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Cys tail)	VSDVPRDLEVVAATPTSLLISWLPGKLR YQYYRITYGETGGNSPVQEFTVPHDLRT ATISGLKPGVDYTITVYAVTNMMHVEY SEYPISINYRTEIDK**GSGSGSGSGSGSGS GSGSGS**VSDVPRDLEVVAATPTSLLISW SARLKVARYYRITYGETGGNSPVQEFTV PKNVYTATISGLKPGVDYTITVYAVTRF RDYQPISINYRTEIDKPCQ
88	I1-GS10-E3: I/E tandem having	VSDVPRDLEVVAATPTSLLISWSARLKV

SEQ ID NO:	Description	Sequence
	I1 (with N-terminal extension (N+8) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to E3 (with N-terminal extension (N+8) and Cys tail)	ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI SINYRTEIDK**GSGSGSGSGSGSGSGSGS GS**VSDVPRDLEVVAATPTSLLISWLPGK LRYQYYRITYGETGGNSPVQEFTVPHDL RTATISGLKPGVDYTITVYAVTNMMHV EYSEYPISINYRTEIDKPCQ
89	E1-GS10-I1: E/I tandem having E1 (with N-terminal extension (N+8) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Cys tail)	VSDVPRDLEVVAATPTSLLISWVAGAE DYQYYRITYGETGGNSPVQEFTVPHDL VTATISGLKPGVDYTITVYAVTDMMHV EYTEHPISINYRTEIDK**GSGSGSGSGSGS GSGSGSGS**VSDVPRDLEVVAATPTSLLI SWSARLKVARYYRITYGETGGNSPVQE FTVPKNVYTATISGLKPGVDYTITVYAV TRFRDYQPISINYRTEIDKPCQ
90	E2-GS10-I1: E/I tandem having E2 (with N-terminal extension (N+8) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Cys tail)	VSDVPRDLEVVAATPTSLLISWDSGRGS YQYYRITYGETGGNSPVQEFTVPGPVHT ATISGLKPGVDYTITVYAVTDHKPHAD GPHTYHESPISINYRTEIDK**GSGSGSGSG SGSGSGSGSGS**VSDVPRDLEVVAATPTS LLISWSARLKVARYYRITYGETGGNSPV QEFTVPKNVYTATISGLKPGVDYTITVY AVTRFRDYQPISINYRTEIDKPCQ
91	I1-GS10-E1: I/E tandem having I1 (with N-terminal extension (N+8) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to E1 (with N-terminal extension (N+8) and Cys tail)	VSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI SINYRTEIDK**GSGSGSGSGSGSGSGSGS GS**VSDVPRDLEVVAATPTSLLISWVAG AEDYQYYRITYGETGGNSPVQEFTVPH DLVTATISGLKPGVDYTITVYAVTDMM HVEYTEHPISINYRTEIDKPCQ
92	I1-GS10-E2: I/E tandem having I1 (with N-terminal extension (N+8) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to E2 (with N-terminal extension (N+8) and Cys tail)	VSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI SINYRTEIDK**GSGSGSGSGSGSGSGSGS GS**VSDVPRDLEVVAATPTSLLISWDSGR GSYQYYRITYGETGGNSPVQEFTVPGPV HTATISGLKPGVDYTITVYAVTDHKPHA DGPHTYHESPISINYRTEIDKPCQ
93	PA3 Linker	PAPAPA
94	PA6 Linker	PAPAPAPAPAPA
95	PA9 Linker	PAPAPAPAPAPAPAPAPA
96	Modified Ser tail	EGSGS
97	Modified Cys tail	EGSGC

SEQ ID NO:	Description	Sequence
98	E3-$(PA)_n$-I1: E/I tandem having E3 (with N-terminal extension (N+8) and an E tail) fused via $(PA)_n$ linker ($(PA)_n$ is SEQ ID NO: 488) to I1 (with N-terminal extension (N+8) and a modified Ser or Cys tail), wherein n = 3, 6 or 9, and X = Ser or Cys	VSDVPRDLEVVAATPTSLLISWLPGKLR YQYYRITYGETGGNSPVQEFTVPHDLRT ATISGLKPGVDYTITVYAVTNMMHVEY SEYPISINYRTE**(PA)$_n$**VSDVPRDLEVVAA TPTSLLISWSARLKVARYYRITYGETGG NSPVQEFTVPKNVYTATISGLKPGVDYT ITVYAVTRFRDYQPISINYRTEGSGX
99	I1-$(PA)_n$-E3: I/E tandem having I1 (with N-terminal extension (N+8) and an E tail) fused via $(PA)_n$ linker ($(PA)_n$ is SEQ ID NO: 488) to E3 (with N-terminal extension (N+8) and a modified Ser or Cys tail), wherein n = 3, 6 or 9, and X = Ser or Cys	VSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI SINYRTE**(PA)$_n$**VSDVPRDLEVVAATPTSL LISWLPGKLRYQYYRITYGETGGNSPVQ EFTVPHDLRTATISGLKPGVDYTITVYA VTNMMHVEYSEYPISINYRTEGSGX
100	E1-$(PA)_n$-I1: E/I tandem having E1 (with N-terminal extension (N+8) and an E tail) fused via $(PA)_n$ linker ($(PA)_n$ is SEQ ID NO: 488) to I1 (with N-terminal extension (N+8) and a modified Ser or Cys tail), wherein n = 3, 6 or 9, and X = Ser or Cys	VSDVPRDLEVVAATPTSLLISWVAGAE DYQYYRITYGETGGNSPVQEFTVPHDL VTATISGLKPGVDYTITVYAVTDMMHV EYTEHPISINYRTE**(PA)$_n$**VSDVPRDLEVV AATPTSLLISWSARLKVARYYRITYGET GGNSPVQEFTVPKNVYTATISGLKPGVD YTITVYAVTRFRDYQPISINYRTEGSGX
101	E2-$(PA)_n$-I1: E/I tandem having E2 (with N-terminal extension (N+8) and an E tail) fused via $(PA)_n$ linker ($(PA)_n$ is SEQ ID NO: 488) to I1 (with N-terminal extension (N+8) and a modified Ser or Cys tail), wherein n = 3, 6 or 9, and X = Ser or Cys	VSDVPRDLEVVAATPTSLLISWDSGRGS YQYYRITYGETGGNSPVQEFTVPGPVHT ATISGLKPGVDYTITVYAVTDHKPHAD GPHTYHESPISINYRTE**(PA)$_n$**VSDVPRDL EVVAATPTSLLISWSARLKVARYYRITY GETGGNSPVQEFTVPKNVYTATISGLKP GVDYTITVYAVTRFRDYQPISINYRTEG SGX
102	I1-$(PA)_n$-E1: I/E tandem having I1 (with N-terminal extension (N+8) and an E tail) fused via $(PA)_n$ linker ($(PA)_n$ is SEQ ID NO: 488) to E1 (with N-terminal extension (N+8) and a modified Ser or Cys tail), wherein n = 3, 6 or 9, and X = Ser or Cys	VSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI SINYRTE**(PA)$_n$**VSDVPRDLEVVAATPTSL LISWVAGAEDYQYYRITYGETGGNSPV QEFTVPHDLVTATISGLKPGVDYTITVY AVTDMMHVEYTEHPISINYRTEGSGX
103	I1-$(PA)_n$-E2: I/E tandem having I1 (with N-terminal extension (N+8) and an E tail) fused via $(PA)_n$ linker ($(PA)_n$ is SEQ ID NO: 488) to E2 (with N-terminal extension (N+8) and a modified Ser or Cys tail), wherein n = 3, 6	VSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI SINYRTE**(PA)$_n$**VSDVPRDLEVVAATPTSL LISWDSGRGSYQYYRITYGETGGNSPVQ EFTVPGPVHTATISGLKPGVDYTITVYA VTDHKPHADGPHTYHESPISINYRTEGS

SEQ ID NO:	Description	Sequence
	or 9, and X = Ser or Cys	GX
104	E3-GS10-I1: E/I tandem having E3 (with N-terminal extension (N+8) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Ser tail)	VSDVPRDLEVVAATPTSLLISWLPGKLR YQYYRITYGETGGNSPVQEFTVPHDLRT ATISGLKPGVDYTITVYAVTNMMHVEY SEYPISINYRTEIDK**GSGSGSGSGSGSGS GSGSGS**VSDVPRDLEVVAATPTSLLISW SARLKVARYYRITYGETGGNSPVQEFTV PKNVYTATISGLKPGVDYTITVYAVTRF RDYQPISINYRTEIDKPSQ
105	I1-GS10-E3: I/E tandem having I1 with N-terminal extension (N+8) and short tail) fused via GS_{10} linker (GS10 is SEQ ID NO: 11) to E3 (with N-terminal extension (N+8) and Ser tail)	VSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI SINYRTEIDK**GSGSGSGSGSGSGSGS GS**VSDVPRDLEVVAATPTSLLISWLPGK LRYQYYRITYGETGGNSPVQEFTVPHDL RTATISGLKPGVDYTITVYAVTNMMHV EYSEYPISINYRTEIDKPSQ
106	E4 EGFR monomer with N-terminal extension (N+8) and no tail	VSDVPRDLEVVAATPTSLLISWHERDGS RQYYRITYGETGGNSPVQEFTVPGGVRT ATISGLKPGVDYTITVYAVTDYFNPTTH EYIYQTTPISINYRT
107	E4 EGFR monomer with N-terminal extension (N+10) and a Ser with His tag	MGVSDVPRDLEVVAATPTSLLISWHER DGSRQYYRITYGETGGNSPVQEFTVPGG VRTATISGLKPGVDYTITVYAVTDYFNP TTHEYIYQTTPISINYRTEIDKPSQHHHH HH
108	E4 EGFR monomer core sequence: E4 without N-terminal extension or C-terminal tail	EVVAATPTSLLISWHERDGSRQYYRITY GETGGNSPVQEFTVPGGVRTATISGLKP GVDYTITVYAVTDYFNPTTHEYIYQTTP ISINYRT
109	BC loop sequence from EGFR binder E4	SWHERDGSRQ
110	DE loop sequence from EGFR binder E4	PGGVRT
111	FG loop sequence from EGFR binder E4	TDYFNPTTHEYIYQTTP
112	E5 EGFR monomer with N-terminal extension (N+8) and no tail	VSDVPRDLEVVAATPTSLLISWWAPVD RYQYYRITYGETGGNSPVQEFTVPRDV YTATISGLKPGVDYTITVYAVTDYKPHA DGPHTYHESPISINYRT
113	E5 EGFR monomer with N-terminal extension (N+10) and a modified Ser or Cys tail, wherein X = Ser or Cys; may optionally	MGVSDVPRDLEVVAATPTSLLISWWAP VDRYQYYRITYGETGGNSPVQEFTVPR DVYTATISGLKPGVDYTITVYAVTDYKP HADGPHTYHESPISINYRTEIDKPXQ

SEQ ID NO:	Description	Sequence
	comprise a 6X His tag (SEQ ID NO: 487)	
114	E5 EGFR monomer core sequence: E5 without N-terminal extension or C-terminal tail	EVVAATPTSLLISWWAPVDRYQYYRIT YGETGGNSPVQEFTVPRDVYTATISGLK PGVDYTITVYAVTDYKPHADGPHTYHE SPISINYRT
115	BC loop sequence from EGFR binder E5	SWWAPVDRYQ
116	DE loop sequence from EGFR binder E5	PRDVYT
117	FG loop sequence from EGFR binder E5	TDYKPHADGPHTYHESP
118	E4-GS10-I1: E/I tandem having E4 (with N-terminal extension (N+8) and short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and no tail)	VSDVPRDLEVVAATPTSLLISWHERDGS RQYYRITYGETGGNSPVQEFTVPGGVRT ATISGLKPGVDYTITVYAVTDYFNPTTH EYIYQTTPISINYRTEIDK**GSGSGSGSGS GSGSGSGSGS**VSDVPRDLEVVAATPTS LLISWSARLKVARYYRITYGETGGNSPV QEFTVPKNVYTATISGLKPGVDYTITVY AVTRFRDYQPISINYRT
119	E4-GS10-I1: E/I tandem having E4 (with N-terminal extension (N+8) and short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and modified Ser or Cys tail), wherein X = Ser or Cys; may optionally comprise a 6X His tag (SEQ ID NO: 487)	VSDVPRDLEVVAATPTSLLISWHERDGS RQYYRITYGETGGNSPVQEFTVPGGVRT ATISGLKPGVDYTITVYAVTDYFNPTTH EYIYQTTPISINYRTEIDK**GSGSGSGSGS GSGSGSGSGS**VSDVPRDLEVVAATPTS LLISWSARLKVARYYRITYGETGGNSPV QEFTVPKNVYTATISGLKPGVDYTITVY AVTRFRDYQPISINYRTEIDKPXQ
120	E4-GS10-I1: E/I tandem having E4 (with N-terminal extension (N+10) and short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Cys tail) with his tag	MGVSDVPRDLEVVAATPTSLLISWHER DGSRQYYRITYGETGGNSPVQEFTVPGG VRTATISGLKPGVDYTITVYAVTDYFNP TTHEYIYQTTPISINYRTEIDK**GSGSGSG SGSGSGSGSGSGS**VSDVPRDLEVVAAT PTSLLISWSARLKVARYYRITYGETGGN SPVQEFTVPKNVYTATISGLKPGVDYTI TVYAVTRFRDYQPISINYRTEIDKPCQH HHHHH
121	E4-$(PA)_n$-I1: E/I tandem having E4 (with N-terminal extension (N+8) and an E tail) fused via $(PA)_n$ linker ($(PA)_n$ is SEQ ID NO: 488) to I1 (with N-terminal extension (N+8) and modified Ser or Cys tail), wherein n = 3, 6 or 9,	VSDVPRDLEVVAATPTSLLISWHERDGS RQYYRITYGETGGNSPVQEFTVPGGVRT ATISGLKPGVDYTITVYAVTDYFNPTTH EYIYQTTPISINYRTE**(PA)$_n$**VSDVPRDLE VVAATPTSLLISWSARLKVARYYRITYG ETGGNSPVQEFTVPKNVYTATISGLKPG VDYTITVYAVTRFRDYQPISINYRTEIDK

SEQ ID NO:	Description	Sequence
	and X = Ser or Cys; may optionally comprise a 6X His tag (SEQ ID NO: 487)	PCQHHHHHH
122	I1-GS10-E4: I/E tandem having I1 (with N-terminal extension (N+8) and short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E4 (having N-terminal extension (N+8) and no tail)	VSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI SINYRTEIDK**GSGSGSGSGSGSGSGSGS GS**VSDVPRDLEVVAATPTSLLISWHERD GSRQYYRITYGETGGNSPVQEFTVPGGV RTATISGLKPGVDYTITVYAVTDYFNPT THEYIYQTTPISINYRT
123	I1-GS10-E4: I/E tandem having I1 (with N-terminal extension (N+8) and short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E4 (with N-terminal extension (N+8) and modified Ser or Cys tail), wherein X = Ser or Cys; may optionally comprise a 6X His tag (SEQ ID NO: 487)	VSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI SINYRTEIDK**GSGSGSGSGSGSGSGSGS GS**VSDVPRDLEVVAATPTSLLISWHERD GSRQYYRITYGETGGNSPVQEFTVPGGV RTATISGLKPGVDYTITVYAVTDYFNPT THEYIYQTTPISINYRTEIDKPXQ
124	I1-GS10-E4: I/E tandem having I1 (with N-terminal extension (N+10) and short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E4 (with N-terminal extension (N+8) and a Cys tail) with his tag	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWHE RDGSRQYYRITYGETGGNSPVQEFTVPG GVRTATISGLKPGVDYTITVYAVTDYFN PTTHEYIYQTTPISINYRTEIDKPCQHHH HHH
125	I1-$(PA)_n$-E4: I/E tandem having I1 (with N-terminal extension (N+8) and an E tail) fused via $(PA)_n$ linker ($(PA)_n$ is SEQ ID NO: 488) to E4 (with N-terminal extension (N+8) and modified Ser or Cys tail), wherein n = 3, 6 or 9, and X = Ser or Cys; may optionally comprise a 6X His tag (SEQ ID NO: 487)	VSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI SINYRTE**(PA)$_n$**VSDVPRDLEVVAATPTSL LISWHERDGSRQYYRITYGETGGNSPVQ EFTVPGGVRTATISGLKPGVDYTITVYA VTDYFNPTTHEYIYQTTPISINYRTEIDKP XQ
126	E5-GS10-I1: E/I tandem having E5 (with N-terminal extension (N+8) and short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and no tail)	VSDVPRDLEVVAATPTSLLISWWAPVD RYQYYRITYGETGGNSPVQEFTVPRDV YTATISGLKPGVDYTITVYAVTDYKPHA DGPHTYHESPISINYRTEIDK**GSGSGSGS GSGSGSGSGSGS**VSDVPRDLEVVAATP TSLLISWSARLKVARYYRITYGETGGNS PVQEFTVPKNVYTATISGLKPGVDYTIT VYAVTRFRDYQPISINYRT

SEQ ID NO:	Description	Sequence
127	E5-GS10-I1: E/I tandem having E5 (with N-terminal extension (N+8) and short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and modified Ser or Cys tail), wherein X = Ser or Cys; may optionally comprise a 6X His tag (SEQ ID NO: 487)	VSDVPRDLEVVAATPTSLLISWWAPVD RYQYYRITYGETGGNSPVQEFTVPRDV YTATISGLKPGVDYTITVYAVTDYKPHA DGPHTYHESPISINYRTEIDK**GSGSGSGS GSGSGSGSGSGS**VSDVPRDLEVVAATP TSLLISWSARLKVARYYRITYGETGGNS PVQEFTVPKNVYTATISGLKPGVDYTIT VYAVTRFRDYQPISINYRTEIDKPXQ
128	E5-GS10-I1: E/I tandem having E5 (with N-terminal extension (N+10) and short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and a Cys tail), with a His tag	MGVSDVPRDLEVVAATPTSLLISWWAP VDRYQYYRITYGETGGNSPVQEFTVPR DVYTATISGLKPGVDYTITVYAVTDYKP HADGPHTYHESPISINYRTEIDK**GSGSGS GSGSGSGSGSGS**VSDVPRDLEVVAA TPTSLLISWSARLKVARYYRITYGETGG NSPVQEFTVPKNVYTATISGLKPGVDYT ITVYAVTRFRDYQPISINYRTEIDKPCQH HHHHH
129	E5-$(PA)_n$-I1: E/I tandem having E5 (with N-terminal extension (N+8) and an E tail) fused via $(PA)_n$ linker ($(PA)_n$ is SEQ ID NO: 488) to I1 (with N-terminal extension (N+8) and modified Ser or Cys tail), wherein n = 3, 6 or 9, and X = Ser or Cys; may optionally comprise a 6X His tag (SEQ ID NO: 487)	VSDVPRDLEVVAATPTSLLISWWAPVD RYQYYRITYGETGGNSPVQEFTVPRDV YTATISGLKPGVDYTITVYAVTDYKPHA DGPHTYHESPISINYRTE**(PA)$_n$**VSDVPRD LEVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLK PGVDYTITVYAVTRFRDYQPISINYRTEI DKPXQ
130	I1-GS10-E5: I/E tandem having I1 (with N-terminal extension (N+8) and short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E5 (with N-terminal extension (N+8) and no tail)	VSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI SINYRTEIDK**GSGSGSGSGSGSGSGSGS GS**VSDVPRDLEVVAATPTSLLISWWAP VDRYQYYRITYGETGGNSPVQEFTVPR DVYTATISGLKPGVDYTITVYAVTDYKP HADGPHTYHESPISINYRT
131	I1-GS10-E5: I/E tandem having I1 (with N-terminal extension (N+8) and short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E5 (with N-terminal extension (N+8) and modified Ser or Cys tail), wherein X = Ser or Cys; may optionally comprise a 6X His tag (SEQ ID NO: 487)	VSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVY TATISGLKPGVDYTITVYAVTRFRDYQPI SINYRTEIDK**GSGSGSGSGSGSGSGSGS GS**VSDVPRDLEVVAATPTSLLISWWAP VDRYQYYRITYGETGGNSPVQEFTVPR DVYTATISGLKPGVDYTITVYAVTDYKP HADGPHTYHESPISINYRTEIDKPXQ
132	I1-GS10-E5: I/E tandem having I1 (with N-terminal extension	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN

SEQ ID NO:	Description	Sequence
	(N+10) and short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E5 (with N-terminal extension (N+8) and a Cys tail) with a His tag	VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWW APVDRYQYYRITYGETGGNSPVQEFTVP RDVYTATISGLKPGVDYTITVYAVTDY KPHADGPHTYHESPISINYRTEIDKPCQH HHHHH
133	I1-$(PA)_n$-E5: I/E tandem having I1 (with N-terminal extension (N+8) and an E tail) fused via $(PA)_n$ linker ($(PA)_n$ is SEQ ID NO: 488) to E5 (with N-terminal extension (N+8) and modified Ser or Cys tail), wherein n = 3, 6 or 9, and X = Ser or Cys; may optionally comprise a 6X His tag (SEQ ID NO: 487)	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTE**(PA)$_n$**VSDVPRDLEVVAATP TSLLISWWAPVDRYQYYRITYGETGGN SPVQEFTVPRDVYTATISGLKPGVDYTIT VYAVTDYKPHADGPHTYHESPISINYRT EIDKPXQ
134	BC loop sequence from EGFR binder E4, wherein X is any amino acid and g and h are independently selected from 0 to 5 amino acids	X_gHERDGSRQX_h
135	DE loop sequence from EGFR binder E4, wherein X is any amino acid and i and j are independently selected from 0 to 5 amino acids	X_iGGVRX_j
136	FG loop sequence from EGFR binder E4, wherein X is any amino acid and k and l are independently selected from 0 to 5 amino acids	X_kDYFNPTTHEYIYQTTX_l
137	BC loop sequence from EGFR binder E5, wherein X is any amino acid and g and h are independently selected from 0 to 5 amino acids	X_gWAPVDRYQX_h
138	DE loop sequence from EGFR binder E5, wherein X is any amino acid and i and j are independently selected from 0 to 5 amino acids	X_iRDVYX_j
139	FG loop sequence from EGFR binder E5, wherein X is any amino acid and k and l are independently selected from 0 to	X_kDYKPHADGPHTYHESX_l

SEQ ID NO:	Description	Sequence
	5 amino acids	
140	E85 EGFR monomer with N-terminal extension (N+10) and Ser tail with his tag	MGVSDVPRDLEVVAATPTSLLISWTQG STHYQYYRITYGETGGNSPVQEFTVPG MVYTATISGLKPGVDYTITVYAVTDYF DRSTHEYKYRTTPISINYRTEIDKPSQHH HHHH
141	E85 EGFR monomer core: E85 monomer without N-terminal extension or C-terminal tail	EVVAATPTSLLISWTQGSTHYQYYRITY GETGGNSPVQEFTVPGMVYTATISGLKP GVDYTITVYAVTDYFDRSTHEYKYRTT PISINYRT
142	E85 EGFR monomer, wherein X_1 is selected from the group consisting of SEQ ID NOs: 69-77 and X_2 is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81; in exemplary emobidments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10; may optionally comprise a his tag	X_1EVVAATPTSLLISWTQGSTHYQYYRIT YGETGGNSPVQEFTVPGMVYTATISGL KPGVDYTITVYAVTDYFDRSTHEYKYR TTPISINYRTX_2
143	BC loop sequence from EGFR binder E85	SWTQGSTHYQ
144	DE loop sequence from EGFR binder E85	PGMVYT
145	FG loop sequence from EGFR binder E85	TDYFDRSTHEYKYRTTP
146	BC loop sequence from EGFR binder E85, wherein X is any amino acid and g and h are independently selected from 0 to 5 amino acids	X_gTQGSTHYQX_h
147	DE loop sequence from EGFR binder E85, wherein X is any amino acid and i and j are independently selected from 0 to 5 amino acids	X_iGMVYX$_j$
148	FG loop sequence from EGFR binder E85, wherein X is any amino acid and k and l are independently selected from 0 to 5 amino acids	X_kDYFDRSTHEYKYRTTX_l
149	E85-GS10-I1: E/I tandem having E85 (with N-terminal extension (N+10) and a short tail) fused via	MGVSDVPRDLEVVAATPTSLLISWTQG STHYQYYRITYGETGGNSPVQEFTVPG MVYTATISGLKPGVDYTITVYAVTDYF

SEQ ID NO:	Description	Sequence
	GS10 linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Cys tail) with a 6X His tag (SEQ ID NO: 487)	DRSTHEYKYRTTPISINYRTEIDK**GSGSGSGSGSGSGSGSGS**VSDVPRDLEVVAATPTSLLISWSARLKVARYYRITYGETGGNSPVQEFTVPKNVYTATISGLKPGVDYTITVYAVTRFRDYQPISINYRTEIDKPCQHHHHHH
150	E85-GS10-I1 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWTQGSTHYQYYRITYGETGGNSPVQEFTVPGMVYTATISGLKPGVDYTITVYAVTDYFDRSTHEYKYRTTPISINYRTEIDK**GSGSGSGSGSGSGSGSGSGS**VSDVPRDLEVVAATPTSLLISWSARLKVARYYRITYGETGGNSPVQEFTVPKNVYTATISGLKPGVDYTITVYAVTRFRDYQPISINYRTX_2
151	E85-$(PA)_n$-I1 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWTQGSTHYQYYRITYGETGGNSPVQEFTVPGMVYTATISGLKPGVDYTITVYAVTDYFDRSTHEYKYRTTPISINYRTE**(PA)$_n$**VSDVPRDLEVVAATPTSLLISWSARLKVARYYRITYGETGGNSPVQEFTVPKNVYTATISGLKPGVDYTITVYAVTRFRDYQPISINYRTX_2
152	I1-GS10-E85: I/E tandem having I1 (with N-terminal extension (N+10) and a short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E85 (with N-terminal extension (N+8) and Cys tail) with a 6X His tag (SEQ ID NO: 487)	MGVSDVPRDLEVVAATPTSLLISWSARLKVARYYRITYGETGGNSPVQEFTVPKNVYTATISGLKPGVDYTITVYAVTRFRDYQPISINYRTEIDK**GSGSGSGSGSGSGSGS**VSDVPRDLEVVAATPTSLLISWTQGSTHYQYYRITYGETGGNSPVQEFTVPGMVYTATISGLKPGVDYTITVYAVTDYFDRSTHEYKYRTTPISINYRTEIDKPCQHHHHHH
153	I1-GS10-E85 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is	X_1EVVAATPTSLLISWSARLKVARYYRITYGETGGNSPVQEFTVPKNVYTATISGLKPGVDYTITVYAVTRFRDYQPISINYRTEIDK**GSGSGSGSGSGSGSGSGSGS**VSDVPRDLEVVAATPTSLLISWTQGSTHYQYYRITYGETGGNSPVQEFTVPGMVYTATISGLKPGVDYTITVYAVTDYFDRSTHEYKYRTTPISINYRTX_2

SEQ ID NO:	Description	Sequence
	SEQ ID NO: 9 or 10	
154	I1-$(PA)_n$-E85 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLK PGVDYTITVYAVTRFRDYQPISINYRTE(**PA)$_n$**VSDVPRDLEVVAATPTSLLISWTQG STHYQYYRITYGETGGNSPVQEFTVPG MVYTATISGLKPGVDYTITVYAVTDYF DRSTHEYKYRTTPISINYRTX_2
155	E90 EGFR monomer with N-terminal extension (N+10) and Ser tail with his tag	MGVSDVPRDLEVVAATPTSLLISWYWE GLPYQYYRITYGETGGNSPVQEFTVPRD VNTATISGLKPGVDYTITVYAVTDWYN PDTHEYIYHTIPISINYRTEIDKPSQHHHH HH
156	E90 EGFR monomer core: E90 monomer without N-terminal extension or C-terminal tail	EVVAATPTSLLISWYWEGLPYQYYRITY GETGGNSPVQEFTVPRDVNTATISGLKP GVDYTITVYAVTDWYNPDTHEYIYHTIP ISINYRT
157	E90 EGFR monomer, wherein X_1 is selected from the group consisting of SEQ ID NOs: 69-77 and X_2 is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81; in exemplary emobidments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10; may optionally comprise a his tag	X_1EVVAATPTSLLISWYWEGLPYQYYRI TYGETGGNSPVQEFTVPRDVNTATISGL KPGVDYTITVYAVTDWYNPDTHEYIYH TIPISINYRTX_2
158	BC loop sequence from EGFR binder E90	SWYWEGLPYQ
159	DE loop sequence from EGFR binder E90	PRDVNT
160	FG loop sequence from EGFR binder E90	TDWYNPDTHEYIYHTIP
161	BC loop sequence from EGFR binder E90, wherein X is any amino acid and g and h are independently selected from 0 to 5 amino acids	X_gYWEGLPYQX_h
162	DE loop sequence from EGFR binder E90, wherein X is any amino acid and i and j are	X_iRDVNX_j

SEQ ID NO:	Description	Sequence
	independently selected from 0 to 5 amino acids	
163	FG loop sequence from EGFR binder E90, wherein X is any amino acid and k and l are independently selected from 0 to 5 amino acids	X_kDWYNPDTHEYIYHTIX_l
164	E90-GS10-I1: E/I tandem having E90 (with N-terminal extension (N+10) and a short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Cys tail) with a 6X His tag (SEQ ID NO: 487)	MGVSDVPRDLEVVAATPTSLLISWYWE GLPYQYYRITYGETGGNSPVQEFTVPRD VNTATISGLKPGVDYTITVYAVTDWYN PDTHEYIYHTIPISINYRTEIDK**GSGSGSG SGSGSGSGSGSGS**VSDVPRDLEVVAAT PTSLLISWSARLKVARYYRITYGETGGN SPVQEFTVPKNVYTATISGLKPGVDYTI TVYAVTRFRDYQPISINYRTEIDKPCQH HHHHH
165	E90-GS10-I1 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWYWEGLPYQYYRI TYGETGGNSPVQEFTVPRDVNTATISGL KPGVDYTITVYAVTDWYNPDTHEYIYH TIPISINYRTEIDK**GSGSGSGSGSGSGSG SGSGS**VSDVPRDLEVVAATPTSLLISWS ARLKVARYYRITYGETGGNSPVQEFTVP KNVYTATISGLKPGVDYTITVYAVTRFR DYQPISINYRTX_2
166	E90-$(PA)_n$-I1 core, wherein X1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWYWEGLPYQYYRI TYGETGGNSPVQEFTVPRDVNTATISGL KPGVDYTITVYAVTDWYNPDTHEYIYH TIPISINYRTE**(PA)$_n$**VSDVPRDLEVVAATP TSLLISWSARLKVARYYRITYGETGGNS PVQEFTVPKNVYTATISGLKPGVDYTIT VYAVTRFRDYQPISINYRTX_2
167	I1-GS10-E90: I/E tandem having I1 (with N-terminal extension (N+10) and a short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E90 (with N-terminal extension (N+8) and Cys tail) with a 6X His tag (SEQ ID NO: 487)	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWY WEGLPYQYYRITYGETGGNSPVQEFTV PRDVNTATISGLKPGVDYTITVYAVTD WYNPDTHEYIYHTIPISINYRTEIDKPCQ HHHHHH

SEQ ID NO:	Description	Sequence
168	I1-GS10-E90 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLK PGVDYTITVYAVTRFRDYQPISINYRTEI DK**GSGSGSGSGSGSGSGSGSGS**VSDVP RDLEVVAATPTSLLISWYWEGLPYQYY RITYGETGGNSPVQEFTVPRDVNTATIS GLKPGVDYTITVYAVTDWYNPDTHEYI YHTIPISINYRTX_2
169	I1-$(PA)_n$-E90 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLK PGVDYTITVYAVTRFRDYQPISINYRTE(**PA)$_n$**VSDVPRDLEVVAATPTSLLISWYW EGLPYQYYRITYGETGGNSPVQEFTVPR DVNTATISGLKPGVDYTITVYAVTDWY NPDTHEYIYHTIPISINYRTX_2
170	E96 EGFR monomer with N-terminal extension (N+10) and Ser tail with his tag	MGVSDVPRDLEVVAATPTSLLISWASN RGTYQYYRITYGETGGNSPVQEFTVPG GVSTATISGLKPGVDYTITVYAVTDAFN PTTHEYNYFTTPISINYRTEIDKPSQHHH HHH
171	E96 EGFR monomer core: E96 monomer without N-terminal extension or C-terminal tail	EVVAATPTSLLISWASNRGTYQYYRITY GETGGNSPVQEFTVPGGVSTATISGLKP GVDYTITVYAVTDAFNPTTHEYNYFTTP ISINYRT
172	E96 EGFR monomer, wherein X_1 is selected from the group consisting of SEQ ID NOs: 69-77 and X_2 is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81; in exemplary emobidments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10; may optionally comprise a his tag	X_1EVVAATPTSLLISWASNRGTYQYYRI TYGETGGNSPVQEFTVPGGVSTATISGL KPGVDYTITVYAVTDAFNPTTHEYNYF TTPISINYRTX_2
173	BC loop sequence from EGFR binder E96	SWASNRGTYQ
174	DE loop sequence from EGFR binder E96	PGGVST

SEQ ID NO:	Description	Sequence
175	FG loop sequence from EGFR binder E96	TDAFNPTTHEYNYFTTP
176	BC loop sequence from EGFR binder E96, wherein X is any amino acid and g and h are independently selected from 0 to 5 amino acids	X_gASNRGTYQX_h
177	DE loop sequence from EGFR binder E96, wherein X is any amino acid and i and j are independently selected from 0 to 5 amino acids	X_iGGVSX_j
178	FG loop sequence from EGFR binder E96, wherein X is any amino acid and k and l are independently selected from 0 to 5 amino acids	X_kDAFNPTTHEYNYFTTX_l
179	E96-GS10-I1: E/I tandem having E96 (with N-terminal extension (N+10) and a short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Cys tail) with a 6X His tag (SEQ ID NO: 487)	MGVSDVPRDLEVVAATPTSLLISWASN RGTYQYYRITYGETGGNSPVQEFTVPG GVSTATISGLKPGVDYTITVYAVTDAFN PTTHEYNYFTTPISINYRTEIDK**GSGSGS GSGSGSGSGSGSGS**VSDVPRDLEVVAA TPTSLLISWSARLKVARYYRITYGETGG NSPVQEFTVPKNVYTATISGLKPGVDYT ITVYAVTRFRDYQPISINYRTEIDKPCQH HHHHH
180	E96-GS10-I1 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWASNRGTYQYYRI TYGETGGNSPVQEFTVPGGVSTATISGL KPGVDYTITVYAVTDAFNPTTHEYNYF TTPISINYRTEIDK**GSGSGSGSGSGSGSG SGSGS**VSDVPRDLEVVAATPTSLLISWS ARLKVARYYRITYGETGGNSPVQEFTVP KNVYTATISGLKPGVDYTITVYAVTRFR DYQPISINYRTX_2
181	E96-$(PA)_n$-I1 core, wherein X1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is	X_1EVVAATPTSLLISWASNRGTYQYYRI TYGETGGNSPVQEFTVPGGVSTATISGL KPGVDYTITVYAVTDAFNPTTHEYNYF TTPISINYRTE**(PA)$_n$**VSDVPRDLEVVAAT PTSLLISWSARLKVARYYRITYGETGGN SPVQEFTVPKNVYTATISGLKPGVDYTI TVYAVTRFRDYQPISINYRTX_2

SEQ ID NO:	Description	Sequence
	SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	
182	I1-GS10-E96: I/E tandem having I1 (with N-terminal extension (N+10) and a short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E96 (with N-terminal extension (N+8) and Cys tail) with a 6X His tag (SEQ ID NO: 487)	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWAS NRGTYQYYRITYGETGGNSPVQEFTVP GGVSTATISGLKPGVDYTITVYAVTDAF NPTTHEYNYFTTPISINYRTEIDKPCQHH HHHH
183	I1-GS10-E96 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLK PGVDYTITVYAVTRFRDYQPISINYRTEI DK**GSGSGSGSGSGSGSGSGS**VSDVP RDLEVVAATPTSLLISWASNRGTYQYY RITYGETGGNSPVQEFTVPGGVSTATISG LKPGVDYTITVYAVTDAFNPTTHEYNY FTTPISINYRTX_2
184	I1-$(PA)_n$-E96 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLK PGVDYTITVYAVTRFRDYQPISINYRTE**(PA)$_n$**VSDVPRDLEVVAATPTSLLISWASN RGTYQYYRITYGETGGNSPVQEFTVPG GVSTATISGLKPGVDYTITVYAVTDAFN PTTHEYNYFTTPISINYRTX_2
185	E105 EGFR monomer with N-terminal extension (N+10) and Ser tail with his tag	MGVSDVPRDLEVVAATPTSLLISWDAP TSRYQYYRITYGETGGNSPVQEFTVPGG LSTATISGLKPGVDYTITVYAVTDYKPH ADGPHTYHESPISINYRTEIDKPSQHHHH HH
186	E105 EGFR monomer core: E105 monomer without N-terminal extension or C-terminal tail	EVVAATPTSLLISWDAPTSRYQYYRITY GETGGNSPVQEFTVPGGLSTATISGLKP GVDYTITVYAVTDYKPHADGPHTYHES PISINYRT
187	E105 EGFR monomer, wherein X_1 is selected from the group consisting of SEQ ID NOs: 69-77 and X_2 is selected from the group	X_1EVVAATPTSLLISWDAPTSRYQYYRIT YGETGGNSPVQEFTVPGGLSTATISGLK PGVDYTITVYAVTDYKPHADGPHTYHE SPISINYRTX_2

SEQ ID NO:	Description	Sequence
	consisting of SEQ ID NOs: 9, 10, or 78-81; in exemplary emobidments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10; may optionally comprise a his tag	
188	BC loop sequence from EGFR binder E105	SWDAPTSRYQ
189	DE loop sequence from EGFR binder E105	PGGLST
117	FG loop sequence from EGFR binder E105	TDYKPHADGPHTYHESP
190	BC loop sequence from EGFR binder E105, wherein X is any amino acid and g and h are independently selected from 0 to 5 amino acids	X_gDAPTSRYQX_h
191	DE loop sequence from EGFR binder E105, wherein X is any amino acid and i and j are independently selected from 0 to 5 amino acids	X_iGGLSX_j
139	FG loop sequence from EGFR binder E105, wherein X is any amino acid and k and l are independently selected from 0 to 5 amino acids	X_kDYKPHADGPHTYHESX_l
192	E105-GS10-I1: E/I tandem having E105 (with N-terminal extension (N+10) and a short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Cys tail) with a 6X His tag (SEQ ID NO: 487)	MGVSDVPRDLEVVAATPTSLLISWDAP TSRYQYYRITYGETGGNSPVQEFTVPGG LSTATISGLKPGVDYTITVYAVTDYKPH ADGPHTYHESPISINYRTEIDK**GSGSGSG SGSGSGSGSGSGS**VSDVPRDLEVVAAT PTSLLISWSARLKVARYYRITYGETGGN SPVQEFTVPKNVYTATISGLKPGVDYTI TVYAVTRFRDYQPISINYRTEIDKPCQH HHHHH
193	E105-GS10-I1 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is	X_1EVVAATPTSLLISWDAPTSRYQYYRIT YGETGGNSPVQEFTVPGGLSTATISGLK PGVDYTITVYAVTDYKPHADGPHTYHE SPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWSA RLKVARYYRITYGETGGNSPVQEFTVPK NVYTATISGLKPGVDYTITVYAVTRFRD YQPISINYRTX_2

SEQ ID NO:	Description	Sequence
	SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	
194	E105-$(PA)_n$-I1 core, wherein X1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWDAPTSRYQYYRIT YGETGGNSPVQEFTVPGGLSTATISGLK PGVDYTITVYAVTDYKPHADGPHTYHE SPISINYRTE**(PA)$_n$**VSDVPRDLEVVAATP TSLLISWSARLKVARYYRITYGETGGNS PVQEFTVPKNVYTATISGLKPGVDYTIT VYAVTRFRDYQPISINYRTX_2
195	I1-GS10-E105: I/E tandem havingI1 (with N-terminal extension (N+10) and a short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E105 (with N-terminal extension (N+8) and Cys tail) with a 6X His tag (SEQ ID NO: 487)	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWDA PTSRYQYYRITYGETGGNSPVQEFTVPG GLSTATISGLKPGVDYTITVYAVTDYKP HADGPHTYHESPISINYRTEIDKPCQHH HHHH
196	I1-GS10-E105 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLK PGVDYTITVYAVTRFRDYQPISINYRTEI DK**GSGSGSGSGSGSGSGSGS**VSDVP RDLEVVAATPTSLLISWDAPTSRYQYYR ITYGETGGNSPVQEFTVPGGLSTATISGL KPGVDYTITVYAVTDYKPHADGPHTYH ESPISINYRTX_2
197	I1-$(PA)_n$-E105 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLK PGVDYTITVYAVTRFRDYQPISINYRTE(**PA)$_n$**VSDVPRDLEVVAATPTSLLISWDAP TSRYQYYRITYGETGGNSPVQEFTVPGG LSTATISGLKPGVDYTITVYAVTDYKPH ADGPHTYHESPISINYRTX_2
198	E112 EGFR monomer with N-terminal extension (N+10) and Ser tail with his tag	MGVSDVPRDLEVVAATPTSLLISWDAG AVTYQYYRITYGETGGNSPVQEFTVPG GVRTATISGLKPGVDYTITVYAVTDYKP

SEQ ID NO:	Description	Sequence
		HADGPHTYHEYPISINYRTEIDKPSQHH HHHH
199	E112 EGFR monomer core: E112 monomer without N-terminal extension or C-terminal tail	EVVAATPTSLLISWDAGAVTYQYYRITY GETGGNSPVQEFTVPGGVRTATISGLKP GVDYTITVYAVTDYKPHADGPHTYHEY PISINYRT
200	E112 EGFR monomer, wherein X_1 is selected from the group consisting of SEQ ID NOs: 69-77 and X_2 is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81; in exemplary emobidments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10; may optionally comprise a his tag	X_1EVVAATPTSLLISWDAGAVTYQYYRI TYGETGGNSPVQEFTVPGGVRTATISGL KPGVDYTITVYAVTDYKPHADGPHTYH EYPISINYRTX_2
201	BC loop sequence from EGFR binder E112	SWDAGAVTYQ
110	DE loop sequence from EGFR binder E112	PGGVRT
202	FG loop sequence from EGFR binder E112	TDYKPHADGPHTYHEYP
203	BC loop sequence from EGFR binder E112, wherein X is any amino acid and g and h are independently selected from 0 to 5 amino acids	X_gDAGAVTYQX_h
135	DE loop sequence from EGFR binder E112, wherein X is any amino acid and i and j are independently selected from 0 to 5 amino acids	X_iGGVRX_j
204	FG loop sequence from EGFR binder E112, wherein X is any amino acid and k and l are independently selected from 0 to 5 amino acids	X_kDYKPHADGPHTYHEYX_l
205	E112-GS10-I1: E/I tandem having E112 (with N-terminal extension (N+10) and a short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to I1 (with N-terminal extension (N+8) and Cys tail) with a 6X His tag (SEQ ID	MGVSDVPRDLEVVAATPTSLLISWDAG AVTYQYYRITYGETGGNSPVQEFTVPG GVRTATISGLKPGVDYTITVYAVTDYKP HADGPHTYHEYPISINYRTEIDK**GSGSG SGSGSGSGSGSGSGS**VSDVPRDLEVVA ATPTSLLISWSARLKVARYYRITYGETG GNSPVQEFTVPKNVYTATISGLKPGVDY TITVYAVTRFRDYQPISINYRTEIDKPCQ

SEQ ID NO:	Description	Sequence
	NO: 487)	HHHHHH
206	E112-GS10-I1 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWDAGAVTYQYYRI TYGETGGNSPVQEFTVPGGVRTATISGL KPGVDYTITVYAVTDYKPHADGPHTYH EYPISINYRTEIDK**GSGSGSGSGSGSGSG SGSGS**VSDVPRDLEVVAATPTSLLISWS ARLKVARYYRITYGETGGNSPVQEFTVP KNVYTATISGLKPGVDYTITVYAVTRFR DYQPISINYRTX_2
207	E112-$(PA)_n$-I1 core, wherein X1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWDAGAVTYQYYRI TYGETGGNSPVQEFTVPGGVRTATISGL KPGVDYTITVYAVTDYKPHADGPHTYH EYPISINYRTE**(PA)$_n$**VSDVPRDLEVVAAT PTSLLISWSARLKVARYYRITYGETGGN SPVQEFTVPKNVYTATISGLKPGVDYTI TVYAVTRFRDYQPISINYRTX_2
208	I1-GS10-E112: I/E tandem having I1 (with N-terminal extension (N+10) and a short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E112 (with N-terminal extension (N+8) and Cys tail) with a 6X His tag (SEQ ID NO: 487)	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWDA GAVTYQYYRITYGETGGNSPVQEFTVP GGVRTATISGLKPGVDYTITVYAVTDY KPHADGPHTYHEYPISINYRTEIDKPCQ HHHHHH
209	I1-GS10-E112 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLK PGVDYTITVYAVTRFRDYQPISINYRTEI DK**GSGSGSGSGSGSGSGSGS**VSDVP RDLEVVAATPTSLLISWDAGAVTYQYY RITYGETGGNSPVQEFTVPGGVRTATIS GLKPGVDYTITVYAVTDYKPHADGPHT YHEYPISINYRTX_2
210	I1-$(PA)_n$-E112 core, wherein X_1 is optional and when present is selected from the group consisting of SEQ ID NOs: 69-	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLK PGVDYTITVYAVTRFRDYQPISINYRTE(**PA)$_n$**VSDVPRDLEVVAATPTSLLISWDAG

SEQ ID NO:	Description	Sequence
	77, X_2 is optional and when present is selected from the group consisting of SEQ ID NOs: 9, 10, or 78-81, and n = 3, 6 or 9; in exemplary embodiments, X_1 is SEQ ID NO: 69 or 71 and X_2 is SEQ ID NO: 9 or 10	AVTYQYYRITYGETGGNSPVQEFTVPG GVRTATISGLKPGVDYTITVYAVTDYKP HADGPHTYHEYPISINYRTX2
211	I1-GSGCGS8-E5: I/E tandem having I1 (with N-terminal extension (N+10) and a modified short tail) fused via GSGCGS8 linker (GSGCGS8 is SEQ ID NO: 218) to E5 (with N-terminal extension (N+8) and an E tail) with an optional 6X His tag (SEQ ID NO: 487)	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIEK**GSGCGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWW APVDRYQYYRITYGETGGNSPVQEFTVP RDVYTATISGLKPGVDYTITVYAVTDY KPHADGPHTYHESPISINYRTEHHHHHH
212	I1-GS10-E5-GSGC: I/E tandem having I1 (with N-terminal extension (N+10) and a modified short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E5 (with N-terminal extension (N+8) and a modified Cys tail) with an optional 6X His tag (SEQ ID NO: 487)	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIEK**GSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWW APVDRYQYYRITYGETGGNSPVQEFTVP RDVYTATISGLKPGVDYTITVYAVTDY KPHADGPHTYHESPISINYRTEGSGCHH HHHH
213	I1(S62C)-GS10-E5: I/E tandem having I1 (with N-terminal extension (N+10), an S62C substitution (boxed), and a modified short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E5 (with N-terminal extension (N+8) and an E tail) with an optional 6X His tag (SEQ ID NO: 487); position 62 refers to the amino acid corresponding to position 62 of SEQ ID NO:1	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATICGLKPGVDYTITVYAVTRFRDY QPISINYRTEIEK**GSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWW APVDRYQYYRITYGETGGNSPVQEFTVP RDVYTATISGLKPGVDYTITVYAVTDY KPHADGPHTYHESPISINYRTEHHHHHH
214	I1-GS10-E5(S62C): I/E tandem having I1 (with N-terminal extension (N+10) and a modified short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E5 (with N-terminal extension (N+8), an S62C substitution (boxed), and an E tail) with an optional 6X His tag (SEQ ID NO: 487); position 62 refers to the	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIEK**GSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWW APVDRYQYYRITYGETGGNSPVQEFTVP RDVYTATICGLKPGVDYTITVYAVTDY KPHADGPHTYHESPISINYRTEHHHHHH

SEQ ID NO:	Description	Sequence
	amino acid corresponding to position 62 of SEQ ID NO:1	
215	I1(S91C)-GS10-E5: I/E tandem having I1 (with N-terminal extension (N+10), an S91C substitution (boxed), and a modified short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E5 (with N-terminal extension (N+8) and an E tail) with an optional 6X His tag (SEQ ID NO: 487); position 91 refers to the amino acid corresponding to position 91 of SEQ ID NO:1	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPI[C]INYRTEIEK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWW APVDRYQYYRITYGETGGNSPVQEFTVP RDVYTATISGLKPGVDYTITVYAVTDY KPHADGPHTYHESPISINYRTEHHHHHH
216	I1-GS10-E5(S91C): I/E tandem having I1 (with N-terminal extension (N+10) and a modified short tail) fused via GS10 linker (GS10 is SEQ ID NO: 11) to E5 (with N-terminal extension (N+8), an S91C substitution (boxed), and an E tail) with an optional 6X His tag (SEQ ID NO: 487); position 91 refers to the amino acid corresponding to position 91 of SEQ ID NO:1	MGVSDVPRDLEVVAATPTSLLISWSARL KVARYYRITYGETGGNSPVQEFTVPKN VYTATISGLKPGVDYTITVYAVTRFRDY QPISINYRTEIEK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWW APVDRYQYYRITYGETGGNSPVQEFTVP RDVYTATISGLKPGVDYTITVYAVTDY KPHADGPHTYHESPI[C]INYRTEHHHHHH
217	Modified short tail	EIEK
218	GSGCGS8 Linker	GSGCGSGSGSGSGSGSGS

Example 1: In Cell Western Assay to Screen for EGFR Activity

In Cell Western assays were developed to screen various single ^{10}Fn3 clones for the ability to inhibit EGFR activity in order to identify those that could be linked with IGF1R ^{10}Fn3 binders to construct E/I binders. In Cell Western assays were also used to screen and determine relative potency of specific E/I ^{10}Fn3 binders. Two In Cell Western assays were developed to measure 1) inhibition of EGF-stimulated EGFR phosphorylation or 2) inhibition of EGF-stimulated ERK phosphorylation. Cells were seeded into poly-D-lysine coated 96-well microtiter plates (Becton Dickinson, Franklin Lakes, NJ) at 24,000 cells/well for A431 epidermoid carcinoma or FaDu head & neck carcinoma cells and allowed to adhere overnight. Cells were washed once and then incubated for 24 hours in serum free

media. Serial dilutions of the ^{10}Fn3-based binders were next applied to the cells and incubated for 2-3 hours prior to stimulation with 100 ng/ml EGF for 10 minutes. Following stimulation, cells were fixed for 20 minutes in PBS containing 3.7% formaldehyde and then permeabilized in PBS containing 0.1% triton-X-100 for 15 minutes. Cells were blocked for one hour in Odyssey blocker (Li-Cor Biosciences, Lincoln, Nebraska) and incubated with antibodies to detect either EGFR phosphorylated on tyrosine 1068 (Cell Signaling, Beverly, MA) and β-actin (Sigma, St. Louis, MO) or pERK (MAP kinase phosphorylated on tyrosine 202/threonine 204) and total ERK (Santa Cruz Biotechnology, Santa Cruz, CA). After washing three times in PBS containing 0.1% tween-20, secondary antibodies were added (Invitrogen, Carlsbad, CA or Rockland, Gilbertsville, PA). Cells were washed three times in PBS containing 0.1% tween-20 and imaged on a Li-Cor Odyssey Infrared Imaging System (Li-Cor Biosciences, Lincoln, Nebraska). Each clone was assayed in duplicate or triplicate and values were normalized to β-actin for the pEGFR assay and total ERK for the pERK assay. IC50 values were calculated from linear regression analysis of percent inhibition of maximum signal minus background.

Results yielded various ^{10}Fn3 clones that had ability to inhibit activity of EGFR, and showed that certain specific E/I ^{10}Fn3 binders possessed similar activity to the example shown in Figure 9.

Example 2: Expression of ^{10}Fn3-based binders

E/I binders were produced by covalently linking an EGFR-binding ^{10}Fn3 to an IGFIR-binding ^{10}Fn3 using a glycine-serine linker, thereby generating ^{10}Fn3 dimers, wherein each ^{10}Fn3 domain binds to a different target. The IGFIR-binding ^{10}Fn3 (I1) was previously described as SEQ ID NO: 226 in PCT Publication No. WO 2008/066752. Two novel EGFR-binding ^{10}Fn3 (E2 and E1) were identified by screening an RNA-protein fusion library, as described in PCT Publication No. WO 2008/066752, for binders to EGFR-Fc (R&D Systems, Minneapolis, MN). The following examples describe results using a variety of His-tagged E/I ^{10}Fn3-based binders (non-pegylated): E2-GS10-I1 (SEQ ID NO: 25), E1-GS10-I1 (SEQ ID NO: 31), I1-GS10-E1 (SEQ ID NO: 28), and I1-GS10-E2 (SEQ ID NO: 22).

The following examples also describe results with the following pegylated, His-tagged E/I ^{10}Fn3-based binders: E1-GS10-I1 (SEQ ID NO: 55), E2-GS10-I1 (SEQ ID NO: 56), E3-GS10-I1 (SEQ ID NO: 53), I1-GS10-E1 (SEQ ID NO: 57), I1-GS10-E2 (SEQ ID NO: 58), I1-GS10-E3 (SEQ ID NO: 54), E4-GS10-I1 (SEQ ID NO: 120), I1-GS10-E4 (SEQ ID NO: 124), E5-GS10-I1 (SEQ ID NO: 128), I1-GS10-E5 (SEQ ID NO: 132), E85-GS10-I1 (SEQ ID NO: 149), I1-GS10-E85 (SEQ ID NO: 152), E90-GS10-I1 (SEQ ID NO: 164), E96-GS10-I1 (SEQ ID NO: 179), E105-GS10-I1 (SEQ ID NO: 192), I1-GS10-E105 (SEQ ID NO: 195), E112-GS10-I1 (SEQ ID NO: 205), I1-GS10-E112 (SEQ ID NO: 208), I1-GSGCGS8-E5 (SEQ ID NO: 211), I1-GS10-E5-GSGC (SEQ ID NO: 212), I1(S62C)-GS10-E5 (SEQ ID NO: 213), I1-GS10-E5(S62C) (SEQ ID NO: 214), I1(S91C)-GS10-E5 (SEQ ID NO: 215), and I1-GS10-E5(S91C) (SEQ ID NO: 216).

The examples also describe results using a His-tagged IGFRIR ^{10}Fn3-based binder, I1 (SEQ ID NO: 4), and ten His-tagged EGFR ^{10}Fn3-based binders, E2 (SEQ ID NO: 6), E1 (SEQ ID NO: 8), E3 (SEQ ID NO: 52), E4 (SEQ ID NO: 107), E5 (SEQ ID NO: 113, wherein X = Ser and with a His tag at the C-terminus), E5 pegylated (SEQ ID NO: 113, wherein X = Cys and with a His tag at the C-terminus), E85 (SEQ ID NO: 140), E90 (SEQ ID NO: 155), E96 (SEQ ID NO: 170), E105 (SEQ ID NO: 185), and E112 (SEQ ID NO: 198). Examples 32 also describes a variety of E monomers having the sequences set forth in Figure 45 and including a His tag at the C-terminus.

The various ^{10}Fn3-based binders were purified using a high throughput protein production process (HTPP). Selected binders were cloned into the pET9d vector in order to generate His_6 tag (SEQ ID NO: 487) fusions. DNA was transformed into *E. coli* HMS174(DE3), and cells were inoculated in 5 ml LB medium containing 50 μg/mL kanamycin in a 24-well format and grown at 37 °C overnight. Fresh 5 ml LB medium (50 μg/mL kanamycin) cultures were prepared for inducible expression by aspirating 200 μl from the overnight culture and dispensing it into the appropriate well. The cultures were grown at 37 °C until A_{600} 0.6-0.9. After induction with 1 mM isopropyl-β-thiogalactoside (IPTG), the culture was grown for another 6 hours at 30 °C and harvested by centrifugation for 10 minutes at 3220 x g at 4 °C. Cell pellets were frozen at 80 °C.

Cell pellets (in 24-well format) were lysed by resuspension in 450 µl of Lysis buffer (50 mM NaH_2PO_4, 0.5 M NaCl, 1x Complete™ Protease Inhibitor Cocktail-EDTA free (Roche), 1 mM PMSF, 10 mM CHAPS, 40 mM imidazole, 1 mg/ml lysozyme, 30 ug/ml DNAse, 2 µg/ml aprotonin, pH 8.0) and shaken at room temperature for 1 hour. Lysates were clarified and re-racked into a 96-well format by transfer into a 96-well Whatman GF/D Unifilter fitted with a 96-well, 650 µl catch plate and centrifuged for 5 minutes at 200 x g. The clarified lysates were transferred to a 96-well Ni-Chelating Plate that had been equilibrated with equilibration buffer (50 mM NaH_2PO_4, 0.5 M NaCl,10 mM CHAPS, 40 mM imidazole, pH 8.0) and incubated for 5 minutes. Unbound material was removed by vacuum. The resin was washed 2 x 0.3 ml/well with Wash buffer #1 (50 mM NaH_2PO_4, 0.5 M NaCl, 5 mM CHAPS, 40 mM imidazole, pH 8.0) with each wash removed by vacuum. Next, the resin was washed with 3 x 0.3 ml/well with PBS with each wash step removed by vacuum. Prior to elution, each well was washed with 50 µl Elution buffer (PBS + 20 mM EDTA), incubated for 5 minutes, and the wash discarded by vacuum. Protein was eluted by applying an additional 100 µl of Elution buffer to each well. After a 30 minute incubation at room temperature, the plate(s) were centrifuged for 5 minutes at 200 x g and eluted protein collected in 96-well catch plates containing 5 µl of 0.5 M $MgCl_2$ affixed to the bottom of the Ni-plates. Eluted protein was quantified using a BCA Protein assay with SEQ ID NO: 2 as the protein standard.

HTPP yielded active ^{10}Fn3-based binders that were expressed in a soluble form and purified from the soluble fraction of the bacterial cytosol. Figure 1 depicts an exemplary SDS-PAGE analysis from one of the E/I ^{10}Fn3-based binders. SEC analysis on a Superdex 200 5/150 GL in a mobile phase of 100 mM NaPO4, 100 mM NaSO4, 150 mM NaCl, pH 6.8 (GE Healthcare) demonstrated predominantly monomeric proteins (see Example 4).

In addition, midscale expression and purification of select ^{10}Fn3-based binders was performed. The selected binders, fused to a His_6 tag (SEQ ID NO: 487), were cloned into a pET9d or pET29 vector and expressed in *E. coli* HMS174(DE3) or BL212(DE3) (EMD Biosciences, San Diego, CA) cells. 20 ml of an inoculum culture (generated from a single plated colony) was used to inoculate 1 liter of LB

medium containing 50 μg/mL kanamycin. The culture was grown at 37 °C until A_{600} 0.6-1.0. After induction with 1 mM isopropyl-β-thiogalactoside (IPTG), the culture was grown for another 6 hours at 30 °C. Alternatively, expression was carried out at 18 °C after initial growth at 37 °C using autoinduction media ("ONE" medium, EMD Biosciences, San Diego, CA). Cell pellets were harvested by centrifugation for 30 minutes at ≥10,000 x g at 4 °C and frozen at 80 °C. The cell pellet was resuspended in 25 mL of lysis buffer (20 mM NaH_2PO_4, 0.5 M NaCl, 1x Complete™ Protease Inhibitor Cocktail-EDTA free (Roche), pH 7.4) using an Ultra-turrax homgenizer on ice. Cell lysis was achieved by high pressure homogenization (≥18,000psi) using a Model M-110S Microfluidizer (Microfluidics). The soluble fraction was separated by centrifugation for 30 minutes at 23,300 x g at 4 °C. The supernatant was clarified via 0.45 μm filter. The clarified lysate was loaded onto a HisTrap column (GE) pre-equilibrated with 20 mM NaH_2PO_4, 0.5 M NaCl, pH 7.4. The column was then washed with 25 column volumes of 20 mM NaH_2PO_4, 0.5 M NaCl, pH 7.4, followed by 20 column volumes of 20 mM NaH_2PO_4, 0.5 M NaCl, 25 mM imidazole, pH 7.4, and then 35 column volumes of 20 mM NaH_2PO_4, 0.5 M NaCl, 40 mM imidazole, pH 7.4. Protein was eluted with 15 column volumes of 20 mM NaH_2PO_4, 0.5 M NaCl, 500 mM imidazole, pH 7.4, fractions pooled based on absorbance at A_{280} and dialyzed against 1x PBS, 50 mM Tris, 150 mM NaCl, pH 8.5 or 50 mM NaOAc, 150 mM NaCl, pH4.5. Any precipitate was removed by filtering at 0.22 μm .

Midscale expression and purification yielded highly pure and active proteins that were expressed in a soluble form and purified from the soluble fraction of the bacterial cytosol. SEC analysis on a Superdex 200 10/30GL in a mobile phase of 100 mM $NaPO_4$, 100 mM $NaSO_4$, 150 mM NaCl, pH 6.8 (GE Healthcare) demonstrated predominantly monomeric proteins (see Example 4).

Example 3: Pegylation of E/I ^{10}Fn3-Based Binders

Multi-valent fibronectin based scaffold proteins, such as E/I ^{10}Fn3-based binders, can be pegylated with various sizes and types of PEG. To allow for pegylation, the protein is typically modified near the C-terminus by a single point mutation of an amino acid, typically a serine, to a cysteine. PEGylation of the

protein at the single cysteine residue is accomplished through conjugation with various maleimide-derivatized PEG forms by combining the derivitized-PEG reagent with the protein solution and incubating. Progress and confirmation of the PEGylation conjugation reaction can be confirmed by SDS-PAGE and/or SE-HPLC methods that separate the non-PEGylated protein from the PEGylated protein.

For example, the construct E2-GS10-I1 (SEQ ID NO: 25) was pegylated by replacing a serine that was at position 221 with a cysteine. The resulting construct, SEQ ID NO: 56, was then conjugated with a maleimide-derivatized 40 kDa branched PEG (NOF America Corporation, White Plains, NY). The derivatized PEG reagent was mixed with the protein construct in solution and incubated at pH 7.40 at Room temperature until the reaction was complete, typically 30 minutes or overnight at 4 °C. The pH was lowered to pH 4.5 or pH 5.0 by dialysis or rapid desalting using size exclusion column chromotography into in 50 NaOAc, 150 mM NaCl buffer. The mixture of products and excess reactants from the PEGylation reaction were then loaded onto a cation exchange chromotography column at the lowered pH and eluted with a 150 mM to 1 M NaCl gradient. Studies to confirm the pegylation were also conducted as described in the paragraph above. The conjugations can be performed with the His tagged or the His-Tag free versions of the protein.

On occasions in which *E coli* endotoxin contamination needed to be depleted in the sample, two methods used either separately or in conjunction with one another were empoloyed. The first was to wash the cation exchange column with typically 5 column volumes NaOAc buffer supplemented with 0.5% Triton X-100, followed by 20 column volumes (or more) of the same buffer without Triton X-100. Additionally or in place of this procedure, the protein was passed very slowly through a Sartorius Sartobind® Q filter (Sartorius Stedim Biotech Bohemia, New York).

Two of the E/I ^{10}Fn3-based binders, E2-GS10-I1-cys (with his) (SEQ ID NO: 56) and E3-GS10-I1-Cys (with his) (SEQ ID NO: 53), were pegylated using an alternative procedure. Five ml of an inoculum culture of BL21(DE3) *E. coli* cells containing a T7 ploymerase driven pET29 plasmid encoding either E2-GS10-I1-cys (with his) or E3-GS10-I1-Cys (with his), were generated from a single plated colony

and used to inoculate 1 liter of auto-induction media ("ONE" medium, EMD Biosciences, San Diego, CA) containing 50 μg/mL kanamycin. Expression was carried out at 18 °C after initial growth at 37 °C and harvested by centrifugation for 10 minutes at ~10,000 x g at 4 °C. Cell pellets were frozen at 80 °C. The cell pellet was resuspended in 10 mL of lysis buffer (20 mM NaH_2PO_4, 0.5 M NaCl, 5 mM Immidazole, pH 7.4) and mechanically lysed using an Avestin homgenizer. The soluble fraction was separated by centrifugation for 15 minutes at 23,300 x g at 4 °C. The supernatant was decanted and the pellet was solubilized in Lysis buffer (above) supplemented with 4 M to 6 M guanidine hydrochloride (GdnHCl). Solubilized protein was then purified on a suitably sized NiNTA column (Qiagen, Inc.) pre-equilibrated with the GdnHCL supplemented Lysis Buffer. The column was then washed with 5 to 10 column volumes of the same buffer, followed by elution with the same buffer supplemented with 300 mM Immidazole. The fractions eluted off the column containing the protein of interest were diluted to 2-3 mgs/mL protein and then combined with a 1.2-1.5 molar excess of solid NEM-PEG (40 kDa branched or other). The mixture was allowed to react at room temperature for 30 minutes or until the reaction was complete. The entire reaction volume was then placed into a dialysis bag (5,000 Da Molecular Weight cutoff) and the mixture was subjected to a dialysis refolding process. For example, this process may consist of two 10-16 hour 500:1 (buffer: dialysate) dialysis exchanges against 50mM NaOAc, 150 mm NaCl, pH 4.5. The dialysate from this procedure contains properly folded, PEGylated materials plus excess reactants. The mixture of products and excess reactants from the PEGylation reaction were clarified via centrifugation or filtration prior to loading them onto a cation exchange chromotography column (SP Sepharose or Resource S, GE Healthcare). The column was developed with 150 mM to 1 M NaCl gradient in the NaOAc background buffer. Studies to confirm the pegylation were conducted as described above.

Example 4: Biophysical Characterization of ^{10}Fn3-Based Binders

Standard size exclusion chromatography (SEC) was performed on the proteins purified from the HTPP and the midscale processes (0.1 to 1 μg of protein for HTPP and 10-50 ug for midscale). SEC of HTPP derived material was

performed using a Superdex 200 5/150 column (GE Healthcare) or on a Superdex 200 10/30 column (GE Healthcare) for midscaled material on an Agilent 1100 or 1200 HPLC system with UV detection at A_{214}nm and A_{280}nm and with fluorescence detection (excitation = $_{280}$nm, emission = $_{350}$nm). A buffer of 100 mM sodium sulfate, 100 mM sodium phosphate, 150 mM sodium chloride, pH 6.8 at appropriate flow rate of the SEC column employed. Gel filtration standards (Bio-Rad Laboratories, Hercules, CA) were used for molecular weight calibration.

The results of the SEC on the HTPP purified ^{10}Fn3-based binders showed predominantly monomeric proteins and elution in the approximate range of 25 kDa vs. globular Gel Filtration standards (BioRad).

The results of the SEC on the midscaled purified ^{10}Fn3-based binders showed predominantly monomeric proteins and elution in the approximate range of 25 kDa vs. globular Gel Filtration standards (BioRad). Figure 2 depicts exemplary SEC profiles for E/I ^{10}Fn3-based binders (I1-GS10-E2 in Figure 2A and E2-GS10-Il in Figure 2B).

Select midscale ^{10}Fn3-based binders were further analyzed by LC-MS (Water's 2695 liquid chromatography HPLC system coupled with Waters Q-TOF API mass spectrometer, Waters Corporation, Milford, MA). Samples were diluted to approximately 0.5 mg/ml with HPLC grade water. Approximately 5 µl of diluted sample was injected onto a Jupiter C18 column (Catalog number 00G-4053-80, Phenomenex). Buffer A: 0.02%TFA+0.08% formic acid in HPLC grade water. Buffer B: 0.02% TFA + 0.08 % formic acid in HPLC grade acetonitrile. Sample was eluted with gradient (Table 1) at flow rate 0.2 ml/minutes.

Table 1

Time	%A	B%
0	95	5
5.00	75	25
25.00	55	45
30.00	5	95
32.00	95	5
45.00	95	5

HPLC elution was split at approximately to 1:1 ratio and half sent to UV detector and the other half to mass spectrometer. Mass spectrometer had the following instrument settings: capillary voltage 3.5 KV, cone voltage 40, source

temperature 80 °C, desolvation temperature 250 °C, desolvation gas flow 450 and multi channel photo detector voltage 2200. Raw spectra were deconvoluted with MaxEn1 (Waters Corporation).

The molecular weight of I1-GS10-E2 (SEQ ID NO: 22) as measured by LC-MS is 24,445 Dalton, which is within 1 Dalton from the molecular weight calculated from the amino acid composition. This indicates that the protein has the correct amino acid composition and the N terminal methionine is processed. There is no other post translational modification on the protein.

Differential Scanning Calorimetry (DSC) analysis of the midscaled I1-GS10-E2 was performed to determine the T_m. A 1 mg/ml solution was scanned in a N-DSC II calorimeter (Calorimetry Sciences Corp) by ramping the temperature from 5 °C to 95 °C at a rate of 1 degree per minute under 3 atm pressure. The data was analyzed versus a control run of the appropriate buffer using a best fit using Orgin Software (OrginLab Corp). The results of this assay demonstrate that the E/I binder has a T_m of 50.69 °C (see Figure 3A). Using the same methods, the T_m of E2-GS10-I1 (with Peg) was determined to be 50.72 °C and the T_m of E2-GS10-Il (without Peg) was determined to be 56.82 °C (see Figure 3B).

Example 5: Determination of Binding Affinity

Surface plasmon resonance (BIAcore) analysis was performed on solution-phase ^{10}Fn3-based binders in order to determine off-rates and/or binding affinities using captured EGFR-Fc and IGF1R-Fc. The extracellular domain of human IGF1R (aa 1-932) was cloned into a mammalian expression vector containing the hinge and constant regions of human IgG1. Transient transfection of the plasmid produced a fusion protein, IGF1R-Fc which was subsequently purified by Protein A chromatography. Recombinant human EGFR-Fc (aa 1-645 of the extracellular domain of human EGFR fused to human Fc) was purchased from R&D systems (Minneapolis, MN). IGF1R-Fc was captured on immobilized Protein A whereas EGFR-Fc was captured on immobilized anti-human antibody.

In a typical experiment, anti-human IgG was immobilized on flow cells 1 and 2 of a CM5 chip following the manufacturer's recommendations (GE Healthcare, Piscataway, NJ). EGFR-Fc (50 nM) was injected at 5 uL for 2 minutes

on flow cell 2 (Fc2). Two 30 second injections of 3 M $MgCl_2$ were used for regeneration of the bound EGFR-Fc from the anti-human IgG surface. Protein A was diluted to 80 ug/mL in acetate pH 4.5 and immobilized to ~3000 RU on flow cells 3 and 4 of a CM5 chip surface. Approximately 1300 RU of IGF1R-Fc was captured on Fc 4. Two 30 second injections of 50 mM glycine pH 1.5 were used to regenerate the surface between samples.

A concentration series of 100 nM to 1 nM of HTPP purified protein (three data points collected) or 300 nM to 0.05 nM of midscale purified protein (eleven data points collected) was evaluated for binding to EGFR-Fc or IGF1R-Fc. Sensorgrams were obtained at each concentration and were evaluated using Biacore T100 Evaluation Software, Version 1.1.1 (GE healthcare/Biacore) to determine the rate constants k_a (k_{on}) and k_d (k_{off}). For the HTPP evaluation the off-rate was fitted from the 3 point curves. The affinity K_D was calculated from the ratio of rate constants k_{off}/k_{on}.

The EGFR ^{10}Fn3-based binders were evaluated for specificity in a similar format using anti-human IgG to capture HER2-Fc. The ^{10}Fn3-based binders did not show any discernible binding to captured HER2-Fc under conditions where robust binding was seen for EGFR-Fc.

As shown in Table 2, both domains of the E/I ^{10}Fn3-based binders are functional, retaining their binding properties to the respective targets. The off rates shown in Table 2 are from midscale material and are similar to the qualitative results obtained with the HTPP material.

Table 2: Summary of binding constants for ^{10}Fn3-based binders

Target	Protein	ka (1/Ms)	kd (1/s)	K_D (nM)
EGFR-Fc	E1	1.19E+05 1.43E+05	1.18E-03 1.89E-03	9.92 13.2
	E1-GS10-I1	6.29E+04 3.82E+04	4.74E-04 3.89E-04	7.53 10.17
	I1-GS10-E1	1.26E+05 4.13E+04	6.03E-04 4.25E-04	4.8 10.28
	E2	3.73E+05 3.27E+05	2.72E-04 3.2E-04	0.73 0.98
	E2-GS10-I1	3.93E+05 3.75E+05	1.75E-04 1.67E-04	0.45 0.45
	I1-GS10-E2	6.47E+05 3.90E+05	1.42E-04 1.14E-04	0.22 0.29

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Target	Protein	ka (1/Ms)	kd (1/s)	K_D (nM)
	E3	2.83E+05	3.98E-04	3.4 1.4
	E3-GS10-I1	3.49E+05	2.29E-04	0.66
	I1-GS10-E3	1.17E+05	2.91E-04	2.48
IGF1R-Fc	I1	3.84E+06	4.34E-04	0.11
	E1-GS10-I1	5.13E+05	3.38E-04	0.66
	I1-GS10-E1	1.47E+06	3.98E-04	0.27
	E2-GS10-I1	1.24E+06	3.95E-04	0.32
	I1-GS10-E2	3.82E+06	4.79E-04	0.13
	E3-GS10-I1	1.8E+06	2.09E-04	0.12
	I1-GS10-E3	1.37E+06	4.54E-05	0.03

Example 6: Inhibition of IGFR activity in H292 Cells

The ability of E/I ^{10}Fn3-based binders to inhibit phosphorylation of IGF1R on tyrosine 1131 was determined using an H292 cell in vitro assay. Briefly, 65 X 10^3 H292 cells were plated in 96-well microplates (Biocoat Poly-D-Lysine coated 96-well plate, cat#356640, Becton Dickinson, Franklin Lakes, NJ) in RPMI-1640 culture medium containing 10 mM Hepes pH 7.4 and 10% fetal bovine serum. Cells were allowed to adhere for 24 hours at 37 °C, 5% CO_2. The next day cells were washed once with 200 microliters per well of serum free RPMI-1640 and incubated overnight in 100 µL per well of serum free RPMI-1640. Serial dilutions of HTPP material was added and cells were incubated for an additional 3 hours. Cells were stimulated with 100 ng/ml of IGF-1 (cat#500-P11, PeproTech, Rocky Hill, NJ) for 10 minutes at 37 °C. Media was dumped from the plate and 100 µL of cell lysis buffer (Cell Signaling cat#9803, Beverly, MA) was added to each well. Cells were incubated at room temperature for 15 minutes to allow lysis and lysate was transferred to a phospho-IGFR ELISA (cat#7302, Cell Signaling, Beverly, MA). The manufacturer's procedure was followed to carry out the ELISA.

As demonstrated in Figure 4, His tagged E1-GS10-I1 inhibited IGF1-stimulated phosphorylation of the IGF1R (IC_{50} = 0.004 uM) with comparable potency to the isolated IGF1R binder, I1 (IC_{50} = 0.018uM). The EGFR binder, E1, alone had very little effect on IGF1R phosphorylation (IC_{50} > 3.5uM). As shown in Figure 9, additional E/I binders demonstrated ability to inhibit IGF1R-stimulated phosphorylation with an IC50 in the range of 0.1 nM to 19 nM, including several

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pegylated E/I binders that were tested . In particular, for the pegylated E/I binders E1-GS10-I1, and I1-GS10-E1, inhibition of pIGFR was shown at 0.9 nM and 4 nM, respectively. For pegylated E/I binders E2-GS10-I1 and I1-GS10-E2, inhibition of pIGFR was shown at 0.3 nM and 0.8 nM, respectively.

Example 7: Inhibition of EGFR activity in H292 Cells

The ability of E/I ^{10}Fn3-based binders to inhibit phosphorylation of the EGFR on tyrosine 1068 was determined using an H292 cell in vitro assay. The assay was carried out as described in Example 6, except that cells were stimulated with 100 ng/ml of EGF (cat#236-EG-200, R & D Systems, Minneapolis, MN) and a phospho-EGFR ELISA was performed (cat#7240, Cell Signaling, Beverly, MA). The manufacturer's procedure was followed to carry out the ELISA.

As demonstrated in Figure 5, His-tagged E1-GS10-I1 inhibited EGF-stimulated phosphorylation of the EGFR (IC_{50} = 0.020uM) with comparable potency to the isolated EGFR binder, E1 (IC_{50} = 0.007uM). The IGF1R binder, I1 alone had very little effect on EGFR phosphorylation (IC_{50} > 6.21uM). As shown in Figure 9, additional E/I binders demonstrated ability to inhibit EGF-stimulated phosphorylation with an IC50 in the range of 7 nM to 127 nM, including several pegylated E/I binders that were tested. In particular, for pegylated E2-GS10-I1 and I1-GS10-E2, inhibition of pEGFR was shown at 32 nM and 47 nM, respectively. Similar data is shown in Figure 11 for the pegylated E/I binders E2-GS10-I1, and I1-GS10-E2.

Example 8: Inhibition of EGF+IGF1-induced pAKT in H292 Cells

The ability of E/I ^{10}Fn3-based binders to inhibit phosphorylation of AKT on serine 473 was determined using an H292 cell in vitro assay. The assay was carried out as described in Example 6, except that cells were simultaneously stimulated with both EGF and IGF1 as described above and lysates were analyzed with a phospho-AKT ELISA (cat#7160, Cell Signaling, Beverly, MA). The manufacturer's procedure was followed to carry out the ELISA.

Signal transduction at EGFR and IGF1R feeds into the PI3K-AKT signaling pathway and stimulates phosphorylation of AKT. As demonstrated in Figure 6, E1-

GS10-I1 inhibited EGF and IGF1-stimulated phosphorylation of AKT in H292 cells. The E/I ^{10}Fn3-based binder was slightly more potent in its ability to block AKT activation (IC_{50} = 0.004 uM) than the IGF1R binder, I1, by itself (IC_{50} = 0.031 uM). The EGFR binder, E1, exhibited only modest activity in its ability to block AKT activation by both ligands (IC_{50} = 1.28 uM). As shown in Figure 9, additional E/I binders demonstrated ability to inhibit EGF and IGF1-stimulated phosphorylation of AKT with an IC50 in the range of 0.1 nM to 26 nM, including several pegylated E/I binders that were tested.

Example 9: Inhibition of cell proliferation in RH41 and H292 cells

E/I ^{10}Fn3-based binders were evaluated for antiproliferative activity in the H292 non-small cell lung carcinoma cell line, which depends on EGFR signaling for growth, or the RH41 Ewing sarcoma cell line, which depends on IGF1R signaling for growth. Antiproliferative activity of binders was assessed in monolayer cultures by staining cellular DNA with the CyQuantNF fluorescent stain (cat#C35006, Invitrogen, Carlsbad, CA). Briefly, 2 X 10^3 H292 or 5 X 10^3 RH41 cells were plated into 96-well microplates (View Plates 96F cat#6005225, Perkin-Elmer, Waltham, MA) in RPMI-1640 culture medium containing 10 mM Hepes pH 7.4 and 10% fetal bovine serum and allowed to adhere for 24 hours at 37 °C, 5% CO_2. Cells were maintained as exponentially growing monolayers and remained in logarithmic growth phase during the period of the assay without reaching confluence during the course of the assay. Twenty-four hours after plating, serial dilutions of midscale material was added and cells were incubated for an additional 72 hours. Following this incubation, cells were treated with CyQuantNF reagent and allowed to incorporate dye into cellular DNA for 1 hour at 37 °C. Total DNA was quantified by reading fluorescence at 485 nm excitation and 530 nm emission on a CytoFluor 4000 instrument (Applied Biosystems, Framingham, MA). Total time that cells were exposed to drug was 72 hours. Standard compounds were included in each experiment to verify assay performance and reproducibility. Linear regression analysis of the percent of inhibition by test compound was used to determine IC_{50} values.

As demonstrated in Figure 7, in RH41 cells, His-tagged E1-GS10-I1 inhibited proliferation with comparable potency (IC_{50} = 0.009 uM) to the IGFR binder, I1 (IC_{50} = 0.028 uM). The EGFR binder, E1, by itself had very little effect on the proliferation in this cell line (IC_{50} > 12.5 uM).

As demonstrated in Figure 8, in H292 cells, His-tagged E2-GS10-I1 inhibited proliferation with greater potency (IC_{50} = 0.329 uM) than the IGFR binder, I1, (IC_{50} = 0.699 uM) or the EGFR binder, E2 (IC_{50} = 0.553 uM). See Table 4 below for the IC50 values for the E and I monomers.

Example 10: Competitive EGF ligand binding Assay

The E/I binders E1-GS10-I1, I1-GS10-E1, E2-GS10-I1 and I1-GS10-E2 (HTPP material) were tested in an EGF ligand binding cell-based competition assay in A431 cells and compared to EGFR ^{10}Fn3-based binders E1 and E2 (midscale material). A431 cells were plated at 15000 cells/well in 96-well plates in DMEM + 10% FBS and incubated 48 hours. Cells were washed with starvation media (DMEM + 0.1% BSA) and incubated in starvation media for 1 hour. Starvation media was removed and replaced with ^{10}Fn3-based binders that were diluted in starvation media and cells were pre-incubated for 30 minutes at 37 °C to allow proteins to bind to EGF receptors on cell surfaces. 10 nM final concentration of Europium (Eu)-labeled EGF (Perkin Elmer, Boston, MA) diluted in starvation media was added to pre-incubated cells and plates were incubated for 3 hours at 4 °C in the dark. Plates were washed twice with cold PBS and 50 ul/well of Enhancement solution (Perkin Elmer, Boston, MA) was added to plates and incubated 1 hour at 37 °C. Plates were read on the Flexstation II (Molecular Devices). The data was plotted with Softmax plus software and IC50 values, i.e., the concentration of ^{10}Fn3-based binders required to inhibit 50% of the Eu-EGF ligand from binding to the EGF receptor on the cell surfaces, were calculated.

The results for E2 and E1 compared with E2-GS10-I1, I1-GS10-E2, E1-GS10-I1 and I1-GS10-E1 are summarized in Table 3. This data indicates that the E/I ^{10}Fn3-based binders compete with, and inhibit the binding of, EGF to the EGFR receptor on A431 cells with similar potency to the EGFR ^{10}Fn3-based binders. See Table 4 below for the IC50 values for the E and I monomers.

Table 3: Summary of IC50 values for inhibition of EGF Binding to EGFR on A431 cell surfaces

Protein	IC50 (nM)
E2	7
E1	14
E2-GS10-I1	1.8
I1-GS10-E2	1.4
E1-GS10-I1	14.6
I1-GS10-E1	7

Example 11: Activation and Signaling Activity in Cell-Based Assays

Target effects of the various E/I ^{10}Fn3-based binders were evaluated in DiFi colon carcinoma cells by immunoblotting. Cells were seeded at 4 x 10^5 cells in each 25 cm^2 flask and incubated overnight at 37 °C in 5% CO_2. The next day, treatments were initiated and cells were further incubated for various times from 1.5 to 120 hours. Cells were then lysed in HNTG (50 mM Hepes, 150 mM NaCl, 0.5% triton-X-100, 8% glycerol, 2 mM Na_3VO_4, 1.5 mM $MgCl_2$, 1 mM EDTA containing the protease inhibitors AEBSF, aprotinin, leupeptin, bestatin, pepstatin-A and E64) and total protein was quantified with the BCA protein assay (Pierce, Waltham, MA). Levels of total EGFR, total IGF1R and the phosphorylation state of the EGFR, MAP kinase protein ERK1/2 isoforms, was detected by SDS-PAGE analysis of 20 micrograms of total protein followed by transfer of proteins to nitrocellulose and immunoblotting with specific antibodies. Blots were also probed with β-actin to demonstrate equal loading of each sample.

The pegylated E/I ^{10}Fn3-based binders E1-GS10-I1 (SEQ ID NO: 55), E2-GS10-I1 (SEQ ID NO: 56), and E3-GS10-I1 (SEQ ID NO: 53), demonstrated the ability to degrade EGFR in this assay. In addition, for E3-GS10-I1 (SEQ ID NO: 53), degradation of IGF1R was also observed. The effect on EGFR degradation for the pegylated binder E2-GS10-I1 is shown in Figure 10, as are other effects on signaling molecules. Additionally, the non-pegylated version of the binder E2-GS10-I1 demonstrated similar EGFR degradation (data not shown). Figure 10 shows that for the pegylated binder I1-GS10-E2, there was no EGFR degradation. Table 4 below summarizes various properties of the E monomers.

Table 4. Summary of properties of E monomers.

EGFR					
Monomer	BIAcore KD IC50	Neutralizes EGF Binding IC50	Inhibition of pEGFR IC50	Inhibition of pERK IC50	Inhibition of H292 Proliferation IC50
E1	14.6 nM	0.53 nM	18 nM	17 nM	18 nM
E2	1.4 nM	1.46 nM	20 nM	40 nM	30 nM
E3	0.72 nM	0.87 nM	11 nM	97 nM	26 nM

Example 12: Evaluation of Certain E/I ^{10}Fn3-Based Binders on H292 Tumor Xenografts Grown In Nude Mice

The pegylated E/I binders E2-GS10-I1 and E3-GS10-I1 as well as the monoclonal antibody panitumumab were evaluated in an H292 tumor xenograft model. For *in vivo* models, panitumumab was obtained as the marketed drug and E/I binders were purified as described above. In vitro activity of all E/I binders was validated prior to administration in animals by testing functionality of each end in the EGF-stimulated pEGFR and the IGF1-stimulated pIGFR assay in H292 cells. E/I binders were diluted in phosphate buffered saline (PBS) at the beginning of the experiment and stored at 2-4 °C for the duration of each study. Both compounds were administered i.p. in a total volume of 500 µl/inj/mouse and were equilibrated to room temperature prior to administration.

Mice and tumor propagation. Female athymic (nude) mice 5-6 weeks of age were obtained from Harlan Sprague-Dawley Co. (Indianapolis, IN). and were quarantined for approximately 3 weeks prior to their use for tumor propagation or drug efficacy testing. The animals were provided food and water *ad libitum*. Animal care was performed in keeping with AAALAC and Bristol-Myers Squibb guidelines. Tumors were propagated by subcutaneous (s.c.) implantation in nude mice. Tumor passages occurred approximately every two to four weeks.

In vivo antitumor testing. Estimated tumor weight was calculated using the formula: Tumor weight (mg) = $(w^2 * l)/2$; where w = width and l = length in mm. Antitumor activity was evaluated in terms of % tumor growth inhibition (TGI) where a %TGI of >50% was considered active. Relative % tumor growth inhibition was calculated as $\%TGI=[(C_t-T_t)/(C_t-C_0)] \times 100$ where C_t=median tumor weight of control mice at time t in days after tumor implant, T_t=median tumor weight of treated mice at time t, C_0= median tumor weight of control mice at time 0. %TGI

value was calculated at various time points beginning after 1.5 tumor volume doubling times and sustained over a time period of 3 tumor volume doubling times (TVDT) where possible. Where, TVDT = median time (days) for control tumors to reach target size – median time (days) for control tumors to reach half the target size. The definition of a cured mouse was one whose tumor was undetectable, or <35 mg, when assessed more than 10 TVDTs post-treatment. The dose of a compound which yielded the maximum therapeutic effect, was termed the optimal dose (OD). Treatment groups (typically 8 mice) with more than one death attributable to drug toxicity were considered to have had excessively toxic treatments and their data were not used in the evaluation of antitumor activity. The maximum tolerated dose (MTD) is defined as the dose level immediately below which excessive toxicity (i.e. more than one death) occurred. Treated mice dying prior to having their tumors reach target size were considered to have died from drug toxicity. Statistical evaluations of data were performed using Gehan's generalized Wilcoxon test (Gehan, EA, A Generalized Wilcoxon Test for Comparing Arbitrarily Slightly-Censored Samples, Biometrika 52:203-223, 1965).

Measurement of pharmacodynamic endpoints in tumors. Tumors were harvested from untreated or drug treated mice and snap frozen in liquid nitrogen. Samples were weighed and homogenized in 10 µl of lysis buffer (50 mM Hepes, 150 mM NaCl, 0.5% triton-X-100, 8% glycerol, 2 mM Na_3VO_4, 1.5 mM $MgCl_2$, 1mM EDTA containing one complete mini protease inhibitor tablet Sigma #S8820 per 15 ml buffer and phosphatase inhibitor cocktail Sigma #P5726) for each mg of tissue. Tissues were minced in a 100 mm petri dish with two scalpels, transferred to Falcon#2059 polypropylene round bottom tubes and macerated with a hand held homogenizer for 30 seconds. Homogenate was transferred to 1.5 ml eppendorf tubes and centrifuged at 15000 x g for 2 minutes in a microfuge. Clarified supernatant was transferred to a new tube and total protein concentration was determined with the Pierce BCA protein assay (Pierce Biotechnology). Samples were analyzed by immunoblotting or on a Meso scale MSD Sector Imager 6000 multi spot assay system as recommended by the manufacturer (Meso Scale Discovery, Gaithersburg, MD).

The pegylated E/I binders E2-GS10-I1 and E3-GS10-I1 were tested in an H292 NSCLC in athymic mice. Tumors were implanted subcutaneously with 1 mm^3 H292 tumor fragments in the hind flank and allowed to establish to a size of 50-150 mg prior to initiation of treatment on Day 6 post-tumor implant. The pegylated E/I binders were administered i.p. at a dose of 100 mg/kg on a TIWX3 schedule to assess antitumor activity. Panitumumab was obtained as marketed drug and administered i.p. at its optimal dose of 1 mg/mouse and at a lower dose of 0.1 mg/mouse on a Q3DX5 schedule. Mean tumor sizes calculated from groups of 8 mice are shown in Figure 12A. The 1 mg/mouse and 0.1 mg/mouse doses of panitumumab were both active by %TGI with values of 101% and 100%, respectively and these values were significantly different from control animals (p=0.0002, Table 5). Pegylated E2-GS10-I1 was also significantly active by %TGI with a value of 96% (p=0.0005). Pegylated E3-GS10-I1 was not active in this study with a %TGI value of 31% that was not statistically different from the control group (p=0.416). Post dosing analysis indicated that approximately two thirds of the pegylated E3-GS10-I1 was aggregated (66.64% aggregation/33.36% monomer for one batch and 72.53% aggregation/27.47% monomer for another batch) which could account for the poor activity of pegylated E3-GS10-I1 in this assay. In contrast, the pegylated E2-GS10-I1 showed only a small percentage of aggregation in post dosing studies (1.79% aggregation/98.21% monomer).

All treatments were well tolerated with no treatment related deaths or excessive weight loss over the course of the study. Clinical observations revealed no evidence of toxicity and the average weight change over the course of therapy was within acceptable limits (Figure 12B).

Table 5. Results of the H292 human tumor xenograft study

Group	Compound	Schedule, Route	Dose (mg/kg)	AVE weight change (g)	%TGI	p value for %TGI	Outcome by %TGI
1	Control (untreated)	---	---	5.3	---	1.0	---
2	panitumumab	q3dx5; 6 ip[a]	1mg/mse	9.6	101	0.0002	A
3	panitumumab	q3dx5;	0.1mg/mse	6.3	100	0.0002	A

Group	Compound	Schedule, Route	Dose (mg/kg)	AVE weight change (g)	%TGI	p value for %TGI	Outcome by %TGI
		6 ip[a]					
4	E2-GS10-I1 (w/ PEG)	TIWx3; 6 ip[a]	100	-0.1	94	0.0005	A
5	E3-GS10-I1 (w/ PEG)	TIWx3; 6 ip[a]	100	9.5	28	0.416	I

[a]Vehicle was phosphate buffered saline. Abbreviations used are as follows: ip, intraperitoneal route; %TGI, relative % tumor growth inhibition calculated as %TGI=[(Ct-Tt)/(Ct-C0)] x 100 where Ct=median tumor weight of control mice at time t in days after tumor implant, Tt=median tumor weight of treated mice at time t, C0= median tumor weight of control mice at time 0. %TGI value was calculated at two points as the average inhibition of Day 12 and Day20. Outcome, a treatment regimen was considered active if it produced a statistically significant %TGI value of >50%; q3dx5;6, compound was administered every three days for five doses starting on the sixth day after tumor implant; TIWx3;6, compound was administered three times a week for three weeks starting on the sixth day after tumor implant. p values were calculated on Day 20 relative to the control group in a two tailed paired analysis with 8 measurements per group. Outcome by %TGI, A = active and I = inactive.

Pharmacodynamic endpoints from the H292 tumor study. Samples of tumors from untreated control, panitumumab and E/I binder treated groups were analyzed for levels of phosphorylated EGFR, ErbB2 and IGFR that would indicate target suppression. Tumors were also analyzed for levels of total EGFR to determine if EGF receptor degradation occurred. On day 20, a final treatment was administered and tumors were removed from 2 animals at 1 hour after dosing, 3 animals at 4 hours after dosing and 3 animals at 24 hours after dosing. All treatments showed marked suppression of phosphorylated EGFR and ErbB2 while the basal levels of phosphorylated IGFR were too low to discern a difference in this study (Figure 13). All treatments showed a reduction in the amount of total EGFR indicating degradation of the receptor had occurred.

Example 13: Selection and Characterization of MCF7 Cells Resistant to IGF1R Inhibitor

MCF7 cells (American Type Culture Collection, Cat No. HTB-22, Manassas, VA) were cultured in RPMI medium containing 10 mM hepes and 10% FBS at 37 °C in the presence of 5% CO_2. The small molecule IGF1R inhibitor BMS-754807 was added to the culture medium and the concentration increased at

stepwise increments over a period of 10 months until the cells exhibited continued proliferation in the presence of 200 mM BMS-754807. The resistant cells were designated MCF7r and the IC50 for BMS-754807 was 1239 nM compared to 120 nM for the parental MCF7 cells as measured in a proliferation assay carried out as previously described (Carboni et al., Cancer Res. 69: 161-170 (2009)). The drug was then removed from the culture medium and the MCF7r cells were passaged in complete medium for an additional 20 or 60 days to remove all traces of residual BMS-754807. Analysis of the MCF7r cells by immunoblotting revealed that EGFR was significantly overexpressed in the resistant cells compared to the parental MCF7 cells (Figure 14). In addition, when MCF7 and MCF7r cells were serum starved and then stimulated with EGF for 7 minutes, phosphorylated EGFR could not be detected in the parental MCF7 cells (probably due to low levels of EGFR) but was strongly visible in MCF7r cells. In serum starved cells stimulated with IGF ligand, phosphorylated IGFR was seen in the parental MCF7 cells but despite the slightly higher levels of total IGFR present in the MCF7r cells almost no pIGFR was observed. This shows that the IGFR in the resistant MCF7r cells lost the ability to activate IGFR in response to IGF1 stimulation (Figure 14). Activation of the MAP kinase pathway in response to EGF stimulation was stronger in the MCF7r cells as measured by pERK activation.

Example 14: Antitumor Studies in MCF7 and MCF7r Xenografts

MCF7r cells were scaled up in T75 flasks and isolated by centrifugation. Viable cell numbers were measured by trypan blue exclusion with a Vi-CELL XR (Beckman Coulter, Fullerton, CA), resuspended in PBS to 5 x 10^6 viable cells/ml and implanted subcutaneously in the hind flank of athymic mice in a volume of 0.2 ml. For MCF7 and MCF7r tumor growth, all mice were supplemented with 0.25 mg 90 day release pellets of 17-β-estradiol (Innovative Research of America, Sarasota, FL, Cat. No. NE-121). Tumors were propagated until they reached a median size of 500-1000 mg when they were excised and 1 mm^3 fragments were reimplanted in the hind flank of new athymic mice. Tumors were adapted for solid tumor growth by serial trocar passage in mice through at least four rounds of growth during which tumor volume doubling time and take rate were monitored for each passage.

Growth characteristics were observed to determine if the xenografts exhibited acceptable properties to serve as a reliable, reproducible model. The MCF7r tumor type demonstrated an acceptable take rate and doubling time and therefore satisfied the criteria for use as a xenograft model. The MCF7 parental tumor model had been previously established using the same techniques. For the MCF7 parental xenograft, 1 mm^3 tumor fragments were implanted subcutaneously in the hind flank and allowed to establish to a size of 50-150 mg prior to initiation of treatment on Day 13 post-tumor implant. Cetuximab was obtained as marketed drug and administered i.p. at its optimal dose of 1 mg/mouse and at a lower dose of 0.1 mg/mouse on a Q3DX5 schedule (doses administered on Day 13, 16, 19, 22, 25). Mean tumor sizes calculated from groups of 8 mice are shown in Figure 15A. In the MCF7 xenograft model, neither the 1 mg/mouse or the 0.1 mg/mouse dose of cetuximab was active by %TGI with values of -9% and 3.2%, respectively and the tumor sizes were not statistically different from the control group (Table 6).

For the MCF7r resistant xenograft, 1 mm^3 tumor fragments were implanted subcutaneously in the hind flank and allowed to establish to a size of 50-150 mg prior to initiation of treatment on Day 6 post-tumor implant. Cetuximab was obtained as marketed drug and administered i.p. at its optimal dose of 1 mg/mouse and at a lower dose of 0.1 mg/mouse on a Q3DX5 schedule (doses administered on Day 6, 9, 12, 15, 18). Mean tumor sizes calculated from groups of 8 mice are shown in Figure 15B. In the MCF7r xenograft model, doses of cetuximab were active by %TGI with values of 105% and 75%, respectively. The high dose of cetuximab had a TGI value over 100% which indicates that it caused tumor regression below the starting size at the initiation of treatment. Both doses resulted in a statistically significant difference in tumor size compared to the control group (Table 7).

Table 6. Results of the MCF7 human breast carcinoma tumor xenograft study.

Group	Compound	Schedule, Route	Dose (mg/mouse)	%TGI	p value for %TGI	Outcome by %TGI
1	Control (untreated)	---	---	---	1.0	---
2	cetuximab	q3dx5; 13 ip[a]	1mg/mse	-9	0.223	I

3	cetuximab	q3dx5; 13 ip[a]	0.1mg/mse	3.2	0.220	I

[a]Vehicle was phosphate buffered saline. Abbreviations used are as follows: ip, intraperitoneal route; %TGI, relative % tumor growth inhibition calculated as %TGI=[(Ct-Tt)/(Ct-C0)] x 100 where Ct=median tumor weight of control mice at time t in days after tumor implant, Tt=median tumor weight of treated mice at time t, C0= median tumor weight of control mice at time 0. %TGI value was calculated at three points as the average inhibition of Day 20, 24 and Day 27. Outcome, a treatment regimen was considered active if it produced a statistically significant %TGI value of >50%; q3dx5;13, compound was administered every three days for six doses starting on the thirteenth day after tumor implant. p values were calculated on Day 24 relative to the control group in a two tailed paired analysis with 8 measurements per group. Outcome by %TGI, A = active and I = inactive.

Table 7. Results of the MCF7r human breast carcinoma tumor xenograft study.

Group	Compound	Schedule, Route	Dose (mg/kg)	%TGI	p value for %TGI	Outcome by %TGI
1	Control (untreated)	---	---	---	1.0	---
2	cetuximab	q3dx5; 6 ip[a]	1mg/mse	105	0.001	A
3	cetuximab	q3dx5; 6 ip[a]	0.1mg/mse	75	0.024	A

See footnotes to Table 6. p values were calculated on Day 19 relative to the control group in a two tailed paired analysis with 8 measurements per group.

Example 15: Antitumor Studies in GEO Xenografts

GEO tumors were established by implanting 1 mm^3 tumor fragments subcutaneously in the hind flank of athymic mice and allowing them to reach a size of 50-150 mg prior to initiation of treatment on Day 18 post-tumor implant. Cetuximab was administered ip at 0.25 mg/mouse on a Q3DX5 schedule (doses administered on Day 18, 21, 24, 27, 30). The IGFR kinase inhibitor BMS-754807 was administered at 25 mg/kg on a QDX21 schedule. Mean tumor sizes calculated from groups of 8 mice are shown in Figure 16. Cetuximab was active at 0.25 mg/mouse with a %TGI value of 67%. BMS-754807 was active with a %TGI of 80% and the combination of the two was considerably more active then either agent alone with a %TGI of 94% (Table 8). All treatment groups were statistically different from the control group on Day 26 (Table 8).

Table 8. Results of the GEO human colon carcinoma tumor xenograft study.

	Cetuximab		BMS-754807					
Group	Schedule, Route	Dose (mg/ mouse)	Schedule, Route	Dose (mg/kg)	%TGI	p value	Out come by %TGI	Synergy
1	Control (untreated)	---	---	---	---	---	---	---
2	q3dx5;6 ip[a]	0.25 mg/ mse	---		80		A	---
3	---	---	qdx21;18[b]	25	67		A	---
4	q3dx5;6 ip[a]	0.25 mg/ mse	qdx21;18[b]	25	94		A	YES

[a]Vehicle for cetuximab was phosphate buffered saline. Vehicle for BMS-754807 was 50% polyethylene glycol 400, 50% water. Abbreviations used are as described in Table 6 and synergy is defined as statistically significant activity that is better than either agent in the combination demonstrated on its own. Outcome by %TGI, A = active and I = inactive.

Example 16: Antitumor studies in H292 xenografts

H292 cells were implanted subcutaneously in the hind flank of athymic mice as 1 mm^3 fragments and allowed to establish to a size of 50-150 mg prior to initiation of treatment on Day 12 post-tumor implant. Cetuximab was administered ip at 0.1 mg/mouse on a Q3DX5 schedule. MAB391 is an antibody to IGF1R (R&D Systems, Minneapolis, MN, Cat. No. MAB391) and was administered at a dose of 40 mg/kg on a BIWX3 schedule. Mean tumor sizes calculated from groups of 8 mice are shown in Figure 17. Cetuximab was active at 0.1 mg/mouse with a %TGI value of 95.1% and MAB391 was inactive at 40 mg/kg with a %TGI value of 10.5% (Table 9). Mice dosed with the combination of cetuximab and MAB391 exhibited a %TGI value of 109.2% indicating tumor regression in the combination group (Table 9). After dosing ceased, tumors regrew in the cetuximab treated group more rapidly than in the group treated with the combination of cetuximab and MAB391 (Figure 17).

Table 9. Results of the H292 human NSCLC tumor xenograft study.

	Cetuximab		MAB391					
Group	Schedule, Route	Dose (mg/ mouse)	Schedule, Route	Dose (mg/kg)	%TGI	p value	Out come by %TGI	Synergy
1	Control (untreated)	---	---	---	---	---	---	---
2	q3dx5;12 ip[a]	0.1 mg/ mse	---		95.1		A	---
3	---	---	BIWx3;12[a]	40	10.5		I	---
4	q3dx5;12 ip[a]	0.1 mg/ mse	BIWx3;12[a]	40	109.2		A	YES

[a]Vehicle for cetuximab and MAB391 was phosphate buffered saline. Abbreviations used are as described in Table 6 and 8.

Example 17: Colony Formation Assay

To determine the effects of test compounds on the ability to inhibit colony formation of H292 cells, 400 cells were seeded into 24-well plates (Becton-Dickinson, Franklin Lakes, NJ, Cat. No. 351143) in complete medium and allowed to adhere overnight. The next day medium was removed and replaced with medium containing 2% FBS. Test compound was diluted into medium containing 2% FBS and added to cells in serial dilutions. Cells were incubated at 37 °C for 14 days. After 14 days, media was discarded and wells rinsed once with 2 ml PBS. Cells were stained with 0.5 ml Coomassie Stain Solution (Bio-Rad, Hercules, CA, Cat. No. 161-0436) for 20 min. The stain was aspirated and wells were washed quickly with 1X Destain Solution Coomassie R-250 (Bio-Rad, Cat. No. 161-0438). A final rinse with 1 ml water per well was carried out and plates were inverted and allowed to dry. Colonies consisting of (at least) 50 cells or larger were counted by eye under low power magnification (10X-20X). All samples were tested in triplicate and IC50 values were calculated from linear regression of the percent inhibition of control. Representative results for a PEGylated E/I binder are shown in Figure 18 and IC50 values for various E/I ^{10}Fn3-based binders, monospecific IGF1R ^{10}Fn3-based binder, and EGFR antibody is shown in Table 10.

Table 10. IC50 values of various E/I ^{10}Fn3-based binders, monospecific IGF1R ^{10}Fn3-based binder, and EGFR antibody in the colony formation assay.

SAMPLE	IC50 (nM)
E4-GS10-I1 (with Peg)	5
I1-GS10-E5 (with Peg)	1
I1-GS10-E4	6
E2-GS10-I1 (with Peg)	560
I1 monomer (with Peg)	15,510
panitumumab	140

Example 18: Epitope mapping assay

An epitope mapping assay was developed utilizing commercially available antibodies where the binding site on the EGFR extracellular domain is roughly known according to various literature reports. The antibodies used in this assay are listed in Table 11 and Figure 19A depicts how antibodies were localized to approximate binding domains on EGFR . The assay is a variation of the In Cell Western assay previously described and assesses the ability of EGFR ^{10}Fn3-based binders preincubated with A431 or other cells expressing EGFR to block binding of the detection antibodies from the panel listed in Table 11. The assay was carried out as follows: A431 cells in log phase growth were harvested by trypsinization and seeded in a 96 well plate at 24,000 cells/well in a total volume of 100 µl/well. The next day, media was dumped and the EGFR ^{10}Fn3-based binders diluted in cold DMEM base media were added to the plate and allowed to bind for 1 hour at 4°C to prevent internalization of EGFR. After binding, cells were washed with 0.2 ml PBS+0.1% Tween-20 and fixed for 20 minutes in PBS+3.7% formaldehyde at room temp. Cells were blocked in 0.2 ml of Odyssey blocking buffer for 1 hour at room temp. Next, primary antibodies were diluted in 50 µl of Odyssey blocker per well and incubated for 1-2 hours at room temp. Primary antibodies were dumped by inverting the plate, and each well washed 3X with 200µl of PBS+0.1% Tween-20. Secondary antibodies are the same ones used in the In Cell Western assay and were appropriate for the species of antibody being detected. These secondary antibodies were diluted (1:800) in Odyssey Blocker+0.2% Tween-20 and added in a volume of 50µl per well along with TOPRO3 (Invitrogen, Carlsbad, CA, cat#T3605) diluted at

(1:3000) to counterstain cells for normalization. Cells were incubated on bench for 1 hour at room temp. Secondary antibody was dumped out and each well washed 4X with 200µl of PBS+0.1% Tween-20 for 5 minutes at room temp. Plates were imaged on a Licor instrument at 160µm resolution, medium quality, focus offset of 3mm, intensity of 5. This assay was also carried out with the marketed drug antibodies cetuximab, panitumumab and nimotuzumab to determine if the EGFR^{10}Fn3-based binders were interfering with their binding to EGFR on A431 cells. Representative results are shown in Figure 19B.

Table 11. Commercially available antibodies to the extracellular domain of EGFR.

	Clone	SUPPLIER and cat#	SPECIES	BINDS	EPITOPE	Binding motif
1		Abcam ab38165	Rab	h	Peptide AA 42-58	linear
2	E234	Abcam ab32198	Rab	h,mu,rat	Peptide AA 40-80 (No ICC)	linear
3	N-20	Santa Cruz#31155	Goat IgG	h	AA 110-160	linear
4	ICR10	Abcam ab231 Santa Cruz #57095	Rat IgG2a	h(HN5)	AA 124-176[b], neutralizing[e]	conf
5	EGFR 1	Abcam ab30 Chemicon MAB88910 Labvision MS-311	Mu IgG1	h(A431)	AA 176-294, neutralizing[b] ab30&MAB88910 @(1mg/ml)	conf
6	199.12	Labvision MS-396-P	Mu IgG2a	h	AA 124-176, non-neutralizing[b]	conf
7	LA22	Upstate 05-104	Mu IgG2a	h(A431)	AA 351-364, neutralizing[a]	linear
8		Abcam ab15669	Rab	Mu,rat	Peptide AA376-394[d]	linear
9	225	Sigma E2156 Labvision MS-269-P	Mu IgG1	h(A431)	AA 294-475, neutralizing[b,c]	conf
10	528	Abcam ab3103 Santa Cruz#120 Labvision MS-268-P	Mu IgG2a	h(A431)	AA 294-475, neutralizing[b,c]	conf
11	B1D8	Labvision MS-666-P	Mu IgG2a	h(A431)	AA 294-475[b]	conf
12	LA1	Upstate 05-101	Mu IgG1	h	neutralizing	
13	H11	Labvision MS-316-P	Mu IgG1	h	AA 294-475, non-neutralizing[b]	linear
14	111.6	Labvision	Mu IgG1	h	AA 294-475,	linear

	Clone	SUPPLIER and cat#	SPECIES	BINDS	EPITOPE	Binding motif
		MS-378-P Imgenex IMG-80179			neutralizing[b]	
15	29.1	Sigma E2760 Abcam ab10414	Mu IgG1	h(A431)	External carbohydrate non-neutralizing	

Abbreviations: conf: epitope conformationally specific; linear: epitope independent of conformation. [a]JBC 264(1989)17469 Ala351-Asp364, [b]J Immunological Methods 287(2004)147, [c]Mol Biol Med1(1983)511, [d]Raised against a peptide to mouse EGFR [FKGDSFTRTPPLDPRELEI (SEQ ID NO: 491)], [e]Int J Oncol 4(1994)277. [f][EEKKVCQGTSNKLTQLGTFEDHFLSLQRMFNNCEVVLGNLEITYVQRNYDLSFLK TIQEVAGYVLIALNTVERIPLENLQIIRGNMYYENSYALAVLSNY (SEQ ID NO: 492)], [g]Ile-Gln-Cys-Ala-His-Tyr-Ile-Asp-Gly-Pro-His-Cys (SEQ ID NO: 493) (amino acids 580-591). [h]Cancer Cell 7(2005)301.

Using various approaches, we have confirmed that the EGFR monomer E3 binds to domain I of EGFR. Since other E monomers have similar properties in various experiments, it is thought that the other E monomers also bind to domain I of EGFR.

Example 19: Properties of I Monomers

BIAcore analysis of the soluble fibronectin-based scaffold proteins

The kinetics of I monomers binding to the target was measured using BIAcore 2000 or 3000 biosensors (Pharmacia Biosensor). A capture assay was developed utilizing an IGF-IR-Fc fusion. A similar reagent had been described by Forbes et al. (Forbes et al. 2002, European J. Biochemistry, 269, 961-968). The extracellular domain of human IGF-IR (aa 1-932) was cloned into a mammalian expression vector containing the hinge and constant regions of human IgG1. Transient transfection of the plasmid produced a fusion protein, IGF-IR-Fc which was subsequently purified by Protein A chromatography and captured on Protein A immobilized on Biasensor CM5 chips by amine coupling. The kinetic analysis involved the capture of IGF-IR-Fc on Protein A followed by injection of the fibronectin-based scaffold protein in solution and regeneration of the Protein A surface by glycine pH 2.0. Sensorgrams were obtained at each concentration and were evaluated using a program Biaevaluation, BIA Evaluation 2.0 (BIAcore), to determine the rate constants k_a (k_{on}) and k_d (k_{off}) The dissociation constant, K_D was calculated from the ratio of rate constants k_{off}/k_{on}. Typically, a concentration series

(2 uM to 0 uM) of purified fibronectin-based scaffold protein was evaluated for binding to protein A captured human IGF-IR-Fc fusion protein.

For experiments determining binding to human insulin receptor, recombinant human insulin receptor (IR) and recombinant human VEGF-R2-Fc were directly coupled to a CM5 Biasensor chip by amine group linkage following standard procedures recommended by Biacore (Uppsala, Sweden). In brief, 60 ug/mL of IR diluted in acetate 4.5 was coupled/immobilized to a level of 8300 RU and 11.9 ug/mL of VEGF-R2-Fc diluted in acetate 5.0 was immobilized to a level of 9700 RU on flow cells 2 and 3. A blank reference surface was prepared on FC1. Specific binding to either IR or VEGF-R2-Fc was calculated by subtracting the binding observed to the blank reference flow cell 1. Fibronectin-based scaffold proteins were diluted to 10 uM in HBS-EP (10 mM Hepes, 150 mM NaCl, 3 mM EDTA, 0.05% Surfactant P20) and injected at 20 uL/min for 3 minutes over the flow cells at 25 °C and dissociation was observed over 10 mins.

Cell-based Receptor Blocking Assay

The human breast adenocarcinoma MCF-7 (ATCC, Manassas, VA) was plated in 24 well plates at a concentration of 50,000 cells per well in RPMI 1640 (Invitrogen, Carlsbad, CA) containing 10% fetal bovine serum (Hyclone, Logan, UT). The following day, cells were washed in binding buffer consisting of RPMI 1640 containing 0.1% BSA (Sigma, St. Louis, MO), and then pre-incubated for 30 minutes on ice in 200 µL binding buffer containing IGF-IR competitor. After the pre-incubation period, 40 pM [^{125}I]-IGF-I (Perkin Elmer, Wellesley, MA), equivalent to approximately 60000 counts per minute, was added to each well and allowed to incubate for an additional three hours on ice with gentle agitation. The wells were then washed with ice cold PBS containing 0.1% BSA. Cells were lysed with 500 µL buffer consisting of 0.1% SDS + 0.5 N NaOH. Radioactivity of the lysates was measured using a Wallac 1470 Gamma Counter (Perkin Elmer, Wellesley, MA), and the data were analyzed using SigmaPlot (Systat Software, Point Richmond, CA).

pIGFR Assay

Fibronectin-based scaffold proteins fused to Fc were evaluated for their ability to inhibit IGF-1R phosphorylation in Rh41 human rhabdomyosarcoma cells.

A Western Blot was employed to assess the ability of the I monomer to inhibit IGF-1R phosphorylation in Rh41 human rhabdomyosarcoma cells. Cells were stimulated with IGF-I, IGF-II, insulin ligands (50ng/ml), or no stimulation (NS) and then treated with various concentrations of the I monomer. Membranes were probed with phospho-specific antibodies.

Cellular Proliferation in Rh41 (human Rhabdomyosarcoma and H929 human Multiple Myeloma)

Proliferation was evaluated by incorporation of [^{3}H]-thymidine into DNA after a 72 hour exposure to reagents. Rh41 cells were plated at a density of 3500 cells/well in 96-well microtiter plates and 24 hours later they were exposed to a range of I monomer concentrations. After 72 hours incubation at 37°C, cells were pulsed with 4μCi/ml [^{3}H] thymidine (Amersham Pharmacia Biotech, UK) for 3 hours, trypsinized, harvested onto UniFilter-96, GF/B plates (PerkinElmer, Boston, MA) and scintillation was measured on a TopCount NXT (Packard, CT). Results are expressed as an IC50, which is the drug concentration required to inhibit cell proliferation by 50% to that of untreated control cells Data represents the average of triplicate wells with standard deviations shown.

Results of the characterization of the I monomer are shown below in Table 12.

Table 12. Properties of I monomers.

IGFR				
Monomer	BIAcore KD IC50	Neutralizes IGF Binding IC50	Inhibition of pIGFR IC50	Inhibition of RH41 Proliferation IC50
I1	0.11 nM	8 nM	0.2 nM	28 nM

Example 20: Additional Characteristics of Monospecific and Bispecific EGFR and IGF-IR ^{10}Fn3-based binders

^{10}Fn3-based binders that bound either EGFR or IGF-IR were identified using the biochemical selection technique of mRNA display in which a protein is covalently attached to its coding nucleic acid sequences. ^{10}Fn3-based proteins-mRNA fusion populations that bound either IGF-IR or EGFR when the receptors

were presented at concentrations from 1 to 10 nM were cloned into *E. coli* and expressed as ^{10}Fn3-based proteins. A subset of target binders that blocked EGFR or IGF-IR signaling and had suitable biophysical properties were identified (Table 13). These initial clones were optimized for target binding affinity and cellular potency with additional mRNA selection at increasingly lower target concentrations and selection for lower dissociation rate constants. IC_{50} values obtained during the selection procedures ranged from 9 to 304 nM, illustrating the opportunity for choosing molecules from a wide range of potency values for the construction of bi-specific ^{10}Fn3-based binders. EGFR ^{10}Fn3-based binders were tested by In-Cell Western screening assays for the blockade of phosphorylation of EGFR and ERK, a downstream signaling molecule of EGFR activation (methods similar to Example 1). Analogous studies were performed on optimized IGF-IR binders. Optimized EGFR-binding clones (E3, E1, and E2) inhibited EGFR phosphorylation on Y1068 and downstream phosphorylation of ERK on Y204 of p42/p44 *in vitro* with IC_{50} values ranging from 9 to 40 nM, potencies that were more than 100-fold higher than the parental EGFR clone (Table 13, methods similar to Example 1).

I1 bound to IGF-IR with a K_D value of 0.11 nM and inhibited IGF-I-stimulated IGF-IR phosphorylation with an IC_{50} of 0.2 nM (Table 13, methods similar to Example 6). The optimized IGF-IR and EGFR single-domain ^{10}Fn3-based binders were >95% monomeric based on size exclusion chromatography, had melting temperatures >56°C (Table 13, methods similar to Example 4), and exhibited minimal immunogenic potential as predicted from EpiMatrix (<7 for five out of six loops), a matrix-based algorithm for T-cell epitope mapping (De Groot AS, Moise L (2007) Prediction of immunogenicity for therapeutic proteins: state of the art. Curr Opin Drug Discovery Devel 10:332-340). The ^{10}Fn3-based binders E1, E2, and E3 were selected for further development, and had EGFR binding constants in the range of 0.7 to 10 nM as determined from Biacore assay (Table 13, methods similar to Example 5). EGFR-binding of these ^{10}Fn3-based binders was competitive for EGF binding to EGFR (Table 13) as measured by a displacement assay using Europium labeled EGF (methods similar to Example 10). Similarly, IGF-I binding to IGF-IR was inhibited by I1 (Table 13, methods similar to Example19).

Biophysical Characterization of Bi-Specific ^{10}Fn3-based binders. T_m values of selected E/I ^{10}Fn3-based binders ranged from 49-58°C and their SEC profiles indicated the protein was >90% monomer (Table 14, methods similar to Example 4). Monospecific ^{10}Fn3-based binders and E/I ^{10}Fn3-based binders showed comparable binding affinities, although T_m values decreased slightly when the single domain ^{10}Fn3-based binders were linked together (Tables 13 and 14). To increase serum half life for *in vivo* applications, E/I ^{10}Fn3-based binders were PEGylated with a 40 kDa branched PEG (methods similar to Example 3). PEGylation of E/I ^{10}Fn3-based binders resulted in a 10- to 20-fold reduction of binding affinity relative to the un-PEGylated constructs due to decreased association rate constants but did not decrease T_m. Furthermore, PEGylation did not markedly reduce inhibition of EGFR/IGF-IR phosphorylation in cells. The PEGylated E-I orientation (wherein the EGFR binder is at the N terminus, and IGF1R is at the C terminus) exhibited slightly lower IC_{50} values for the inhibition of EGFR and IGF-IR phosphorylation by ELISA compared to the I-E orientation. While minor differences in the K_D values and biological activity were found between PEGylated E-I orientation, vs the I-E orientation, there were no consistent trends.

Table 13. Properties of Monospecific ^{10}Fn3-based binders Relevant to the Construction of E/I ^{10}Fn3-based binders.

Name	T_m °C	SEC Monomer %	EGFR KD nM	IGF-IR KD nM	A431 pEGFR IC_{50}, nM	A431 pERK IC_{50}, nM	H292 pEGFR IC_{50}, nM	H292 pIGF-IR IC_{50}, nM	Competition EGFR/IGF-IR IC_{50}, nM
E-parent	56	ND	42.5		2580	2370	1148 ± 21	ND	29 ± 12.73
E3	60	>80	3.4	NA	15 ± 8	11 ± 7	22 ± 1	>7000	4.75 ± 1.77
E1	64	>95	9.92	NA	24 ± 7	13 ± 3	9 ± 2	>3400	15.9 ± 2.97
E2	72	>95	0.7	NA	38 ± 15	40 ± 9	31 ± 1	>3400	9.4 ± 3.68
I-parent	ND	ND	NA	1.8	ND	ND	ND	ND	13**
I1	61.5	>95	>6210	0.11	NA	NA	NA	0.2	8**

ND, not done; NA, not applicable; SEC, size exclusion chromatography. *IC_{50} values for EGFR and

ERK phosphorylation levles in A431 cells were determined by In-Cell Western assay (ICW). Phosphorylation levels
of EGFR and IGF-IR in H292 cells were determined by Enzyme-linked immunosorbent assay (ELISA).
** Competition for IGF-IR binding. Standard deviations are from 3 - 6 experiments.

Table 14. Properties of the E/I ^{10}Fn3-based binders.

Name	T_m °C	EGFR K_D nM	IGF-IR K_D nM	H292 pEGFR IC_{50}, nM	H292 pIGF-IR IC_{50}, nM	A431 pERK IC_{50}, nM	A431 pEGFR IC_{50}, nM	EGF-EGFR Competition IC_{50}, nM
E3-GS10-I1	52	0.7	0.1	7	6	12	14	25 ± 6.5
E3-GS10-I1-PEG	52.5	10.4	0.74	10	6	40	42	80.5 ± 12.02
E1-GS10-I1	48	3.8	0.8	30	1	51	36	51
E1-GS10-I1-PEG	49	57.9	2.4	123	4	295	297	396 ± 223
E2-GS10-I1	56	0.5	0.2	8	0.1	20	19	2.1 ± 0.57
E2-GS10-I1-PEG	57.5	10.1	1.17	32	0.3	78	77	56.5 ± 24.5
I1-GS10-E2-PEG	60	3.6	0.46	47	0.8	118	97	128 ± 4.95

T_m measurements are from thermal scanning flurometry. K_D values are from Biacore binding assays using recombinant EGFR or IGF-IR domains adsorbed on the chip. In-Cell Western assays (ICW) were conducted to determine the ability of EI-Tandems to inhibit the phosphorylation of EGFR or ERK in A431 cells. Enzyme-linked immunosorbent assays (ELISA) were used to determine the phosphorylation of EGFR or IGF-IR in H292 cells.

Example 21: Species Cross-Reactivity of E/I ^{10}Fn3-based binders

Pegylated E/I ^{10}Fn3-based binders were analyzed for their binding affinities to EGFR from mouse, rat and monkey using surface plasmon resonance (BIAcore) analysis (methods identical to Example 5). Mouse EGFR was purchased from R&D systems (Minneapolis, MN), rat EGFR was produced in house, and monkey EGFR was purchased from KEMP (Frederick, MD)

As shown in Table 15, all pegylated E/I ^{10}Fn3-based binders bound to mouse, rat and monkey EGFR with low nanomolar affinities indicating that all pegylated E/I binders are cross-reactive with human, mouse, rat and monkey EGFR.

Table 15

Analyte	KD (nM) (mouse EGFR)	KD (nM) (rat EGFR)	KD (nM) (monkey EGFR)
I1-GS10-E105 (pegylated)	2.7	2.9	4.4
I1-GS10-E5 (pegylated)	3.4	3.6	5.1
I1-GS10-E4 (pegylated)	5.5	3.7	3.9
E4-GS10-I1 (pegylated)	6.9	5.6	5.7
E2-GS10-I1 (pegylated)	9.6	9.6	18.0
I1-GS10-E85 (pegylated)	13.9	10.7	7.0

Example 22: Characterization of Additional E/I ^{10}Fn3-based binders

Figure 43 summarizes various characteristics of additional E/I ^{10}Fn3-based binders.

The pegylated E/I ^{10}Fn3-based binders were tested to determine inhibition of EGF induced EGFR and ERK phosphorylation in A431, using methods as previously described in Example 1. Results demonstrated that the pegylated E/I ^{10}Fn3-based binders inhibited EGF induced EGFR phosphorylation with IC50's ranging from 12 nM -297 nM and phosphorylation of ERK with IC50's ranging from 12 nM -295 nM (Figure 43, columns a and b).

The ability of the pegylated E/I ^{10}Fn3-based binders to inhibit IGFR and EGFR activity was also examined in H292 cells using methods previously described in Examples 6 and 7. Results indicated that the pegylated E/I ^{10}Fn3-based binders inhibited IGFR activity with IC50's ranging from 0.2 nM – 6 nM (Figure 43, column d) and inhibited EGFR activity with IC50's ranging from 1.3 nM – 123 nM (Figure 43, columns c).

The pegylated E/I ^{10}Fn3-based binders were tested to determine if they could induce degradation of EGFR and IGFR in Difi cells as shown in columns e and f of Table 16. Cells were treated with 1uM of pegylated E/I ^{10}Fn3-based binders and

harvested at time points starting at 7 hrs and ending at 120 hrs and levels of EGFR and IGF1R were determine by Western blot analysis. The strength of degradation was scored as either (+) indicating the tandem degraded that receptor but the degrdation was not sustained and receptor expression reappeared during the time course or (++) which indicates the tandem degraded the receptor and sustained that degradation throughout the time course. Results (Figure 43, column e and f) demonstrated that the pegylated E/I ^{10}Fn3-based binders displayed various patterns of EGFR and IGF1R degradation; degradation of only IGFR, degradation of both EGFR and IGFR or no degradation of either receptor. No tandem tested displayed the ability to degrade only EGFR.

The binding affinity of the pegylated E/I ^{10}Fn3-based binders for EGFR and IGF1R was assessed by surface Plasmon resonance (BIAcore) analysis as previously described in Example 5. Results demonstrated that the pegylated E/I ^{10}Fn3-based binders bound to EGFR with affinities ranging between 3.35 nM- 57.9 nM and bound to IGF1R with affinities ranging between 0.37 nM- 2.43 nM (Figure 43, columns g and h).

The pegylated E/I ^{10}Fn3-based binders were tested to determine their potency for blocking EGF binding to EGFR on the surface of A431 cells using methods previously described in Example 10. The the pegylated E/I ^{10}Fn3-based binders blocked EGF binding to A431 cells with IC50's ranging from 19.5 nM to 238nM (Figure 43, column i).

The pegylated E/I ^{10}Fn3-based binders were assessed for their ability to inhibit colony formation of H292 cells using methods described in Example 17. As shown in Figure 43, column j, the pegylated E/I ^{10}Fn3-based binders inhibited colony formation with IC50 values ranging from 1 nM – 560 nM and three of the four pegylated E/I ^{10}Fn3-based binders tested were 23-140 fold more potent than the anti-EGFR monoclonal antibody panitumumab. The fourth pegylated E/I ^{10}Fn3-based binders was 4 fold less potent than panitumuab. The pegylated I1 monomer was only marginally active in inhibiting colony formation in H292 with an IC50 >15uM and this is expected since H292 cell growth is predominantly driven by EGFR signaling and not IGF1R signaling.

The melting temperature was assessed for pegylated E/I ^{10}Fn3-based binders by DSC (as previously described in Example 4) or thermal dye melt methodology. For thermal dye melt assessment, the pegylated E/I ^{10}Fn3-based binders were diluted to 0.2 mg/mL in 50mM NaAc buffer pH 4.5. Each sample was spiked with 1uL of the 200x Sypro Orange in DMSO buffer for a final concentration of 0.5% dye. Each sample was loaded into the 96 well tray and coated with 5uL of silicone oil. The tray was spun down at 1,000 RPM and loaded onto the Bio-Rad CFX96 system and the following method was selected: 25°C for 10 minutes + Plate Read 25°C to 95°C @ 0.5°C increments for 15 minutes + Plate Read. Data analysis was performed for the inflection point with the CFX software. As shown in Figure 43, column k, all pegylated E/I ^{10}Fn3-based binders had similar Tm measurements, ranging from 49-62.5 degrees celsius. Tm measurements for the pegylated E/I ^{10}Fn3-based binders were independent of concentration and remained consistent at all concentrations tested. DSC analysis of an exemplary binder, I1-GS10-E5 pegylated, measured with a scan range of 15-95°C at 1mg/ml protein concentration in PBS, resulted in a Tm measurement of 55.2°C as shown in Figure 20.

Size exclusion chromatography (SEC) was performed on the pegylated E/I ^{10}Fn3-based binders as previously described in Example 4. SEC analysis revealed that all of the pegylated E/I ^{10}Fn3-based binders were >95% monomeric as shown in Figure 43 (column l of Table).

Example 23: Biochemical and biophysical properties of E/I ^{10}Fn3-based binder I1-GS10-E5 pegylated with selected amino acid changes

I1-GS10-E5 pegylated was constructed without the 6HIS tag (SEQ ID NO: 487) and also with various alterations to the linker region. In addition, a global change was made to all the constructs wherein the C-terminal tail of the first monomer had a single point change of the aspartic acid to glutamic acid (D to an E). Several clones were made with selected serine residues mutated to cysteines (S to C) to provide for alternate PEGylation sites. The effect of these changes on biochemical and biophysical properties of the molecule were compared and are summarized in Table 17. Methods for measuring inhibition of pEGFR are described in Example 7, pIGFR in Example 6, pERK in Example 1, Tm in Example 4, EGFR

and IGFR KD in Example 5. Detailed analysis of the binding kinetics were also carried out on these clones and are presented in Tables 18 and 19 (using methods similar to those described in Example 5).

Table 17.

CLONE NAME	pEGFR IC50 (nM)	pIGFR IC50 (nM)	pERK IC50 (nM)	Tm (°C)	EGFR KD (nM)	IGFR KD (nM)	SEC % mono
I1-GS10-E5 pegylated	28	2.2	12	56	2.7	0.25	96
I1-GS10-E5 pegylated(1)	30	1.2	11	56.8	Sticky(9)	0.23	94.1
I1-GSGCGS8-E5(3)	19.8	1.4	8	54.8	4	0.29	95.2
I1-GS10-E5-GSGC(4)	28.7	1.2	19	55	1.4	0.25	92.7
I1 (S62C)-GS10-E5(5)	21	1.9	10	55.5	8.7	0.7	97.45
I1-GS10-E5 (S62C) (6)	68.4	2.2	30	56	1.7	0.26	96.12
I1 (S91C)-GS10-E5(7)	22.7	6.2	15	52	17	7.16	95.98
I1-GS10-E5(S91C)(8)	22.6	2.1	29	50.5	17.9	0.28	93.39

(1) No His Tag was used for this construct. (2) a global change was made to all the alternative constructs of I1-GS10-E5 pegylated, wherein the C-terminal tail of the first monomer had a single point change of aspartic acid to glutamic acid (D to an E). (3) The I1 mononer linked with GSGC (SEQ ID NO: 489) plus GS8 (SEQ ID NO: 494), to E5. (4) I1 linked with GS10 to E5 with GSGC (SEQ ID NO: 489) at the tail of E5. (5) I1 linked with GS10 to E5, wherein the I1 has a single point change of serine to cysteine at position 62. (6) I1 linked with GS10 to E5, wherein the E5 has a single point change of serine to cysteine at position 62. (7) I1 linked with GS10 to E5, wherein the I1 has a single point change of serine to cysteine at position 91. (8) I1 linked with GS10 to E5, wherein the E5 has a single point change of serine to cysteine at position 91. (9) This construct demonstrated non-specific binding to the flow cell so an accurate determination of affinity was not possible in this experiment.

Table 18. Biacore binding of altered I1-GS10-E5 Pegylated clones to EGFR645-Fc.

Description	ka (1/Ms)	kd (1/s)	Kd (nm)	Δka (fold)	Δkd (fold)	ΔKd (fold)
I1-GS10-E5 Pegylated	2.93 ± 0.67 E+04	7.24 ± 3.14 E-05	2.69 ± 1.53	---	---	---
I1-GS10-E5 pegylated	2.27E+04	1.49E-04	6.6	0.8	0.5	0.4
I1-GS10-E5 pegylated(1)	Non-specific binding to reference cell surface at higher analyte concentrations (600nM, 200nM prohibited kinetic value determination)					
ALTERNATIVE CLONES(2)						
I1-GSGCGS8-E5(3)	2.94E+04	1.18E-04	4.0	1.0	0.6	0.7

I1-GS10-E5-GSGC[4]	3.34E+04	4.52E-05	1.4	1.1	1.6	2.0
I1(S62C)-GS10-E5[5]	2.28E+04	1.99E-04	8.7	0.8	0.4	0.3
I1-GS10-E5(S62C)[6]	1.78E+04	3.04E-05	1.7	0.6	2.4	1.6
I1(S91C)-GS10-E5[7]	1.96E+04	3.34E-04	17.0	0.7	0.2	0.2
I1-GS10-E5(S91C)[8]	1.08E+04	1.93E-04	17.9	0.4	0.4	0.2

(1) No His Tag was used for this construct. (2) a global change was made to all the alternative constructs of I1-GS10-E5 pegylated, wherein the C-terminal tail of the first monomer had a single point change of aspartic acid to glutamic acid (D to an E). (3) The I1 mononer linked with GSGC (SEQ ID NO: 489) plus GS8 (SEQ ID NO: 494), to E5. (4) I1 linked with GS10 to E5 with GSGC (SEQ ID NO: 489) at the tail of E5. (5) I1 linked with GS10 to E5, wherein the I1 has a single point change of serine to cysteine at position 62. (6) I1 linked with GS10 to E5, wherein the E5 has a single point change of serine to cysteine at position 62. (7) I1 linked with GS10 to E5, wherein the I1 has a single point change of serine to cysteine at position 91. (8) I1 linked with GS10 to E5, wherein the E5 has a single point change of serine to cysteine at position 91.

Table 19. Biacore binding of altered I1-GS10-E5 Pegylated clones to IGF1R-Fc.

Description	ka (1/Ms)	kd (1/s)	Kd (nm)	Δka (fold)	Δkd (fold)	ΔKd (fold)
I1-GS10-E5 pegylated	1.04 ± 0.04 E+06	2.62 ± 0.21 E-04	0.25 ± 0.01	---	---	---
I1-GS10-E5 pegylated	1.10E+06	2.78E-04	0.25	1.1	0.9	1.0
I1-GS10-E5 pegylated[1]	1.28E+06, 1.22E+06	2.88E-04, 2.76E-04	0.22, 0.23	1.2	0.9	1.1
ALTERNATIVE CLONES[2]						
I1-GSGCGS8-E5[3]	8.52E+05	2.45E-04	0.29	0.8	1.1	0.9
I1-GS10-E5-GSGC[4]	1.07E+06	2.65E-04	0.25	1.0	1.0	1.0
I1(S62C)-GS10-E5[5]	3.34E+05	2.34E-04	0.70	0.3	1.1	0.4
I1-GS10-E5(S62C)[6]	1.07E+06	2.79E-04	0.26	1.0	0.9	1.0
I1(S91C)-GS10-E5[7]	8.22E+04	5.89E-04	7.16	0.1	0.4	0.04
I1-GS10-E5(S91C)[8]	9.86E+05	2.81E-04	0.28	0.9	0.9	0.9

(1) No His Tag was used for this construct. (2) a global change was made to all the alternative constructs of I1-GS10-E5 pegylated, wherein the C-terminal tail of the first monomer had a single point change of aspartic acid to glutamic acid (D to an E). (3) The I1 mononer linked with GSGC (SEQ ID NO: 489) plus GS8 (SEQ ID NO: 494), to E5. (4) I1 linked with GS10 to E5 with GSGC (SEQ ID NO: 489) at the tail of E5. (5) I1 linked with GS10 to E5, wherein the I1 has a single point change of serine to cysteine at position 62. (6) I1 linked with GS10 to E5, wherein the E5 has a single point change of serine to cysteine at position 62. (7) I1 linked with GS10 to E5, wherein the I1 has a single point change of serine to cysteine at position 91. (8) I1 linked with GS10 to E5, wherein the E5 has a single point change of serine to cysteine at position 91.

Example 24: Inhibition of shared downstream signaling pathways of EGFR and IGFR

Inhibition of downstream signaling pathways were analyzed with a pAKT ELISA identical to those previously described in Example 8. Results of this study demonstrate that I1-GS10-E5 pegylated is more potent than I1 pegylated alone at

blocking IGF1-stimulated AKT activation in H292 cells. E5 pegylated, the EGFR monospecific binder alone did not efficiently prevent activation of AKT by IGF1 stimulation (Figure 21).

Example 25: Inhibition of cell proliferation by ^{10}Fn3-based binders and comparator antibody

H292 and RH41 cell proliferation experiments were conducted as described in Example 9. The EGFR monospecific ^{10}Fn3-based binder E5-pegylated inhibited proliferation of H292 cells with an IC50 value of 0.016 μM. The IGFR monospecific ^{10}Fn3-based binder I1-pegylated had an IC50 value of >8.4 μM while the E/I ^{10}Fn3-based binder I1-GS10-E5 pegylated was slightly more potent with an IC50 value of 0.006 μM (Figure 22). The H292 cell line is of lung cancer origin and sensitive to inhibition of IGFR and EGFR ((Akashi Y, et al. (2008) Enhancement of the antitumor activity of ionising radiation by nimotuzumab, a humanised monoclonal antibody to the epidermal growth factor receptor, in non-small cell lung cancer cell lines of differing epidermal growth factor receptor status. Br. J. Cancer 98:749-755; and Buck E, et al. (2008) Feedback mechanisms promote cooperativity for small molecule inhibitors of epidermal and insulin-like growth factor receptors. Cancer Res. 68:8322-8332.)) In contrast, only the I1-GS10-E5 pegylated binder and the I1-pegylated binder inhibited the proliferation of RH41 cells (IC50 values were 0.0002 and 0.0004 μM, respectively, Figure 23). This was expected, since RH41 is a pediatric rhabdomyosarcoma cell line that is known to be driven predominantly by IGFR signaling ((Huang F, et al. (2009). The mechanisms of differential sensitivity to an insulin-like growth factor-1 receptor inhibitor (BMS-536924) and rationale for combining with EGFR/HER2 inhibitors. Cancer Res. 69:161-170)) and thus not sensitive to EGFR blockade.

Example 26: Inhibition of receptor activation and downstream signaling in vitro by pegylated and non-pegylated ^{10}Fn3-based binders

In order to understand the dynamics of EGFR/IGFR signaling and its inhibition by I1-GS10-E5 pegylated, DiFi, H292 or BxPC3 cells were serum-starved, exposed to 1 μM or 0.1 μM E5 pegylated, I1 pegylated, or I1-GS10-E5

pegylated, or vehicle control for 2 hours, then stimulated with either EGF, IGF-I, or EGF + IGF-I for 10 min.

Cells were cultured in vitro, serum starved overnight and then exposed to ^{10}Fn3-based binders for 2 hours prior to stimulation with 100ng/ml of EGF or IGF. Cell lysates were prepared in lysis buffer (1% Triton X-100, 5% glycerol, 0.15 M NaCl, 20 mM Tris-HCl pH 7.6, Complete Protease Inhibitor Cocktail Tablets [Roche, Indianapolis, IN] and Phosphatase Inhibitor Cocktail 2 [Sigma-Aldrich Corp.]). Lysates (30 μg) were resolved by SDS-PAGE, transferred to membranes, and immunoblotted with antibodies to phospho-EGFR and total EGFR (Santa Cruz Biotechnology, Carlsbad, CA), phospho-AKT (Ser 473), phospho-p44/42 MAPK (Thr202/Tyr204) (Cell Signaling Technology, Beverly, MA), or total actin (Chemicon International, Temecula, CA) in Odyssey Blocking Buffer with 0.1% Tween 20 (LI-COR Biosciences, Lincoln, NE). Membranes were incubated with the appropriate secondary antibodies. Protein visualization was performed using a LI-COR Biosciences Odyssey infrared imaging system.

As shown in Figure 24, the basal levels of phosphorylated EGFR, IGF-IR, and AKT were nearly undetectable after serum deprivation. In DiFi cells, neither I1-GS10-E5 pegylated or E5 pegylated (monospecific EGFR binder) are able to completely suppress EGF-stimulated EGFR phosphorylation. In H292 and BxPC3 cells there is strong inhibition of EGFR phosphorylation by both I1-GS10-E5 pegylated and E5 pegylated. In DiFi and BxPC3 cells, I1-GS10-E5 pegylated blocks IGF-stimulated IGFR phosphorylation more than I1 pegylated (monospeciific IGFR binder) by itself. In H292 cells, IGF-stimulation cross activates the EGFR only when EGFR is blocked. I1-GS10-E5 pegylated inhibited EGF-stimulated pAKT in DiFi; increased pAKT in EGF-stimulated H292 and in BxPC3 EGF did not activate pAKT. In DiFi, H292 and BxPC3 cells I1-GS10-E5 pegylated inhibited IGF-stimulated pIGFR more than the individual E5 pegylated and I1 pegylated by themselves. I1-GS10-E5 pegylated had very little if any effect on EGF-stimulated pERK in DiFi, H292 or BxPC3. IGF-stimulation did not induce pERK in any cell line examined.

In another experiment with unPEGylated_^{10}Fn3-based binders, H292 cells were serum-starved, exposed to 1 μM unPEGylated monospecific EGFR binder E2,

IGFR binder I1, or E2-GS10-I1, or vehicle control for 1 hour, then stimulated with either EGF, IGF-I, or EGF + IGF-I for 10 min. The basal levels of phosphorylated EGFR, IGFR, and AKT were nearly undetectable after serum deprivation (Figure 25). Stimulation with EGF induced EGFR phosphorylation, but did not transactivate IGFR. EGFR phosphorylation was blocked by the E2, and E2-GS10-I1, but not I1. Similarly, stimulation with IGF-I induced strong phosphorylation of IGFR that was blocked by I1and E2-GS10-I1, but not by E2. EGF stimulation only slightly increased AKT phosphorylation, but IGF-I or EGF + IGF-I strongly induced phosphorylation of AKT that was suppressed to basal levels by both I1 and E2-GS10-I1. The combination of IGF-I and EGF induced AKT phosphorylation more than either growth factor alone. E2 partially reduced pAKT induced by the combination of EGF and IGF-I. However, I1 showed the most dramatic reduction in pAKT, suggesting that stimulation with EGF + IGF-I led to strong AKT phosphorylation through the IGFR pathway. Surprisingly, blockade of the EGFR pathway by E2 followed by stimulation with EGF ligand actually increased the phosphorylation of AKT, perhaps as a result of EGFR-independent activation of AKT ((Dobashi Y, et al. (2009) EGFR-dependent and independent activation of Akt/mTOR cascade in bone and soft tissue tumors. Mod Pathol (Epub Ahead of Print)). These results illustrate the complex cross-talk between the EGFR and IGFR pathways and feed-back mechanisms.

Example 27: Competition binding studies with E/I ^{10}Fn3-based binders

For Biacore competition experiments, EGFR-Fc (3μg/mL in Na-acetate pH 5.0) was immobilized on the Biacore CM5 chip surface using standard EDC/NHS amide coupling chemistry to a surface density of 300 RU. EGFR antibodies were obtained as a marketed drug and competition between monospecific EGFR binder E2 and antibodies for binding to EGFR-Fc was assessed by binding 450 nM E2 (30μL/min, 200s contact time), immediately followed by 450 nM E2 alone, or a mixture of 450 nM E2 plus 450 nM cetuximab, panitumumab, or nimotuzumab (30μL/min, 200 sec contact time). The surface was successfully regenerated between cycles using two 10 sec pulses of 50 mM NaOH at a flow rate of 30μL/min. Initial injection of E2 shows binding to EGFR on the surface of the chip. A second

injection of E2 mixed with an equal amount of cetuximab, panitumumab, or nimotuzumab shows no competition for binding of antibodies to EGFR by E2 (Figure 26A).

Surface plasmon resonance (BIAcore) analysis was utilized to demonstrate simultaneous engagement of captured EGFR-Fc and solution phase IGF1R by E/I ^{10}Fn3-based binders. Recombinant human EGFR-Fc (aa 1-645 of the extracellular domain of human EGFR fused to human Fc) was purchased from R&D systems (Minneapolis, MN). Recombinant IGF1R (aa 1-932 of human IGF1R propeptide, proteolytically cleaved and disulfide linked) was purchased from R&D systems (Minneapolis, MN). To demonstrate simultaneous engagement, anti-human IgG was immobilized on flow cells 1 and 2 of a CM5 chip following the manufacturer's recommendations (GE Healthcare, Piscataway, NJ). EGFR-Fc (50 nM) was captured on flow cell 2 at 10uL/min for 2 minutes. Binding of E/I ^{10}Fn3-based binders to EGFR-Fc was achieved by injecting ^{10}Fn3-based protein samples (100nM) over both flow cells at 10uL/min for 2 minutes. Simultaneous engagement of EGFR-Fc and IGF1R was probed by subsequently injecting IGF1R (0,100nM) over both flow cells at 30uL/min for 2 minutes. Dissociation of the complex was monitored for 300 seconds. Two 30 second injections of 3 M $MgCl_2$ were used for regeneration of the bound complex from the anti-human IgG surface. Biacore T100 Evaluation Software, Version 2.0.1 (GE healthcare/Biacore) was utilized to overlay sensograms and remove airspikes. As shown in Figure 26B, both domains of the E/I ^{10}Fn3-based binder are functional and able to bind to EGFR-Fc and IGF1R simultaneously.

Binding specificity of E2-GS10-I1 pegylated to HER family receptors was assessed by Biacore as described in Example 5. HER-2-Fc, HER-3-Fc and HER-4-Fc (R&D Systems) was captured on the surface of the CM5 chip with anti-human IgG. E2-GS10-I1 pegylated did not show any discernible binding to other HER family members under conditions where robust binding was seen for EGFR-Fc (HER-1) (Table 20).

Table 20. Binding affinity of E2-GS10-I1 pegylated to extracellular domains of HER family of receptors.

Name	EGFR-Fc K_D, nM*	HER-2-Fc K_D, nM	HER-3-Fc K_D, nM	HER-4-Fc K_D, nM
E2-GS10-I1 pegylated	10.1	>1000	>1000	>1000

Example 28: Measurement of plasma biomarkers

Levels of soluble biomarkers TGFα and mIGF1 were measured in mouse plasma at the end of xenograft studies or in non tumor bearing mice at various times following treatment. Blood was obtained by terminal cardiac puncture into tubes containing EDTA as an anticoagulant. Plasma was prepared by centrifuging blood at 1300 xg for 10 minutes at 4 degrees C and removing the clarified supernatant to a separate tube. TGFα levels were measured in 0.1ml of plasma, mIGF1 levels were measured in 0.02 ml plasma with an ELISA assay as recommended by manufacturer (R&D Systems, Minneapolis, MN). Plasma levels of TGFα were increased in mice treated with I1-GS10-E5 pegylated or the monospecific EGFR binder E5 pegylated but not cetuximab (Figure 27A-C). The TGFα could be secreted from the human tumor or may represent endogenous mouse TGFα. Due to the high homology between human and mouse TGFα (93% amino acid identity) the ELISA may cross react with mouse TGFα. Furthermore, human TGFα secreted by the implanted tumor can bind to the mouse EGFR. Because I1-GS10-E5 pegylated and E5 pegylated can bind both human and mouse EGFR, all host and tumor EGFR binding sites are blocked by these ^{10}Fn3-based binders while cetuximab does not bind mouse EGFR. To determine if these ^{10}Fn3-based binders cause increases in endogenouse mouse TGFα and if the ELISA cross reacts with mouse TGFα, non-tumor bearing nude mice were dosed with I1-GS10-E5 pegylated at 100mg/kg and plasma samples were taken at 4, 24, 48, 72 hours post dose. Increases in mouse TGFα were in fact observed that persisted out past 72 hours (Figure 28A). Plasma samples from non-tumored mice were also tested for mIGF1 with a mouse specific ELISA and increases in this ligand were also observed (Figure 28B).

Example 29: Results of *in vivo* human tumor xenograft studies for various E/I ^{10}Fn3-based binders

Several E/I ^{10}Fn3-based binders were evaluated in a head-to-head H292 NSCLC study (methods described in Example 12) at a lower dose than previously used so that differences in relative activity could be ascertained. Efficacy of the E/I ^{10}Fn3-based binders E2-GS10-I1 pegylated, E4-GS10-I1 pegylated, I1-GS10-E5 pegylated, I1-GS10-E85 pegylated, I1-GS10-E4 pegylated, I1-GS10-E105 pegylated at a single dose of 0.625mg/mouse and panitumumab at two doses (1 mg/mouse and 0.1 mg/mouse) were compared.

Both doses of panitumumab and all E/I ^{10}Fn3-based binders evaluated in this study were active by a tumor growth inhibition (TGI) endpoint. During the dosing phase, E4-GS10-I1 pegylated, I1-GS10-E5 pegylated, I1-GS10-E4 pegylated and panitumumab all caused tumor regression (Table 21, TGI values greater than 100%) while E2-GS10-I1 pegylated, I1-GS10-E85 pegylated and I1-GS10-E105 pegylated caused tumor growth inhibition (Table 21, TGI values up to 100%). Differences in activity were statistically significant when compared to the control group. All treatments were well tolerated with no treatment related deaths or excessive weight loss over the course of the study. Comparison of the efficacy of the E/I ^{10}Fn3-based binders and panitumumab are presented in Table 21 below and in Figure 29. In Figure 29A, measurements out to day 43 shows the pattern of regrowth of the tumors after dosing ceased. Figure 29B shows measurements out to day 27 and the y-axis is expanded to illustrate the relative differences in activity among the treatment groups.

Table 21. In vivo antitumor activity in the H292 NSCLC study

Group	Compound	Schedule, Route	Dose (mg/kg)	AVE weight change (g)	%TGI	p value for %TGI	Outcome by %TGI
1	Control (untreated)	---	---	3.36	---	1.0	---
2	panitumumab	q3dx5; 6 ip[a]	1mg/ mse	5.19	107	0.0023	A
3	panitumumab	q3dx5; 6 ip[a]	0.1mg/ mse	5.9	105	0.0029	A

4	E2-GS10-I1 pegylated	TIWX3; 6 ip[a]	0.625mg /mse	-1.4	93	0.0067	A
5	E4-GS10-I1 pegylated	TIWX3; 6 ip[a]	0.625mg /mse	-0.23	105	0.0023	A
6	I1-GS10-E5 pegylated	TIWX3; 6 ip[a]	0.625mg /mse	-2.92	103	0.0033	A
7	I1-GS10-E85 pegylated	TIWX3; 6 ip[a]	0.625mg /mse	1.08	86	0.0114	A
8	I1-GS10-E4 pegylated	TIWX3; 6 ip[a]	0.625mg /mse	-1.21	103	0.0034	A
9	I1-GS10-E105 pegylated	TIWX3; 6 ip[a]	0.625mg /mse	-1.54	95	0.0035	A

[a]Vehicle was phosphate buffered saline. Abbreviations used are as follows: ip, intraperitoneal route; %TGI, relative % tumor growth inhibition calculated as $\%TGI=[(C_t-T_t)/(C_t-C_0)] \times 100$ where C_t=median tumor weight of control mice at time t in days after tumor implant, T_t=median tumor weight of treated mice at time t, C_0= median tumor weight of control mice at time 0. %TGI value was calculated at two points as the average inhibition of Day 20, Day 24 and Day 27. Outcome, a treatment regimen was considered active if it produced a statistically significant %TGI value of >50%; q3dx5;6, compound was administered every three days for six doses starting on the sixth day after tumor implant; 6 on/1 off; 6, compound was administered once a day for 6 days then no treatment for 1 day and this regimen started on the sixth day after tumor implant. p values were calculated on Day 20 relative to the control group in a two tailed paired analysis with 8 measurements per group.

Further in vivo studies were carried out with selected E/I ^{10}Fn3-based binders below, in various xenograft models using the methods described in Example 12. A description of the various xenograft models is as follows: H292 is a non-small cell lung carcinoma (NSCLC) and is described in more detail Example 12; MCF7r breast carcinoma is described in Example 14; and GEO colon carcinoma is described in Example 15. The DiFi human colon carcinoma expresses high levels of activated EGFR and also expresses IGFR; RH41 is a pediatric rhabdomyosarcoma cell line that is known to be driven predominantly by IGFR signaling (Huang F, et al. ((2009)) The mechanisms of differential sensitivity to an insulin-like growth factor-1 receptor inhibitor (BMS-536924) and rationale for combining with EGFR/HER2 inhibitors. Cancer Res. 69:161-170) and thus is not sensitive to EGFR blockade; Cal27 is a human head and neck carcinoma expressing high levels of EGFR and moderate levels of IGFR; BxPC3 is a human pancreatic carcinoma; and H441 is a NSCLC.

Comparison of the efficacy of selected E/I ^{10}Fn3-based binders are presented in Table 22. In these efficacy studies, all of the E/I ^{10}Fn3-based binders showed

equivalent activity to panitumumab and all treatments were able to regress H292 tumors below their starting size as indicated by %TGI values over 100%. In the DiFi study, panitumumab regressed tumors at the 1mg/mouse dose and was active at the 0.1mg/mouse dose while all of the E/I ^{10}Fn3-based binders were inactive although the I1-GS10-E5 pegylated showed some inhibition of tumor growth (TGI = 43.8%). In the RH41 study, panitumumab was not active at either dose, the E2-pegylated construct was not active while the E/I ^{10}Fn3-based binders and the I1-pegylated construct were all active. Figure 32 shows antitumor efficacy in the RH41 model for a representative construct E2-GS10-I1 pegylated (data also shown in Table 23). In the Cal27 study panitumumab regressed tumors at the 1mg/mouse dose and was active at the 0.1mg/mouse dose but among the E/I ^{10}Fn3-based binders only the I1-GS10-E5 pegylated E/I ^{10}Fn3-construct was active.

Results of human tumor xenograft studies with I1-GS10-E5 pegylated and individual I1 and E5 components designed to assess synergy are presented in Table 23. These combination (synergy) studies were structured such that the individual pieces of the E/I ^{10}Fn3-based binders (ie., IGFR and EGFR monospecific pegylated versions) were included so antitumor effects beyond the contribution of isolated ends could be discerned. In the MCF7r study, I1 pegylated was not active while the E5 pegylated, (E5 pegylated + I1 pegylated) and the I1-GS10-E5 pegylated clones were all active and exhibited similar activity meaning that all of the antitumor activity likely comes from inhibition of EGFR and blocking the IGFR pathway did not provide any enhancement. Cetuximab regressed tumors at the 1mg/mouse dose and was not active at the 0.1mg/mouse dose. BMS-754807 was also not active showing that blocking the IGFR pathway with a small molecule inhibitor did not result in efficacy in this model.

In the BxPC3 study, I1 pegylated was not active while the E5 pegylated and (E5 pegylated + I1 pegylated) clones were active (TGI = 61.2% and 68.8%, respectively). The I1-GS10-E5 pegylated clone was more active (TGI = 78%) than the individual pieces it is made from and the difference was statistically significant by a two tailed paired t-test showing that it has synergistic activity in this model. Cetuximab was active at all doses studied but adding in IGFR inhibition by combining it with the I1-pegylated did not result in synergy.

In the GEO study, I1 pegylated was not active while the E5 pegylated and (E5 pegylated + I1 pegylated) and I1-GS10-E5 pegylated clones were active (TGI = 83.5%, 92.1 and 92.1%, respectively). While there may have been some enhancement provided by combining EGFR and IGFR inhibition together in this model, the difference was not significantly better than the E5 pegylated by itself. Cetuximab was active at both doses studied but adding in IGFR inhibition by combining it with the I1-pegylated did not result in synergy.

In the H441 study, I1 pegylated and E5 pegylated were not active on their own but (E5 pegylated + I1 pegylated) was active (TGI = 54.5%). The I1-GS10-E5 pegylated clone was more active (TGI = 69.2%) than the individual pieces it is made from but the differences were not statistically significant showing that it provides enhanced activity but not synergy in this model. Cetuximab was active at the 1mg/mouse dose and was not active at the 0.1mg/mouse dose. Adding in IGFR inhibition by combining it with the I1-pegylated did not result in any enhancement in this model.

Table 22. In vivo results of selected E/I ^{10}Fn3-based binders

Group	Compound	Schedule	Dose (mg/kg)[a]	AVE weight change (g)	%TGI	p value for %TGI	Outcome by %TGI
In vivo antitumor activity in the H292 study							
1	Control (untreated)	---	---	5.7	---	1.0	---
2	panitumumab	Q3dx5;6 ip[a]	1mg/mse	5.0	104	0.0006	A
3	panitumumab	Q3dx5;6 ip[a]	0.1mg/mse	1.5	102	0.0005	A
4	E4-GS10-I1 pegylated	TIWX3;6	2mg/mse	-4.86	105	0.0004	A
5	I1-GS10-E5 pegylated	TIWX3;6	2mg/mse	-10.0	102	0.0006	A
6	I1-GS10-E4 pegylated	TIWX3;6	2mg/mse	-1.41	105	0.0005	A
In vivo antitumor activity in the DiFi study							
1	Control (untreated)	---	---	-0.5	---	1.0	---
2	panitumumab	Q3dx5;6 ip[a]	1mg/mse	5.3	109.7	0.006	A
3	panitumumab	Q3dx5;6 ip[a]	0.1mg/mse	2.6	99.9	0.005	A
4	E4-GS10-I1 pegylated	TIWX3;6	3mg/mse	-10.8	-1.1	0.815	I
5	I1-GS10-E5 pegylated	TIWX3;6	3mg/mse	-16.4	43.8	0.310	I
6	I1-GS10-E4 pegylated	TIWX3;6	3mg/mse	-8.5	1.4	0.977	I
In vivo antitumor activity in the RH41study							
1	Control (untreated)	---	---	7.2	---	1.0	---
2	panitumumab	q3dx5;6 ip[a]	1mg/mse	10.7	16.5	0.721	I
3	panitumumab	q3dx5;6 ip[a]	0.1mg/mse	8.6	38.4	0.563	I
4	E4-GS10-I1 pegylated	TIWX3;6	2.5mg/mse	-5.3	72.7	0.02	A
5	I1-GS10-E5 pegylated	TIWX3;6	2.5mg/mse	-7.8	68	0.019	A
6	I1-GS10-E4 pegylated	TIWX3;6	2.5mg/mse	-2.9	64.5	0.018	A
7	Control (untreated)	---	---	12.3	---	1.0	---
8	E2-GS10-I1 pegylated	TIWX3;18	2.5mg/mse	-1.8	58.6	0.044	A
9	E2-pegylated	TIWX3;18	1.25mg/mse	5.9	20.2	0.530	I
10	I1 pegylated	TIWX3;18	1.25mg/mse	7.1	58.6	0.025	A
In vivo antitumor activity in the Cal27 study							

Group	Compound	Schedule	Dose (mg/kg)[a]	AVE weight change (g)	%TGI	p value for %TGI	Outcome by %TGI
1	Control (untreated)	---	---	9.4	---	1.0	---
2	Panitumumab	q3dx5;6 ip[a]	1mg/mse	6.1	109.8	0.0006	A
3	panitumumab	q3dx5;6 ip[a]	0.1mg/mse	5.8	72.9	0.003	A
4	E4-GS10-I1 pegylated	TIWX3;6	2mg/mse	-1.2	-11.4	0.587	I
5	I1-GS10-E5 pegylated	TIWX3;6	2mg/mse	-11.6	57.6	0.037	A
6	I1-GS10-E4 pegylated	TIWX3;6	2mg/mse	-2.2	-9.2	0.177	I

[a]Vehicle was phosphate buffered saline for all treatments. Abbreviations used are as follows: ip, intraperitoneal route; po, oral route; %TGI, relative % tumor growth inhibition calculated as %TGI=[(Ct-Tt)/(Ct-C0)] x 100 where Ct=median tumor weight of control mice at time t in days after tumor implant, Tt=median tumor weight of treated mice at time t, C0= median tumor weight of control mice at time 0. %TGI value was calculated at two points as the average inhibition on Day 19 and 23 for H292, Day 39 and 41 for DiFi, Day 34 and 37 for RH41 for groups 1-6 and Day 35, 36 and 39 for groups 7-10, Day 18 and 20 for Cal27. Outcome, a treatment regimen was considered active if it produced a statistically significant %TGI value of >50%; q3dx5;6, compound was administered every three days for six doses starting on the sixth day after tumor implant; TIWX3;6, compound was administered three times a week for 3 weeks and this regimen started on the sixth day after tumor implant. p values were calculated relative to the control group in a two tailed paired analysis with 8 measurements per group on Day 23 for H292, Day 39 for DiFi, Day 37 for RH41 for groups 1-6 and Day 39 for groups 7-10 and Day 20 for Cal27.

Table 23. Summary of in vivo experiments with ^{10}Fn3-based binders and comparators

Group	Compound	Schedule	Dose (mg/kg)[a]	AVE weight change (g)	%TGI	p value for %TGI	Outcome by %TGI
In vivo antitumor activity in the MCF7r study							
1	Control (untreated)	---	---	6.1	---	1.0	---
2	I1 pegylated[a]	TIWX3;7	50mg/kg, ip	17.1	-40.8	0.195	I
3	E5 pegylated[a]	TIWX3;7	50mg/kg, ip	5.1	75.8	0.007	A
4	E5 pegylated[a] + I1 pegylated[a]	TIWX3;7	50mg/kg, ip	-3.0	81.8	<0.0001	A
5	I1-GS10-E5 pegylated[a]	TIWX3;7	100mg/kg, ip	-4.5	78	0.009	A
6	cetuximab[a]	Q3DX5;7	1mg/mse, ip	11.7	105.4	0.0009	A
7	cetuximab[a]	Q3DX5;7	0.1mg/mse, ip	7.5	34.3	0.031	I
8	BMS-754807[b]	QDX14;7	50mg/kg, po	-4.0	44.5	0.146	I
In vivo antitumor activity in the BxPC3 study							
1	Control (untreated)	---	---	3.1	---	1.0	---
2	I1 pegylated	TIWX3;9	50mg/kg, ip	4.3	14.3	0.315	I
3	E5 pegylated	TIWX3;9	50mg/kg, ip	-5.3	61.2	0.0003	A
4	E5 pegylated + I1 pegylated	TIWX3;9	50mg/kg, ip	-4.9	68.8	0.0019	A
5	I1-GS10-E5 pegylated	TIWX3;9	100mg/kg, ip	-14.0	78.0	0.0002	A
6	cetuximab	Q3DX5;9	1mg/mse, ip	5.2	62.6	0.0026	A
7	cetuximab	Q3DX5;9	0.25mg/mse, ip	2.5	62.8	0.0005	A
8	Cetuximab +I1 pegylated	Q3DX5;9 TIWX3;9	1mg/mse, ip 50mg/kg, ip	3.6	62.1	0.0005	A
In vivo antitumor activity in the GEO study							
1	Control (untreated)	---	---	7.5	---	1.0	---
2	I1 pegylated	TIWX3;9	50mg/kg, ip	-7.2	26.8	0.594	I
3	E5 pegylated	TIWX3;9	50mg/kg, ip	9.7	83.5	0.0028	A
4	E5 pegylated + I1 pegylated	TIWX3;9	50mg/kg, ip	5.4	92.1	0.0005	A

Group	Compound	Schedule	Dose (mg/kg)[a]	AVE weight change (g)	%TGI	p value for %TGI	Outcome by %TGI
5	I1-GS10-E5 pegylated	TIWX3;9	100mg/kg, ip	-7.3	92.1	0.0006	A
6	cetuximab	Q3DX5;9	1mg/mse, ip	7.7	91.8	0.0008	A
7	cetuximab	Q3DX5;9	0.25mg/mse, ip	7.8	92.0	0.0007	A
8	Cetuximab + I1 pegylated	Q3DX5;9 TIWX3;9	1mg/mse, ip 50mg/kg, ip	7.1	91.3	0.0006	A
In vivo antitumor activity in the H441 study							
1	Control (untreated)	---	---	12.4	---	1.0	---
2	I1 pegylated	TIWX3;9	50mg/kg, ip	11.5	30.8	0.701	I
3	E5 pegylated	TIWX3;9	50mg/kg, ip	-8.8	43.1	0.292	I
4	E5 pegyalted + I1 pegylated	TIWX3;9	50mg/kg, ip	-0.8	54.5	0.011	A
5	I1-GS10-E5 pegylated	TIWX3;9	100mg/kg, ip	-3.9	69.2	0.022	A
6	cetuximab	Q3DX5;9	1mg/mse, ip	12.6	65.2	0.002	A
7	cetuximab	Q3DX5;9	0.25mg/mse, ip	13.7	43.9	0.110	I
8	cetuximab +I1 pegylated	Q3DX5;9 TIWX3;9	1mg/mse, ip 50mg/kg, ip	10.2	66.7	0.060	I

[a]Vehicle was phosphate buffered saline for all treatments. Abbreviations used are as follows: ip, intraperitoneal route; po, oral route; %TGI, relative % tumor growth inhibition calculated as %TGI=[(Ct-Tt)/(Ct-C0)] x 100 where Ct=median tumor weight of control mice at time t in days after tumor implant, Tt=median tumor weight of treated mice at time t, C0= median tumor weight of control mice at time 0. %TGI value was calculated at two points as the average inhibition on Day 22 and 26 for MCF7r, Day 23 and 27 for BxPC3, Day 29 and 31 for GEO and Day 17 and for H441. Outcome, a treatment regimen was considered active if it produced a statistically significant %TGI value of >50%; q3dx5;6, compound was administered every three days for six doses starting on the sixth day after tumor implant; TIWX3;6, compound was administered three times a week for 3 weeks and this regimen started on the sixth day after tumor implant. p values were calculated relative to the control group in a two tailed paired analysis with 8 measurements per group on Day 26 for MCF7r, Day 27 for BxPC3, Day 29 for GEO and Day17 for H441.

Example 30: Pharmacokinetic profile of various E/I ^{10}Fn3-based binders in mice

The pharmacokinetic profiles of the pegylated E/I ^{10}Fn3-based binder, E2-GS10-I1, were assessed in mice via intraperitoneal injection. Three nude mice per dose group were dosed with E2-GS10-I1, formulated in PBS, at 10 and 100 mg/kg, ip and plasma samples were collected in citrate phosphate dextrose solution at pre dosing, 0.5, 2, 4, 8, 12, 24, 48, 72, 96, 144, and 168 hours post dosing. Plasma samples were assessed for pegylated E2-GS10-I1 Fn3-based binder levels using a quantitative electrochemiluminescence (ECL) assay developed to detect and quantitate the pegylated E/I ^{10}Fn3-based binder in plasma samples. In this assay, a mouse monoclonal antibody with specificity toward the EGFR binding region was adsorbed to Meso Scale Discovery plates overnight at 4°C to allow capture of the pegylated E/I ^{10}Fn3-based binder in the plasma samples. The plasma samples were added to the plates and incubated at 22°C for 1 h. The captured pegylated E/I ^{10}Fn3-based binder was detected by a rabbit polyclonal antibody specific to the scaffold region of the E/I ^{10}Fn3-based binder, mixed with a goat anti-rabbit antibody linked with a SULFO-TAG. Following a wash to remove unbound SULFO-TAG reagent, a read buffer was added and ECL detection was used. The level of pegylated E2-GS10-I1 in plasma samples was calculated based on comparison to a 4-parameter fit of a standard curve of the pegylated E2-GS10-I1 Fn3-based binder.

Mice administered 10 or 100 mg/kg interperitoneally (ip) of pegylated E2-GS10-I1 resulted in peak levels of approximately 200 and 1700 μg/mL, respectively, indicating dose-proportional pharmacokinetics (Figure 30). Pharmacokinetic parameters for Figure 30 were calculated in a similar fashion to those described in the paragraph below (note that "T 1/2" is interchangeable with "HL_lambda_z"and AUC is interchangeable with "AUCINF_obs". The half-life of pegylated E2-GS10-I1 in mice was 15.75 ± 1.52 h (Figure 30). Based on these pharmacokinetic parameters, administration of 100 mg/kg three times weekly (TIW) in human tumor xenograft studies was able to maintain drug levels 10- to 100-fold higher than the in vitro IC50 value.

Additional pharmacokinetic experiments were conducted on several pegylated E/I ^{10}Fn3-based binders, where mice were administered 10 or 100 mg/kg

interperitoneally (ip) and, for the pegylated I1-GS10-E5, 10 or 64 mg/kg sub-cutaneously (sc), plasma was collected and analyzed as described above to measure the levels of pegylated E/I ^{10}Fn3-based binders. The pharmacokinetic parameters of these various E/I ^{10}Fn3-based binders were obtained by non-compartmental analysis of plasma (serum) concentration vs. time data. WinNonlin software (version 5.1, Pharsight Corp. Mountain View CA) was used to calculate the terminal half-life (HL_lambda_z), maximum observed concentration (Cmax), the area under the curve from time zero extrapolated to infinity (AUCINF_obs), clearance (CL_F_obs), volume of distribution based on the terminal phase (Vz_F_obs) and the mean residence time extrapolated to infinity (MRTINF_obs). Results showed that the half life for the pegylated E/I ^{10}Fn3-based binders were between 12.1-20.9 hours, as shown in Figure 44 and Figure 31.

Example 31: Pharmacodynamics

Samples were taken from the H292 and the DiFi xenograft models described in Table 22 at the end of the study and processed as outlined under *Measurement of pharmacodynamic endpoints in tumors* in Example 12 for analysis of total levels of EGFR and IGFR protein and phosphorylated EGFR and IGFR. Target effects of I1-GS10-E5-pegylated and panitumumab were evaluated by immunoblotting as described in Example 11. In Figure 33A, levels of total EGFR, pEGFR and total IGFR were lower in I1-GS10-E5-pegylated treated tumors than in untreated tumors at the end of the DiFi xenograft model. In Figure 33B, levels of pEGFR were lower in tumors treated with panitumumab and I1-GS10-E5-pegylated. Levels of total EGFR were lower only in I1-GS10-E5-pegylated treated tumors but not in panitumumab treated tumors. Levels of total IGFR were lower in both I1-GS10-E5-pegylated treated tumors and in one panitumumab treated tumor but not the other. The amount of pIGFR in these models was too low to detect differences following treatment. Immunoblots were probed with GAPDH to demonstrate equal loading of protein.

Example 32: EGFR ^{10}Fn3-based binders Optimization and Consensus Sequence Analysis

The ^{10}Fn3-based binder 679F09 (as described in PCT WO 2009/102421) (Figure 34) was identified as a binder to EGFR ectodomain-Fc fusion protein (R&D Systems). Binding activity was selected using a bead coated with EGFR-Fc and ^{10}Fn3-based binders coupled to their nucleic acid coding sequence (see e.g., Xu et al., Directed Evolution of High-Affinity Antibody Mimics Using MRNA Display, Chem. Biol. 9: 933-942 (2002)). More potent variants of the parental EGFR binder 679F09 having alterations to the amino acid sequences in the BC, DE and FG loops were also identified.

Sequence Analysis I: All ^{10}Fn3-based binders selected for high-affinity binding to EGFR

In order to reveal sequence patterns that defined strong affinity for EGFR, all unique EGFR binding sequences (1044) were analyzed using several methods. First, the sequences were analyzed by the frequency of amino acids at each position in the loops (Figures 35-38). Only unique sequences for each loop were analyzed.

From the above sequence analysis, the following broad sequence motif was defined:

Sequence Motif #1

(a) BC loop: "YQ" in positions 7-8 (i.e., corresponding to positions 29 and 30 of SEQ ID NO: 1)

(b) DE loop: aliphatic residue ("V/I/L/M/A") in position 3 (i.e., corresponding to position 54 of SEQ ID NO: 1)

(c) FG loop: "D/N" in position 1 (i.e., corresponding to position 77 of SEQ ID NO: 1)

All 1044 sequences analyzed, except one, follow the FG loop sequence pattern (c). Of all unique sequences analyzed, 90% follow pattern (a) for the BC loop, and 95% follow pattern (b) for the DE loop. All sequences analyzed, except four, follow at least two of the three patterns above. In addition, the 15-amino acid FG loop length is a noteworthy sequence feature.

In addition to the broad Sequence Motif #1 defined above, the data in Figures 35-38 were used to define a second sequence motif based on the dominant residues at each position. Residues were included in this motif if the sum of the top 3 most frequent amino acids had a greater than 50% frequency.

Sequence Motif #2

(a) BC loop: XXXXXXYQ (same as Motif #1), wherein X is any amino acid

(b) DE loop: (G/Y/H)(D/M/G)(V/L/I)X, wherein X is any amino acid

(c) FG loop, 10 amino acid length:
(D/N)(Y/M)(Y/A/M)(Y/H/F)(K/Q/V)(E/P/R)(Y/T/K)X(E/Y/Q)(Y/G/H), wherein X is any amino acid

(d) FG loop, 15 amino acid length:
D(Y/F/W)(Y/F/K)(N/D/P)(P/H/L)(A/T/V)(T/D/S)(H/Y/G)(E/P/V)(Y/H)(T/K/I)(Y/F)(H/N/Q)(T/Q/E)(T/S/I)

The analysis methods used to define Sequence Motifs #1 and #2 evaluate each residue position within a loop separately. To reveal any sequence motifs spanning multiple residues within a loop, the ^{10}Fn3-based binders were subjected to further analysis. In this analysis, the loop sequences were aligned using ClustalW (Thompson JD *et al.* CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice. *Nucleic Acids Research* **22**: 4673–4680, 1994). From this alignment, families of sequences were grouped using manual inspection. For the BC and DE loops, sequence patterns similar to Sequence Motifs #1 and #2 were observed. However, additional sequence motifs could be defined for the 10 and 15 amino acid long FG loops.

Sequence Motif #3

(a) FG loop, 10 amino acid length

(1) DY(A/Y)GKPYXEY (SEQ ID NO: 473), wherein X is any amino acid

(2) DY(A/Y)Y(K/R/Q/T)PYXEY (SEQ ID NO: 474), wherein X is any amino acid

(3) (D/N)Y(A/Y)(Y/F)(K/R/Q/T)EYXE(Y/H) (SEQ ID NO: 475), wherein X is any amino acid

(4) DYY(H/Y)X(R/K)X(E/T)YX (SEQ ID NO: 476), wherein X is any amino acid

(5) DYY(H/Y)(K/H/Q)(R/K)T(E/T)Y(G/P) (SEQ ID NO: 477)

(6) (D/N)MMHV(E/D)YXEY (SEQ ID NO: 478), wherein X is any amino acid

(7) DYMHXXYXEY (SEQ ID NO: 479) (like FG loop of 679F09), wherein X is any amino acid

(8) D(M/Y)YHX(K/R)X(V/I/L/M)YG (SEQ ID NO: 480), wherein X is any amino acid

(b) FG loop, 15 amino acid length

(1) D(Y/F)(Y/F)NPXTHEYXYXXX (SEQ ID NO: 481), wherein X is any amino acid

(2) D(Y/F)(Y/F)D(P/L)X(T/S)HXYXYXXX (SEQ ID NO: 482), wherein X is any amino acid

(3) D(Y/F)(K/R)PHXDGPH(T/I)YXE(S/Y) (SEQ ID NO: 483), wherein X is any amino acid

Sequence Analysis II: ^{10}Fn3-based binders showing more potent inhibition of EGFR phosphorylation

Another overall sequence analysis was performed on the subset of ^{10}Fn3-based binders that showed the most potent activity in a cell-based assay (as opposed to Sequence Analysis I, which was performed on all binders selected for high-affinity binding to EGFR through Profusion). Because many of the binders were only run through single-point cell-based assays, binders that showed greater than 75% inhibition of EGFR phosphorylation at a fixed concentration of 100 nM were included in this analysis. The percent inhibition at a given concentration is related to the IC50 by: % inhibition = 100 x concentration/(concentration + IC50).

Normally, an IC50 is calculated by fitting the data for % inhibition at various concentrations. However, given that only a single data point is available for each binder, it is inappropriate to use this single data point to calculate an IC50.

Therefore, the percent inhibition of EGFR signaling at a single concentration point was used as an approximation of the potency of the binder. Although a binder may show 75% inhibition at a concentration of 100 nM, increasing the concentration will allow the clone to show 100% inhibition at a higher concentration. The % inhibition is inversely related to the IC50; i.e., the higher the % inhibition, the lower the IC50 and the more potent the binder. If a binder showed 75% inhibition at a concentration of 100 nM, we considered this to be a "potent" binder for the purposes of Sequence Analysis II. However, the binders which showed less than 75% inhibition at 100 nM concentration for the most part still bind to EGFR and still have an effect on EGFR signaling. For instance, the anti-EGFR monoclonal antibody Nimotuzumab (Friedlander E *et al.* ErbB-directed immunotherapy: antibodies in current practice and promising new agents. *Immunol Lett* **116**: 126–140, 2008) is currently under development as a therapeutic, but it shows <5% inhibition at a 100 nM concentration in the EGFR phosphorylation assay (data not shown). The sequences of all "potent" binders assayed and their % inhibition of EGFR phosphorylation at 100 nM concentration is shown in Figure 45.

The total number of unique ^{10}Fn3-based binders that showed >75% inhibition at 100 nM concentration was 111. As before, the sequences first were analyzed by the frequency of amino acids at each position in the loops (Figures 39-42). Since these binders are a subset of all the binders selected for high affinity binding to EGFR during Profusion, they also follow Sequence Motif #1 (see above). All "potent" sequences analyzed follow the FG loop sequence pattern ("D/N" in position 1). Of all unique "potent" sequences analyzed, 93% follow the pattern for the BC loop ("YQ" in positions 7-8), and 98% follow the pattern for the DE loop (aliphatic residue ("V/I/L/M/A") in position 3). All "potent" sequences analyzed follow at least two of the three patterns of Sequence Motif #1.

Of note, the 15-amino acid FG loop length also appears to be highly represented in the most "potent" binders. While 15-amino acid long FG loops represent only 55% of all binders selected for high affinity binding to EGFR (Sequence Analysis I), 15-amino acid FG loops represent 86% of the binders with >50% inhibition of EGFR phosphorylation at 100 nM concentration, and 91% of the binders with >75% inhibition ("potent" binders in Sequence Analysis II). Therefore,

the longer 15-amino acid FG loop appears to be a sequence pattern associated with greater potency.

Of the 111 "potent" sequences analyzed, only 10 contain 10-amino acid long FG loops, and 6 of those are unique. Therefore, a single sequence motif can encompass every "potent" 10-amino acid FG loop sequence. Sequence Motif #4 was defined based on these 6 sequences.

Sequence Motif #4

FG loop, 10-amino acid length, "potent" binders

(D/N)(M/Y)(M/A/W)(H/F/Y)(V/K)EY(A/Q/R/S/T)E(Y/H/D)

The sequence analysis of the "potent" binders with 15-amino acid FG loops also further illuminated which residue positions were most conserved, allowing Sequence Motif #5 to be defined. An "X" in this sequence motif denotes positions where there are no three dominant amino acids.

Sequence Motif #5

FG loop, 15-amino acid length, "potent" binders

D(Y/F/W)(Y/F/K)(N/P/D)(P/H/L)X(T/D/S)(H/G/Y)(E/P/Y)(Y/H)XYXXX,

wherein X is any amino acid

All of the EGFR binders that were analyzed are progeny of the parent 679F09 and constitute a sequence "family," i.e. they are all related in sequence according to the aforementioned sequence motifs. Various members of the 679F09 family of binders can tolerate a T51I scaffold mutation and retain binding activity. Therefore, a T51I scaffold mutation could be combined with any of the aforementioned sequence motifs to also yield a binder with high affinity binding to EGFR.

Finally, it should be noted that amino acids with similar properties can often be substituted into protein sequences with little or no effect on structure or function. This indeed is the case for ^{10}Fn3-based binders as well, where conservative amino acid substitutions in either the loop or scaffold regions can still lead to binders which

bind to EGFR. For instance, substituting "Y" for "H" in the second position of the FG loop of binder E98 yields binder E99, and both binders show similar potency in inhibiting EGFR phosphorylation (Figure 45).

CLAIMS:

1. An antibody-like protein dimer comprising a) a tenth fibronectin type III domain (^{10}Fn3) that binds IGF-IR with a K_D of less than 500 nM covalently or non-covalently linked to b) a ^{10}Fn3 that binds EGFR with a K_D of less than 500 nM;

wherein the IGF-IR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 3, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 3, and an FG loop having the amino acid sequence set forth in amino acids 76-83 of SEQ ID NO: 3, and

wherein the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 112, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 112, and an FG loop having the amino acid sequence set forth in amino acids 76-92 of SEQ ID NO: 112.

2. An antibody-like protein dimer comprising a tenth fibronectin type III domain (^{10}Fn3) that binds IGF-IR with a K_D of less than 500 nM covalently or non-covalently linked to a ^{10}Fn3 that binds EGFR with a K_D of less than 500 nM;

wherein the IGFIR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_aSARLKVAX_b$ (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX_d (SEQ ID NO: 48), and an FG loop having the amino acid sequence $X_eRFRDYQX_f$ (SEQ ID NO: 50);

wherein the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_gWAPVDRYQX_h$ (SEQ ID NO: 137), a DE loop having the amino acid sequence X_iRDVYX_j (SEQ ID NO: 138), and an FG loop having the amino acid sequence $X_kDYKPHADGPHTYHESX_l$ (SEQ ID NO: 139); and

wherein X is any amino acid and a, b, c, d, e, f, g, h, i, j, k, and l are integers independently selected from 0 to 5.

3. The antibody-like protein dimer of claim 2,

wherein the IGF-IR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49); and an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWWAPVDRYQ (SEQ ID NO: 115), a DE loop having the amino acid sequence PRDVYT (SEQ ID NO: 116), and an FG loop having the amino acid sequence TDYKPHADGPHTYHESP (SEQ ID NO: 117).

4. The antibody-like protein dimer of anyone of claims 1-3, wherein the IGF-IR binding ^{10}Fn3 has an amino acid sequence at least 90% identical to SEQ ID NO: 3 and the EGFR binding ^{10}Fn3 scaffold has an amino acid sequence at least 90% identical to SEQ ID NO: 112.

5. The antibody-like protein dimer of anyone of claims 1-4, wherein the IGF-IR binding ^{10}Fn3 is covalently linked to the EGFR binding ^{10}Fn3 via a polypeptide linker or a polyethylene glycol moiety.

6. The antibody-like protein dimer of claim 5 comprising an amino acid sequence at least 90% identical to any one of SEQ ID NOs: 126-132.

7. An antibody-like protein comprising a tenth fibronectin type III domain (^{10}Fn3) that binds EGFR with a K_D of less than 500 nM, wherein the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence set forth in amino acids 21-30 of SEQ ID NO: 112, a DE loop having the amino acid sequence set forth in amino acids 51-56 of SEQ ID NO: 112, and an FG loop having the amino acid sequence set forth in amino acids 76-92 of SEQ ID NO: 112.

8. An antibody-like protein comprising a tenth fibronectin type III domain (^{10}Fn3) that binds EGFR with a K_D of less than 500 nM, wherein the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence X_gWAPVDRYQX_h (SEQ ID NO: 137), a DE loop having the amino acid sequence X_iRDVYX$_j$ (SEQ ID

NO: 138), and an FG loop having the amino acid sequence $X_kDYKPHADGPHTYHESX_l$ (SEQ ID NO: 139); and wherein X is any amino acid and a, b, c, d, e, f, g, h, i, j, k, and l are integers independently selected from 0 to 5.

9. The antibody-like protein of claim 8, wherein the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWWAPVDRYQ (SEQ ID NO: 115), a DE loop having the amino acid sequence PRDVYT (SEQ ID NO: 116), and an FG loop having the amino acid sequence TDYKPHADGPHTYHESP (SEQ ID NO: 117).

10. The antibody-like protein of anyone of claims 7-9, further comprising a second tenth fibronectin type III domain (^{10}Fn3).

11. The antibody-like protein of claim 10, wherein the second ^{10}Fn3 binds to IGF-IR.

12. The antibody-like protein of claims 10 or 11, wherein the second ^{10}Fn3 is covalently linked to the EGFR binding ^{10}Fn3 via a polypeptide linker or a polyethylene glycol moiety.

13. An antibody-like protein dimer comprising a tenth fibronectin type III domain (^{10}Fn3) that binds IGF-IR with a K_D of less than 500 nM covalently or non-covalently linked to a ^{10}Fn3 that binds EGFR with a K_D of less than 500 nM;

wherein the IGFIR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_aSARLKVAX_b$ (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX_d (SEQ ID NO: 48), and an FG loop having the amino acid sequence $X_eRFRDYQX_f$ (SEQ ID NO: 50);

wherein the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_gDSGRGSYQX_h$ (SEQ ID NO: 40), a DE loop having the amino acid sequence X_iGPVHX_j (SEQ ID NO: 42), and an FG loop having the amino acid sequence $X_kDHKPHADGPHTYHEX_l$ (SEQ ID NO: 44); and

wherein X is any amino acid and a, b, c, d, e, f, g, h, i, j, k, and l are integers independently selected from 0 to 5.

14. The antibody-like protein dimer of claim 13,

wherein the IGF-IR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49); and an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWDSGRGSYQ (SEQ ID NO: 39), a DE loop having the amino acid sequence PGPVHT (SEQ ID NO: 41), and an FG loop having the amino acid sequence TDHKPHADGPHTYHESP (SEQ ID NO: 43).

15. The antibody-like protein dimer of claims 13 or 14, wherein the IGF-IR binding ^{10}Fn3 has an amino acid sequence at least 90% identical to SEQ ID NO: 3 and the EGFR binding ^{10}Fn3 scaffold has an amino acid sequence at least 90% identical to SEQ ID NO: 5.

16. The antibody-like protein dimer of any one of claims 13-15, wherein the IGF-IR binding ^{10}Fn3 is covalently linked to the EGFR binding ^{10}Fn3 via a polypeptide linker or a polyethylene glycol moiety.

17. The antibody-like protein dimer of claim 16, comprising an amino acid sequence at least 90% identical to SEQ ID NOs: 20, 21, 23, or 24.

18. An antibody-like protein dimer comprising a tenth fibronectin type III domain (^{10}Fn3) that binds IGF-IR with a K_D of less than 500 nM covalently or non-covalently linked to a ^{10}Fn3 that binds EGFR with a K_D of less than 500 nM;

wherein the IGFIR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence X_aSARLKVAX$_b$ (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX$_d$ (SEQ ID NO: 48), and an FG loop having the amino acid sequence X_eRFRDYQX$_f$ (SEQ ID NO: 50);

wherein the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_mVAGAEDYQX_n$ (SEQ ID NO: 34), a DE loop having the amino acid sequence X_oHDLVX_p (SEQ ID NO: 36), and an FG loop having the amino acid sequence $X_qDMMHVEYTEHX_r$ (SEQ ID NO: 38); and

wherein X is any amino acid and a, b, c, d, e, f, m, n, o, p, q, and r are integers independently selected from 0 to 5.

19. The antibody-like protein dimer of claim 18,

wherein the IGF-IR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49), covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWVAGAEDYQ (SEQ ID NO: 33), a DE loop having the amino acid sequence PHDLVT (SEQ ID NO: 35), and an FG loop having the amino acid sequence TDMMHVEYTEHP (SEQ ID NO: 37).

20. The antibody-like protein dimer of claims 18 or 19, wherein the IGF-IR binding ^{10}Fn3 has an amino acid sequence at least 90% identical to SEQ ID NO: 3 and the EGFR binding ^{10}Fn3 has an amino acid sequence at least 90% identical to SEQ ID NO: 7.

21. The antibody-like protein dimer of any one of claims 18-20, wherein the IGF-IR binding ^{10}Fn3 scaffold is covalently linked to the EGFR binding ^{10}Fn3 scaffold via a polypeptide linker or a polyethylene glycol moiety.

22. The antibody-like protein dimer of claim 21, comprising an amino acid sequence at least 90% identical to SEQ ID NOs: 26, 27, 29, or 30.

23. An antibody-like protein dimer comprising a tenth fibronectin type III domain (^{10}Fn3) that binds IGF-IR with a K_D of less than 500 nM covalently or non-covalently linked to a ^{10}Fn3 that binds EGFR with a K_D of less than 500 nM;

wherein the IGFIR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_aSARLKVAX_b$ (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX_d (SEQ ID NO: 48), and an FG loop having the amino acid sequence $X_eRFRDYQX_f$ (SEQ ID NO: 50);

wherein the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_sLPGKLRYQX_t$ (SEQ ID NO: 60), a DE loop having the amino acid sequence X_uHDLRX_w (SEQ ID NO: 62), and an FG loop having the amino acid sequence $X_yNMMHVEYSEYX_z$ (SEQ ID NO: 64); and

wherein X is any amino acid and a, b, c, d, e, f, s, t, u, w, y and z are integers independently selected from 0 to 5.

24. The antibody-like protein dimer of claim 23,

wherein the IGF-IR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49), covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence LPGKLRYQ (residues 3-13 of SEQ ID NO: 59), a DE loop having the amino acid sequence PHDLR (residues 1-5 of SEQ ID NO: 61), and an FG loop having the amino acid sequence TNMMHVEYSEY (residues 1-11 of SEQ ID NO: 63).

25. The antibody-like protein dimer of claims 23 or 24, wherein the IGF-IR binding ^{10}Fn3 has an amino acid sequence at least 90% identical to SEQ ID NO: 3 and the EGFR binding ^{10}Fn3 has an amino acid sequence at least 90% identical to SEQ ID NO: 82.

26. The antibody-like protein dimer of any one of claims 23-25, wherein the IGF-IR binding ^{10}Fn3 scaffold is covalently linked to the EGFR binding ^{10}Fn3 scaffold via a polypeptide linker or a polyethylene glycol moiety.

27. The antibody-like protein dimer of claim 26, comprising an amino acid sequence at least 90% identical to any one of SEQ ID NOs: 53, 54, 87, 88, 98, 99, 104 or 105.

28. An antibody-like protein dimer comprising a tenth fibronectin type III domain (^{10}Fn3) that binds IGF-IR with a K_D of less than 500 nM covalently or non-covalently linked to a ^{10}Fn3 that binds EGFR with a K_D of less than 500 nM;

wherein the IGFIR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_aSARLKVAX_b$ (SEQ ID NO: 46), a DE loop having the amino acid sequence X_cKNVYX_d (SEQ ID NO: 48), and an FG loop having the amino acid sequence $X_eRFRDYQX_f$ (SEQ ID NO: 50);

wherein the EGFR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence $X_gHERDGSRQX_h$ (SEQ ID NO: 134), a DE loop having the amino acid sequence X_iGGVRX_j (SEQ ID NO: 135), and an FG loop having the amino acid sequence $X_kDYFNPTTHEYIYQTTX_l$ (SEQ ID NO: 136); and

wherein X is any amino acid and a, b, c, d, e, f, g, h, i, j, k and l are integers independently selected from 0 to 5.

29. The antibody-like protein dimer of claim 28,

wherein the IGF-IR binding ^{10}Fn3 comprises a BC loop having the amino acid sequence SWSARLKVAR (SEQ ID NO: 45), a DE loop having the amino acid sequence PKNVYT (SEQ ID NO: 47), and an FG loop having the amino acid sequence TRFRDYQP (SEQ ID NO: 49), covalently or non-covalently linked to an EGFR binding ^{10}Fn3 comprising a BC loop having the amino acid sequence SWHERDGSRQ (SEQ ID NO: 109), a DE loop having the amino acid sequence PGGVRT (SEQ ID NO: 110), and an FG loop having the amino acid sequence TDYFNPTTHEYIYQTTP (SEQ ID NO: 111).

30. The antibody-like protein dimer of claims 28 or 29, wherein the IGF-IR binding ^{10}Fn3 has an amino acid sequence at least 90% identical to SEQ ID NO: 3 and the EGFR binding ^{10}Fn3 has an amino acid sequence at least 90% identical to SEQ ID NO: 107.

31. The antibody-like protein dimer of any one of claims 28-30, wherein the IGF-IR binding ^{10}Fn3 scaffold is covalently linked to the EGFR binding ^{10}Fn3 scaffold via a polypeptide linker or a polyethylene glycol moiety.

32. The antibody-like protein dimer of claim 31, comprising an amino acid sequence at least 90% identical to any one of SEQ ID NOs: 118-125.

33. A pharmaceutically acceptable composition comprising the antibody-like protein dimer or antibody-like protein of any one of claims 1-32, wherein the composition is essentially pyrogen free.

34. A method for treating a hyperproliferative disorder in a subject comprising administering to a subject in need thereof a therapeutically effective amount of the composition of claim 33.

35. An antibody-like protein comprising a tenth fibronectin type III domain (^{10}Fn3) that binds EGFR with a K_D of less than 500 nM, wherein the EGFR binding ^{10}Fn3 comprises a BC loop comprising the amino acid sequence XXXXXXYQ, a DE loop comprising the amino acid sequence XX(V/I/L/M/A)X, and an FG loop comprising the amino acid sequence (D/N)X_n, wherein X is any amino acid and n is 9-14 amino acids.

36. The antibody-like protein of claim 35, wherein n is 14.

37. The antibody-like protein of claims 35 or 36, further comprising a second tenth fibronectin type III domain (^{10}Fn3).

38. The antibody-like protein of claim 37, wherein the second ^{10}Fn3 binds to IGF-IR.

39. The antibody-like protein of claim 37 or 38, wherein the second ^{10}Fn3 is covalently linked to the EGFR binding ^{10}Fn3 via a polypeptide linker or a polyethylene glycol moiety.

40. A pharmaceutically acceptable composition comprising the antibody-like protein of any one of claims 35-39, wherein the composition is essentially pyrogen free.

41. A method for treating a hyperproliferative disorder in a subject comprising administering to a subject in need thereof a therapeutically effective amount of the composition of claim 40.

Figure 1

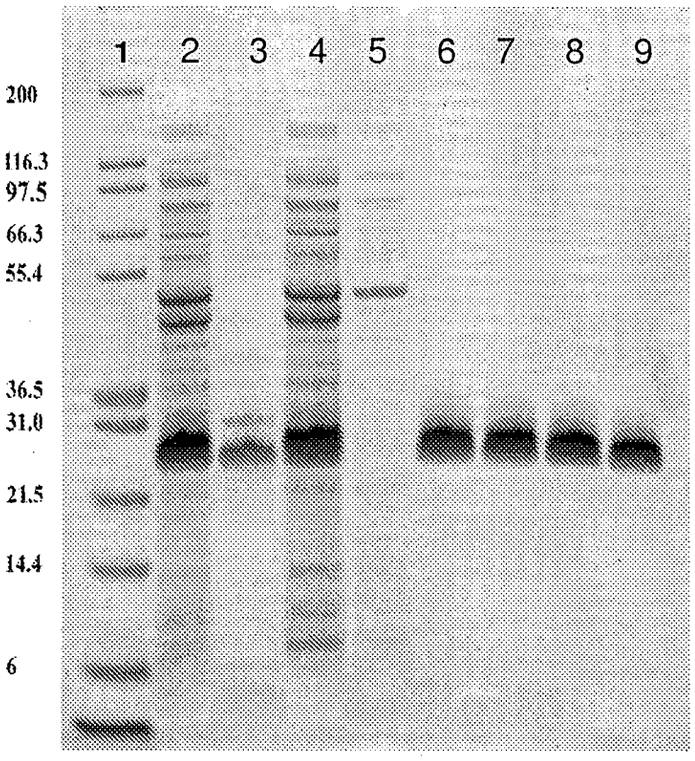
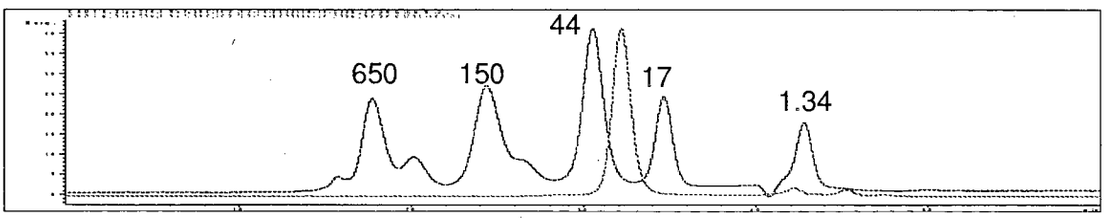


Figure 2

A



B

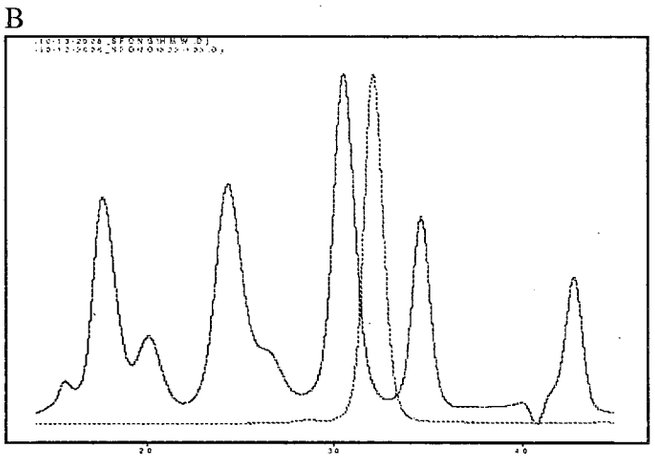
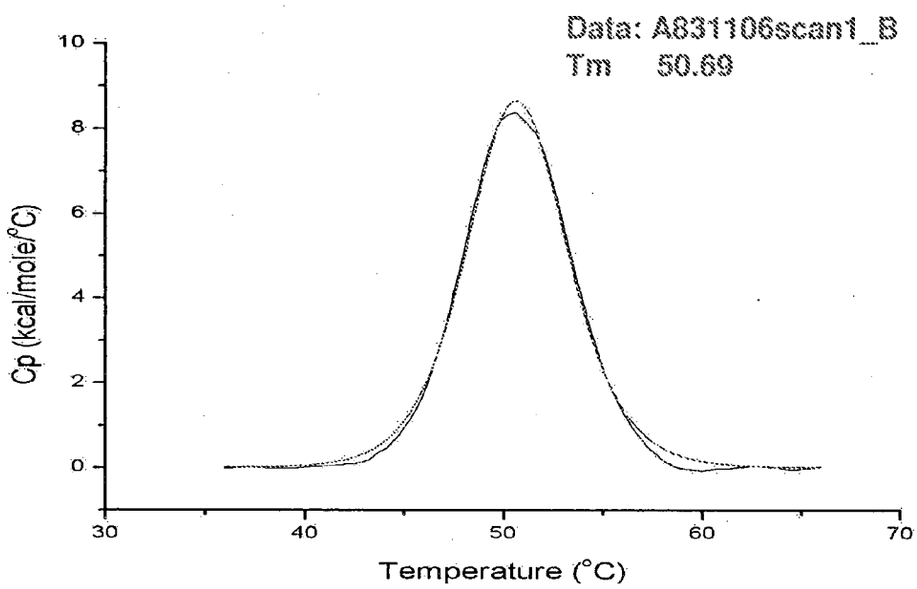


Figure 3

A


Data: A831106scan1_B
Tm 50.69
Cp (kcal/mole/°C)
Temperature (°C)
10
8
6
4
2
0
30
40
50
60
70

B

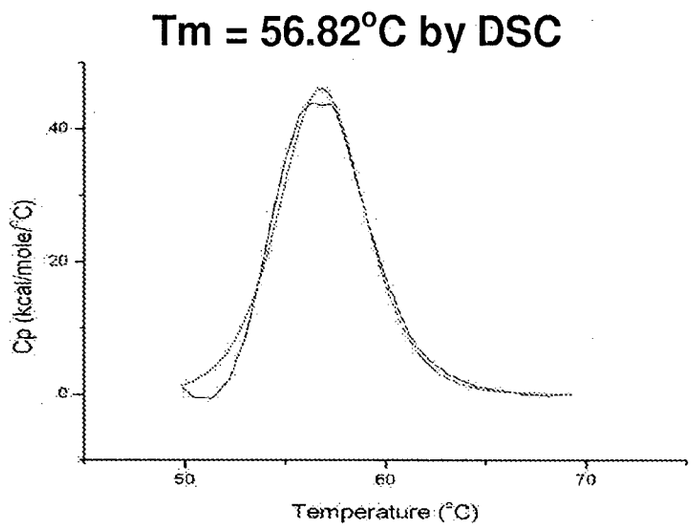

Tm = 56.82°C by DSC
Cp (kcal/mole/°C)
Temperature (°C)
40
20
0
50
60
70

Figure 4

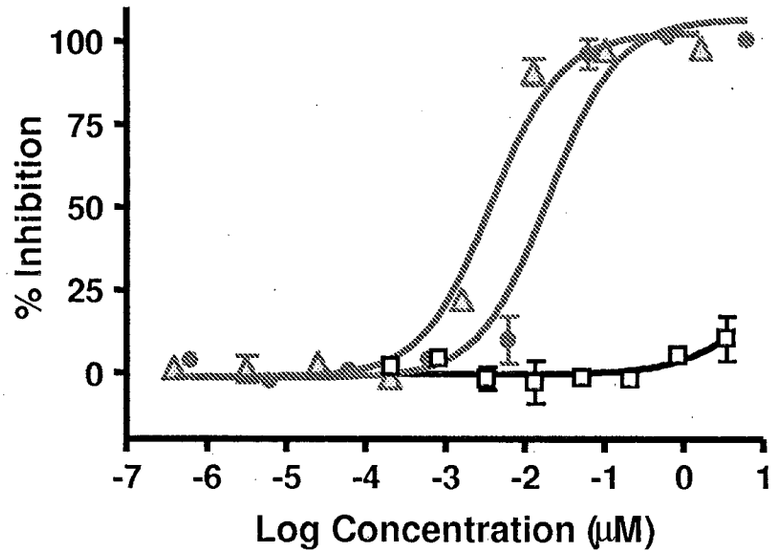


Figure 5

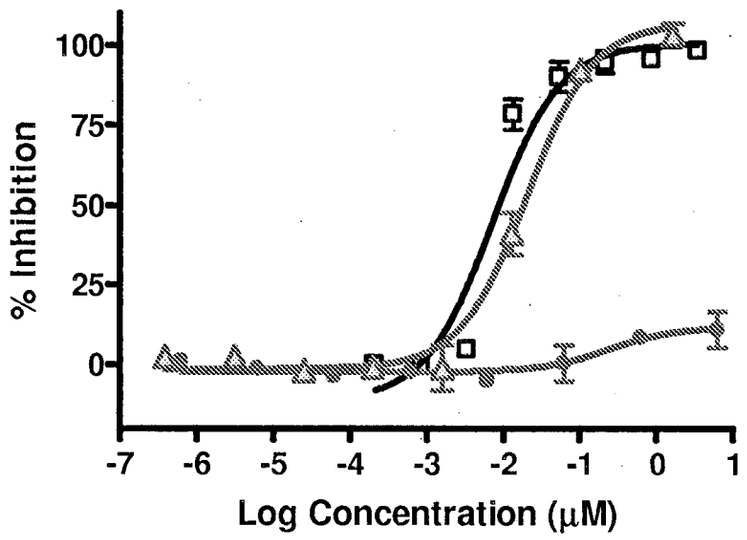


Figure 6

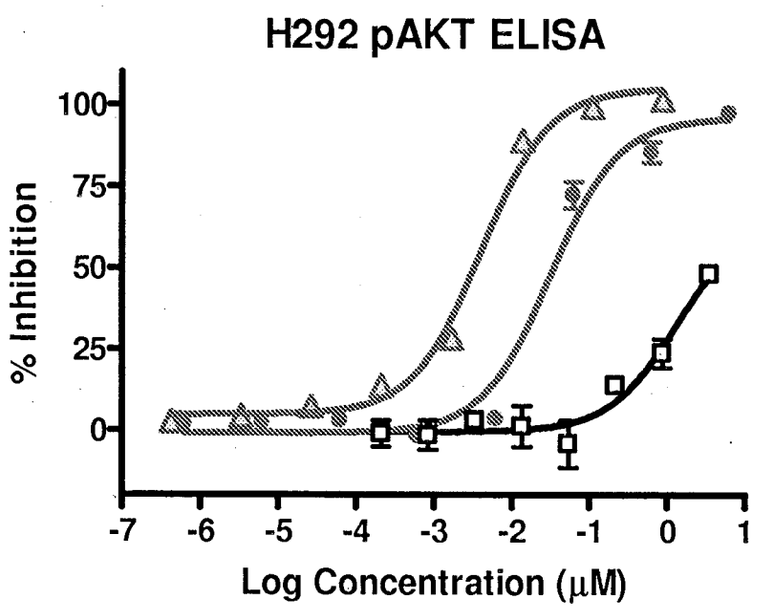


Figure 7

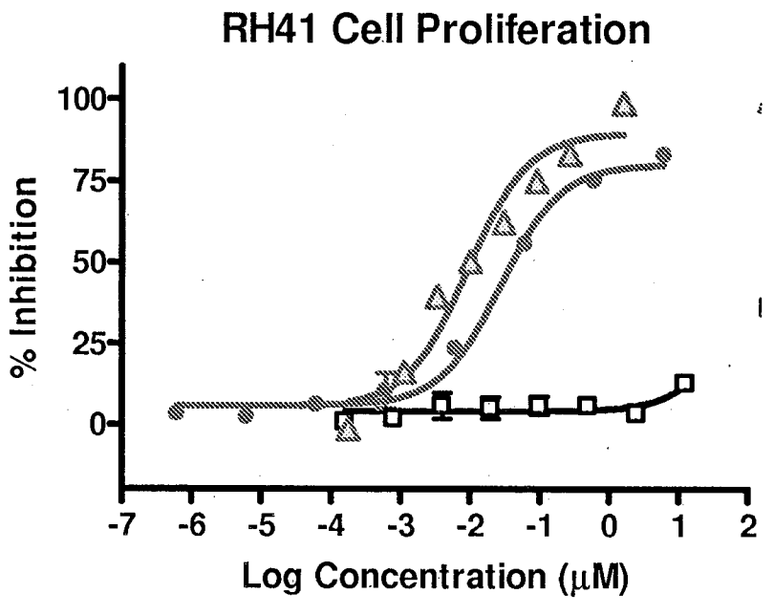


Figure 8

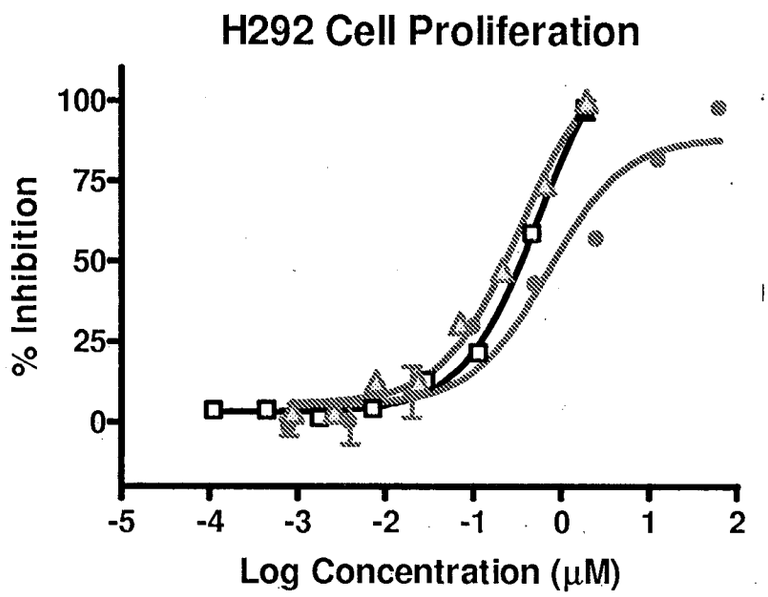


Figure 9

SUMMARY OF ACTIVITY IN CELL BASED ASSAYS

NAME	H292 pEGFR ELISA (nM)	H292 pIGFR ELISA (nM)	H292 pAKT ELISA (nM)	A431 pEGFR ICW (nM)	A431 pERK ICW (nM)
E1	8	---		24	13
E1-GS10-I1 (Pegylated)	123	4	5	297	295
E1-GS10-I1	30	1	1	36	51
I1-GS10-E1 (Pegylated)	127	0.9	0.8	302	300
I1-GS10-E1	42	1	1	93	99
E2	31	---		38	40
E2-GS10-I1 (Pegylated)	32	0.3	0.6	77	78
E2-GS10-I1	8	0.1	0.1	19	20
I1-GS10-E2 (Pegylated)	47	0.8	0.6	97	118
I1-GS10-E2	8	0.1	0.1	11	15
E3	21	---		14	11
E3-GS10-I1 (Pegylated)	10	6	4	42	40
E3-GS10-I1	7	6	3	14	12
I1GS10-E3 (Pegylated)	46	2	2	47	50
I1-GS10-E3	25	19	26	47	42

Figure 10

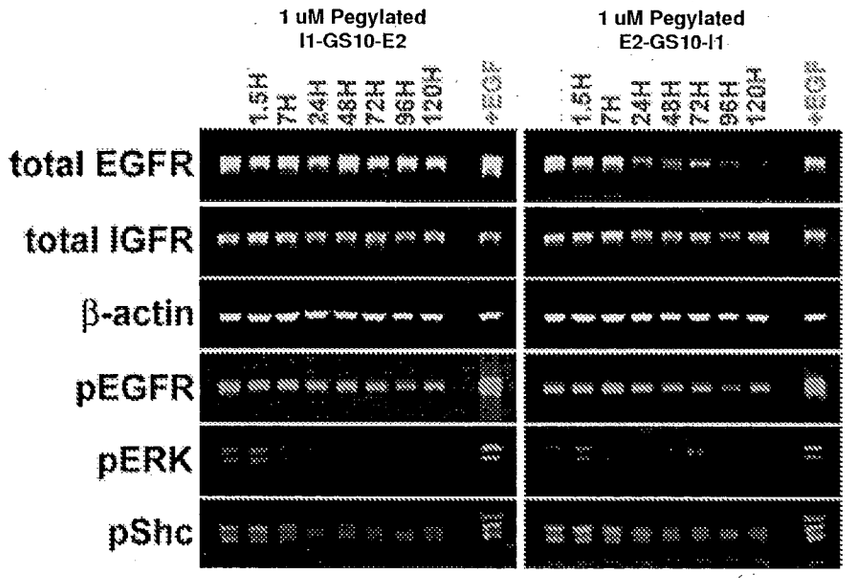


Figure 11

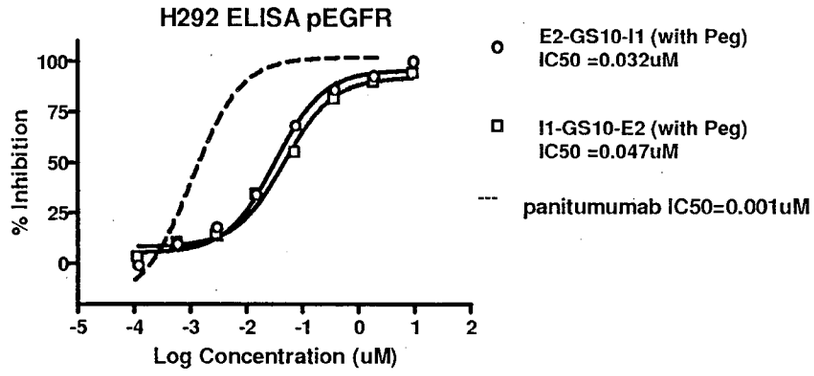


Figure 12A

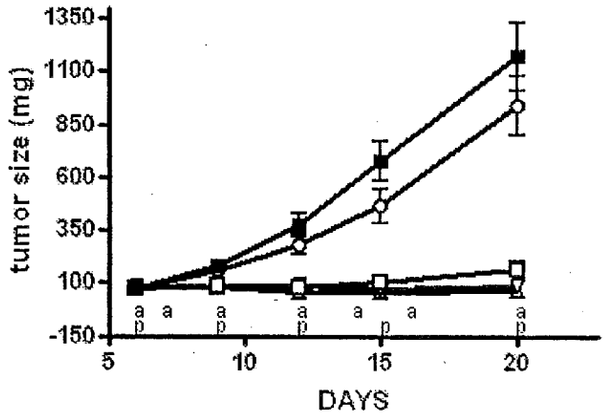


Figure 12B

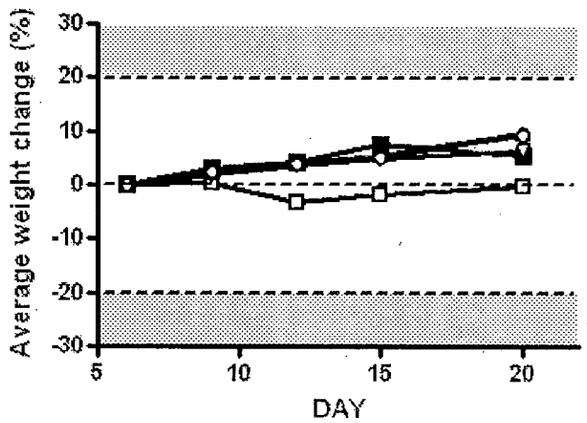


Figure 13

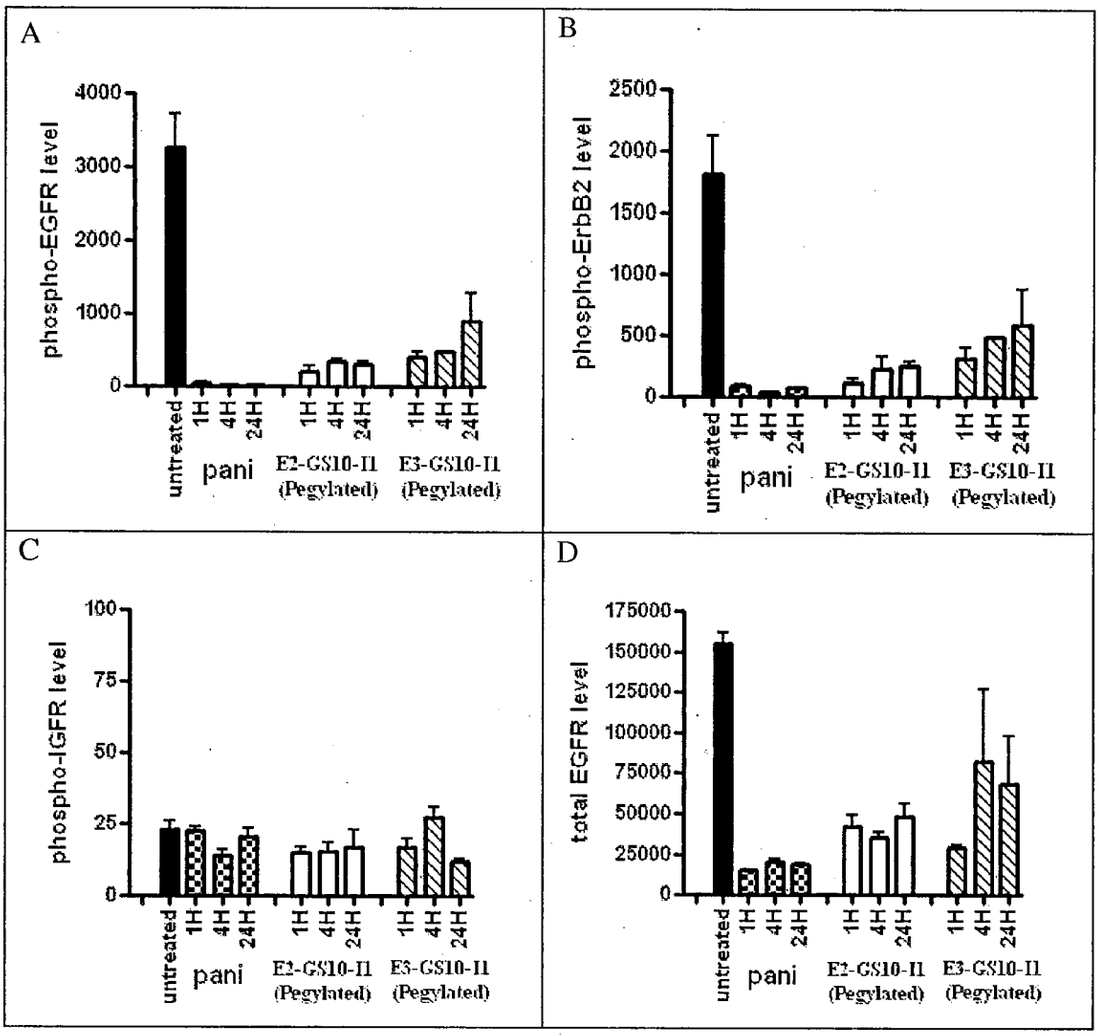

A
phospho-EGFR level
4000
3000
2000
1000
0
untreated
1H
4H
24H
pani
E2-GS10-I1 (Pegylated)
E3-GS10-I1 (Pegylated)
B
phospho-ErbB2 level
2500
2000
1500
1000
500
0
C
phospho-IGFR level
100
75
50
25
D
total EGFR level
175000
150000
125000
100000
75000
50000
25000

Figure 14

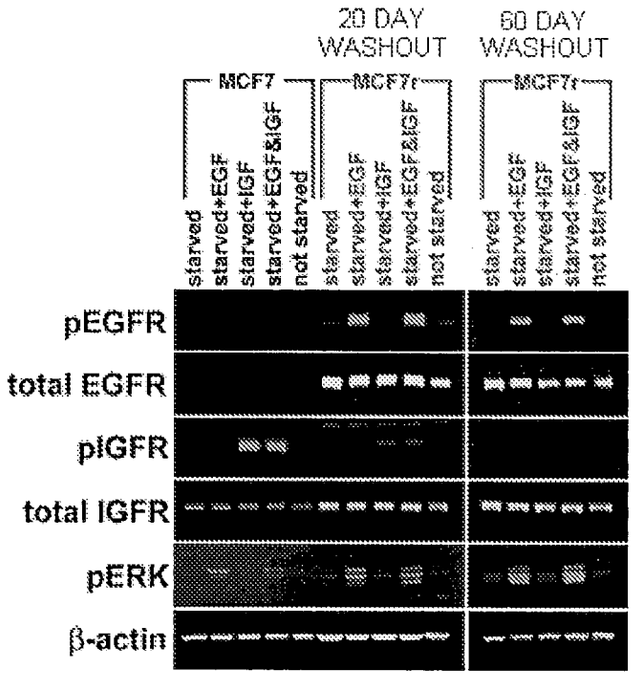


Figure 15

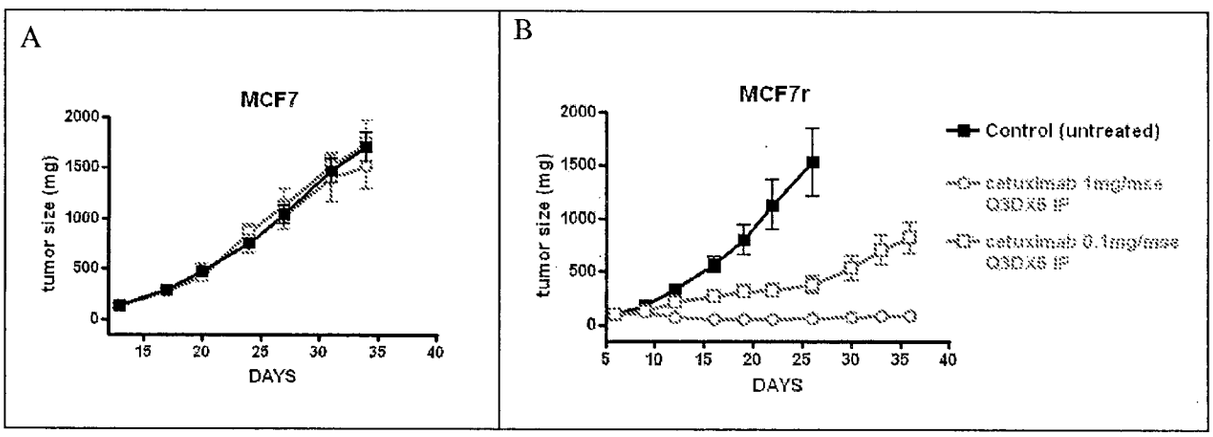
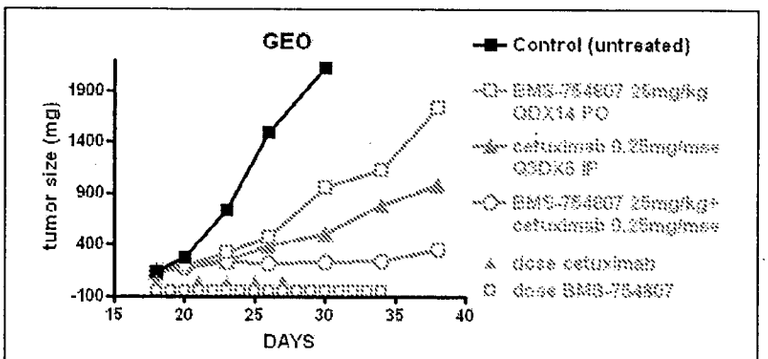
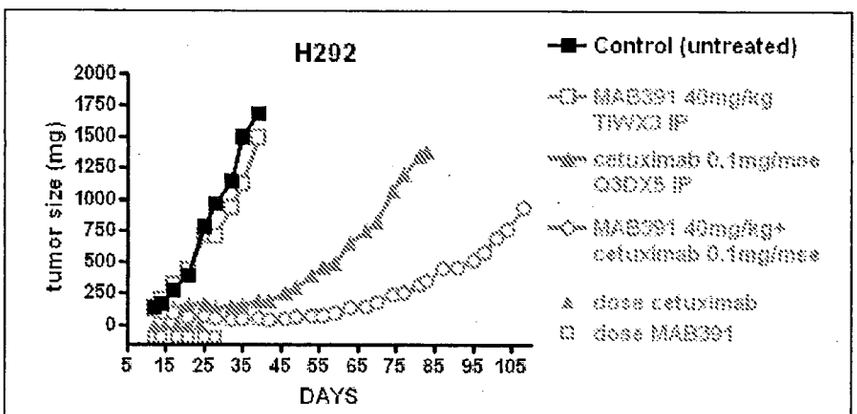


Figure 16



Doses of BMS-754807 and cetuximab are indicated by small boxes and small filled triangles on the x-axis

Figure 17



Doses of BMS-754807 and cetuximab are indicated by small boxes and small filled triangles on the x-axis

Figure 18

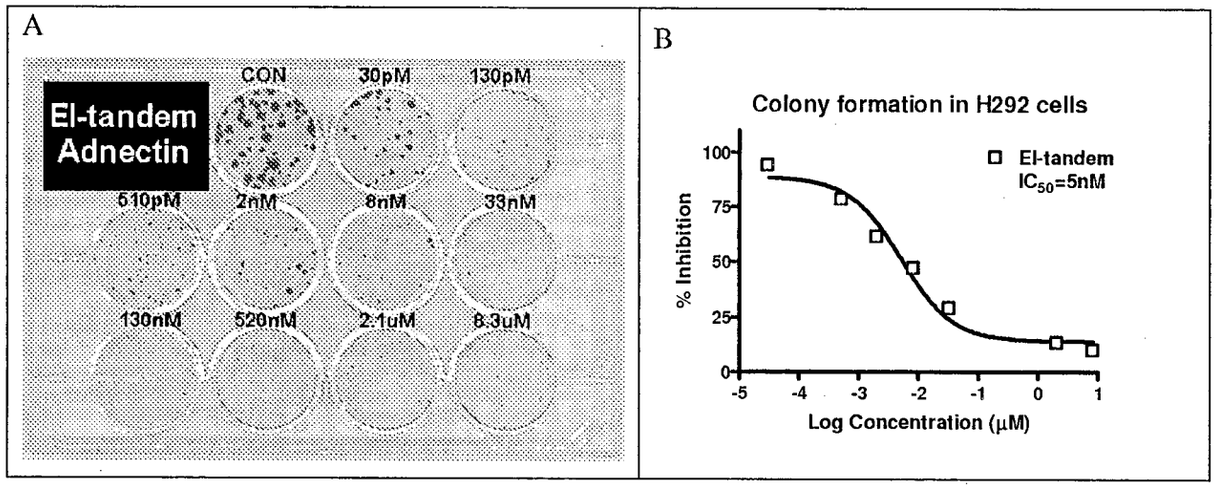


Figure 19

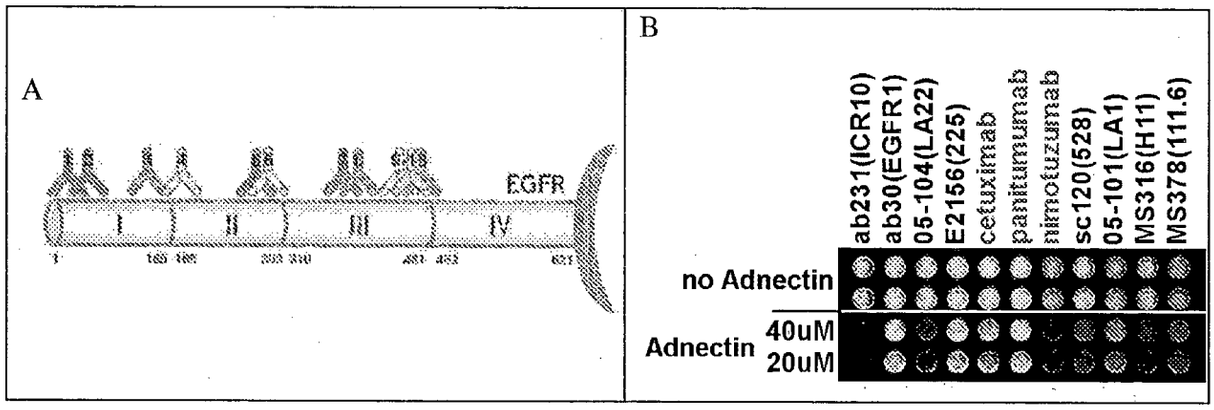


Figure 20

Tm = 55.2°C

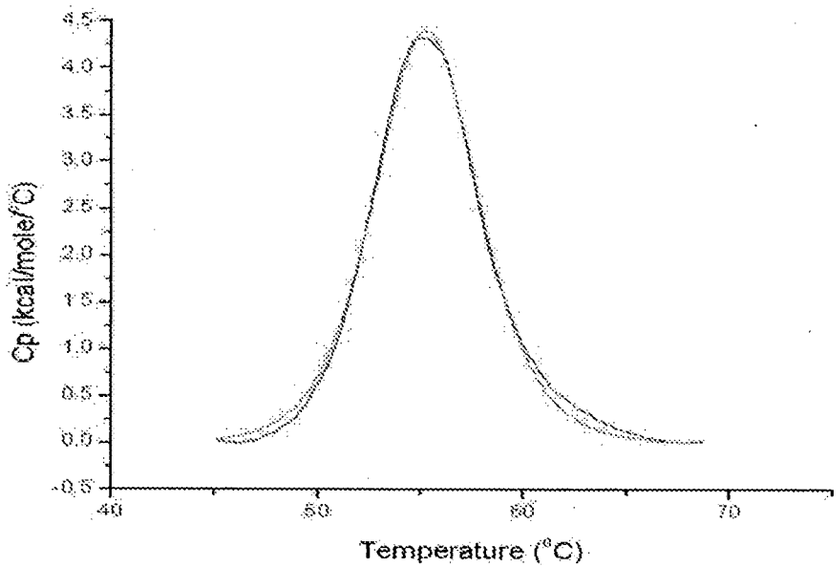


Figure 21

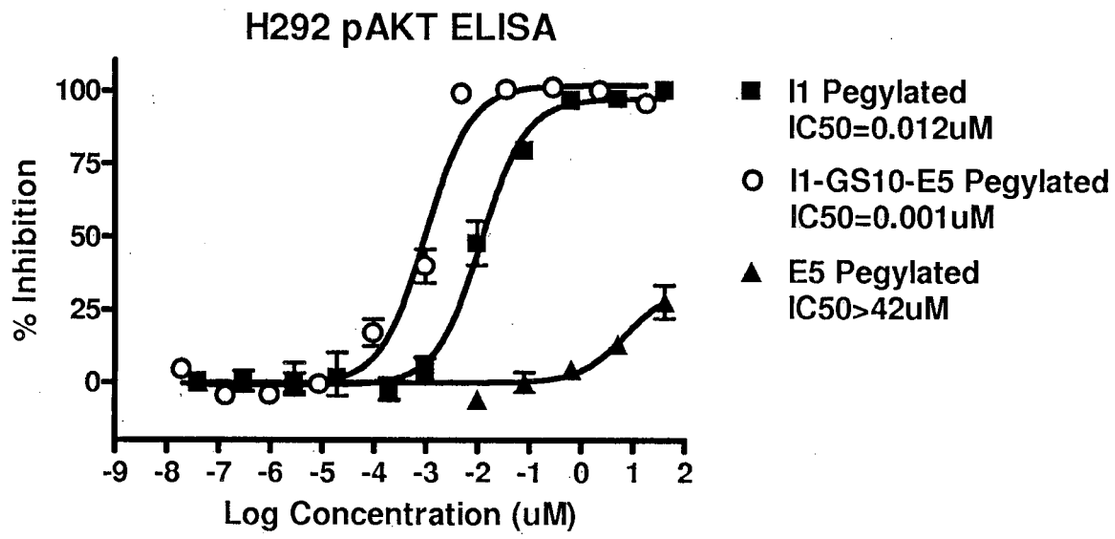


Figure 22

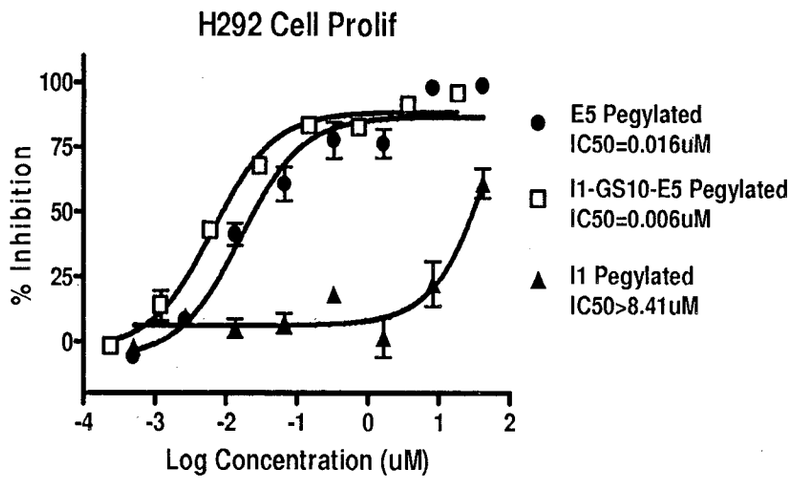


Figure 23

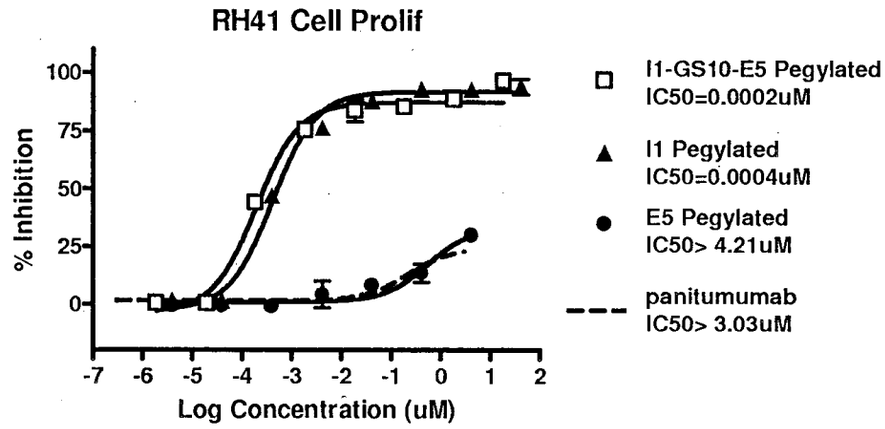
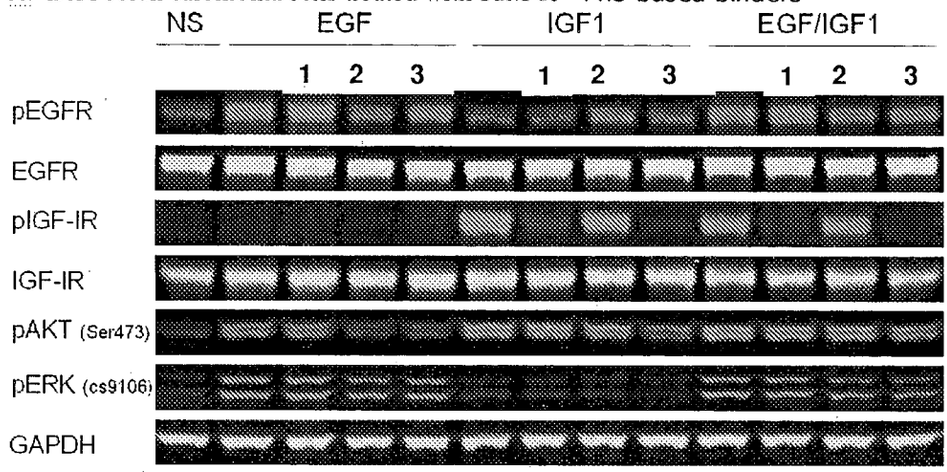


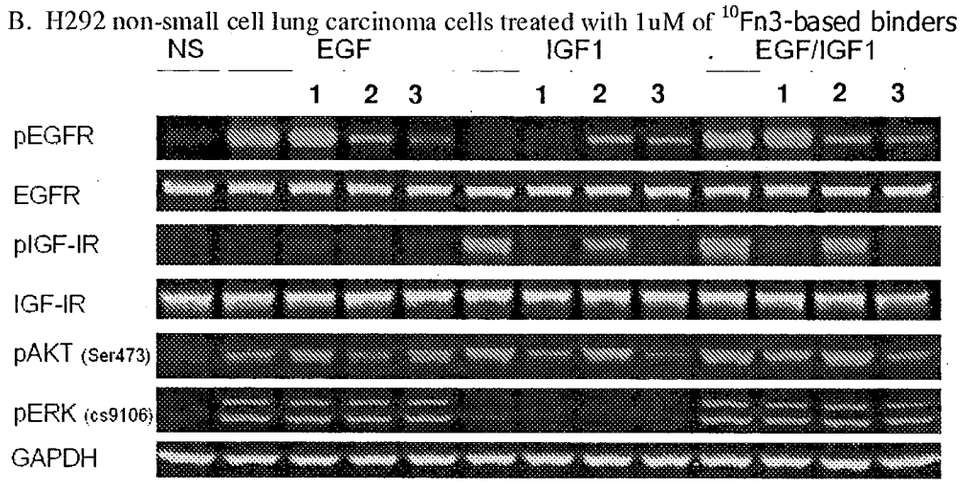
Figure 24

1=I1 pegylated; 2= E5 pegylated; 3=I1-GS10-E5 pegylated

A. DiFi colon carcinoma cells treated with 1uM of ^{10}Fn3-based binders



B. H292 non-small cell lung carcinoma cells treated with 1uM of ^{10}Fn3-based binders



C. BxPC3 pancreatic carcinoma cells treated with 0.1 uM of ^{10}Fn3-based binders

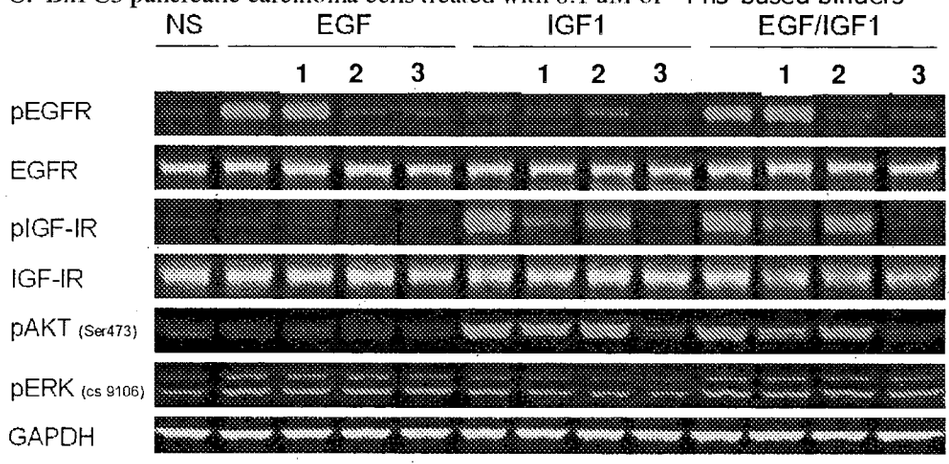
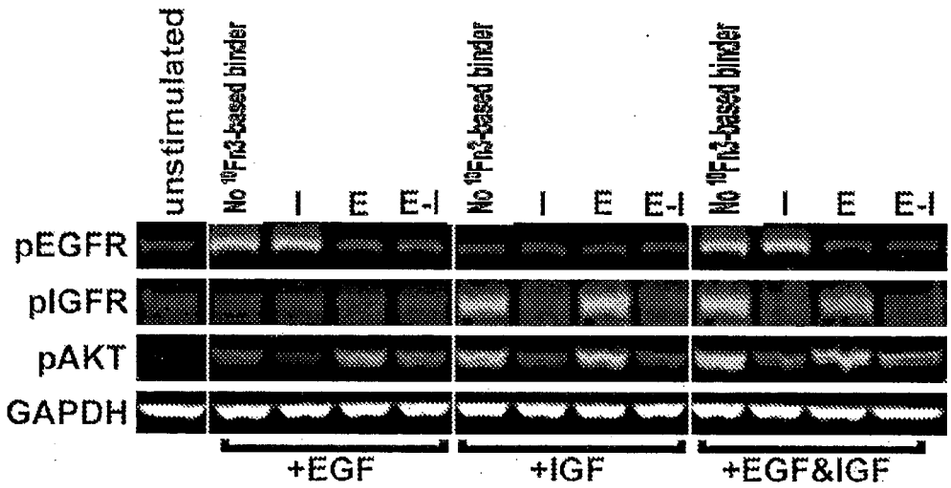


Figure 25



Abbreviations are as follows: I = I1 (unpegylated); E = E2 (unpegylated); EI=E2-GS10-I1 (unpegylated)

Figure 26

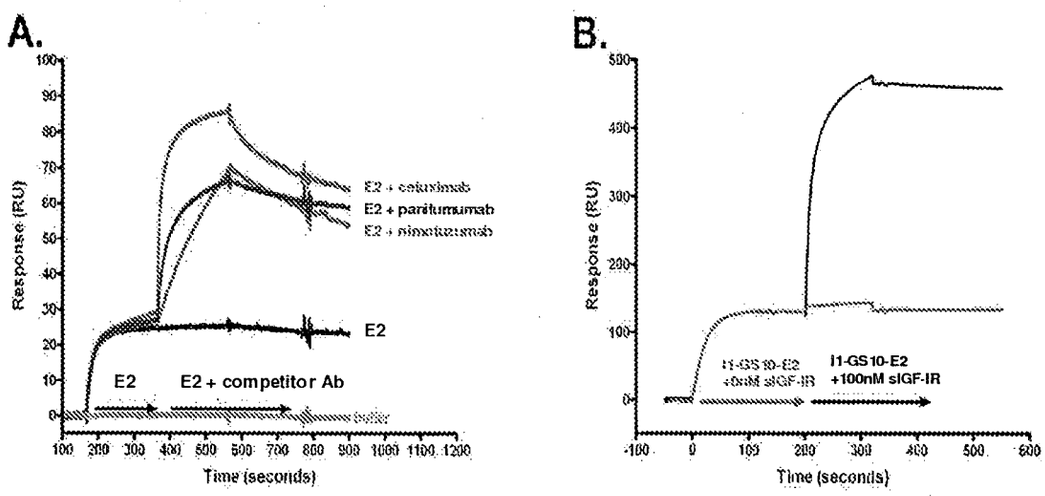


Figure 27

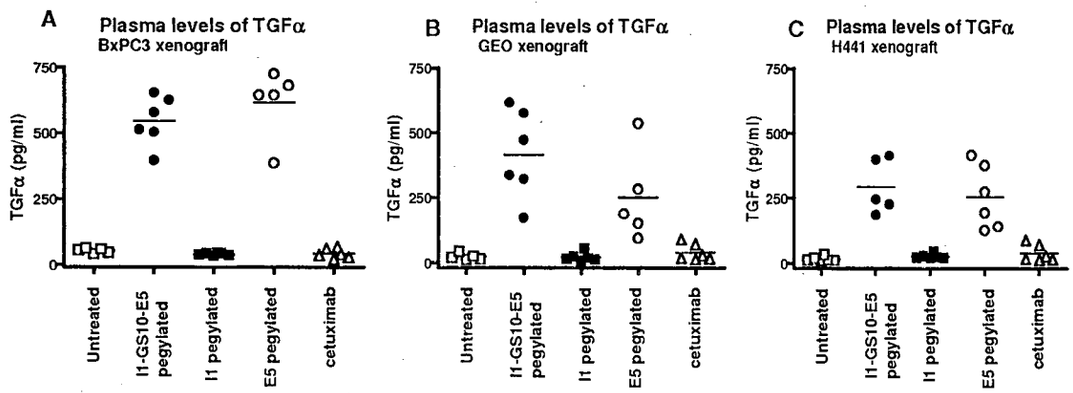


Figure 28

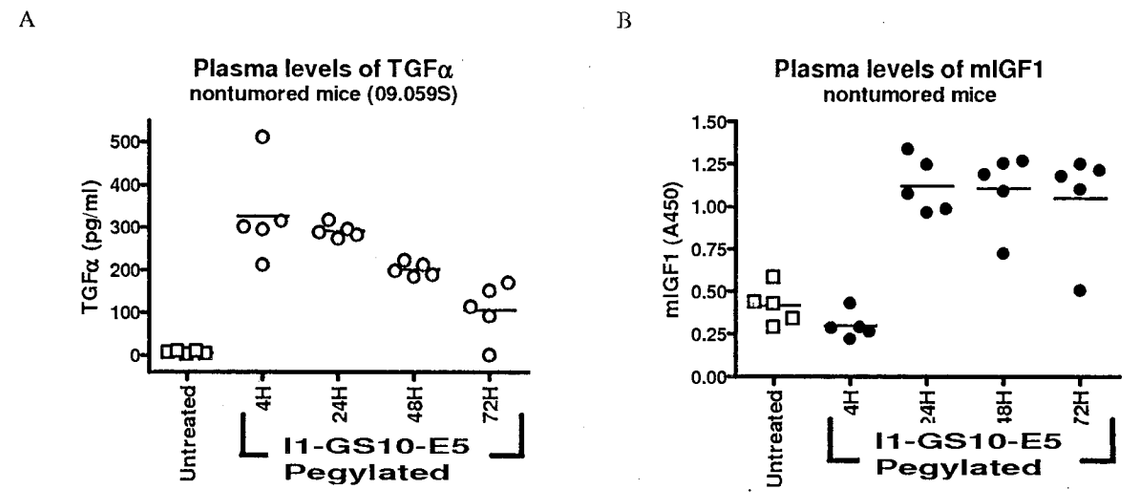
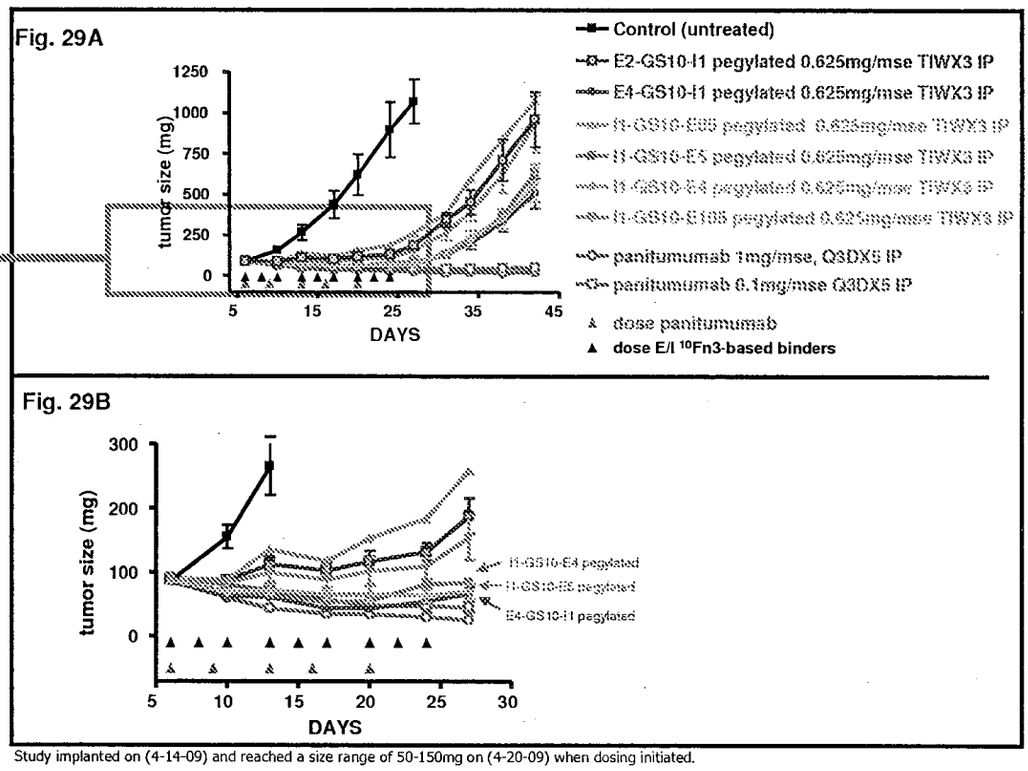
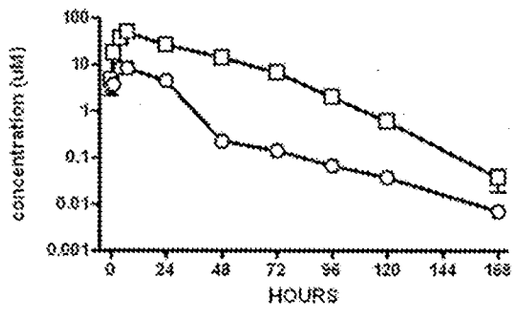


Figure 29



Study implanted on (4-14-09) and reached a size range of 50-150mg on (4-20-09) when dosing initiated.

Figure 30. Pharmacokinetic profile of E2-GS10-I1 pegylated in mice



Dose (mg/kg)	$t_{1/2}$ (h)	C_{max} (µg/mL)	AUC (h*µg/mL)	Vz_F-obs (mL/kg)	Cl_F-obs (mL/h/kg)
10	15.8	205.7	5159	45.6	2.0
100	16.9	1209.6	34491.9	77.9	3.2

Plasma levels E2-GS10-I1 pegylated after dosing this construct at 100 mg/kg (□) and 10 mg/kg (○) by the ip route.

Figure 31

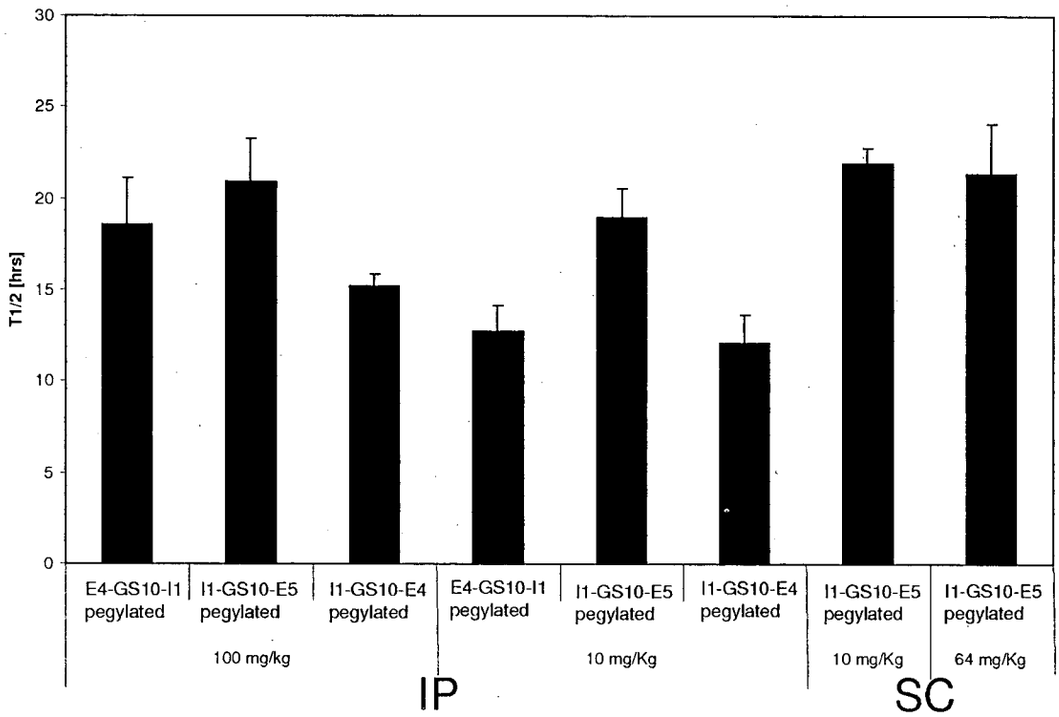


Figure 32

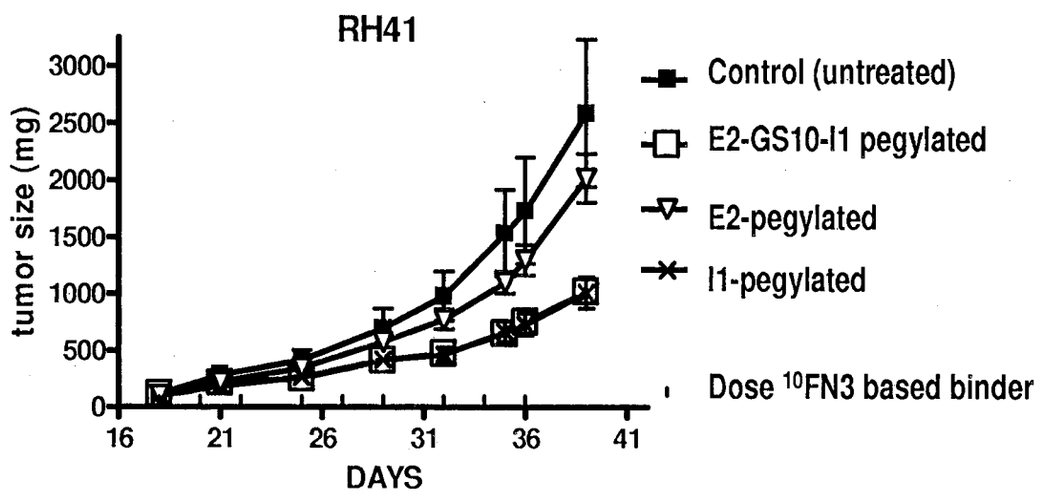


Figure 33

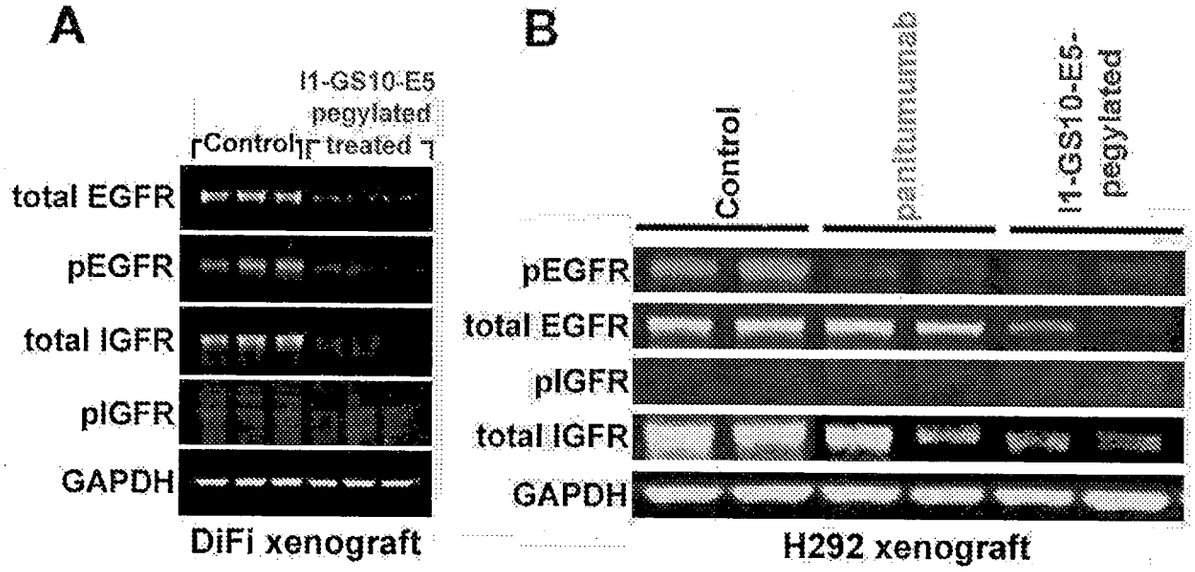


Figure 34

BC loop DE loop

MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPGGVRTATISGL

FG loop

KPGVDYTITVYAVTDYMHSEYRQYPISINYRTEIDKPSQHHHHHH

Figure 35

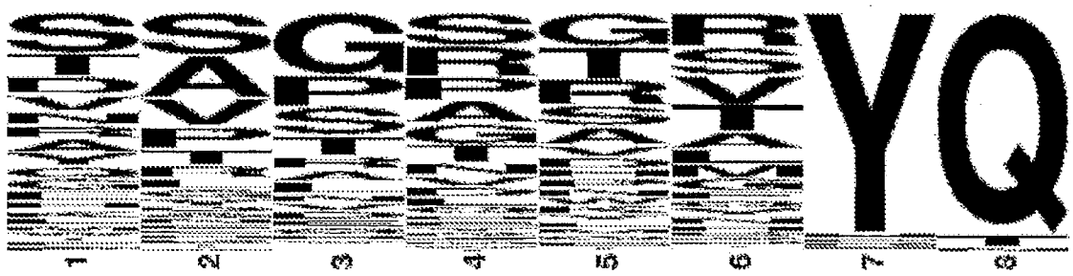


Figure 36



Figure 37

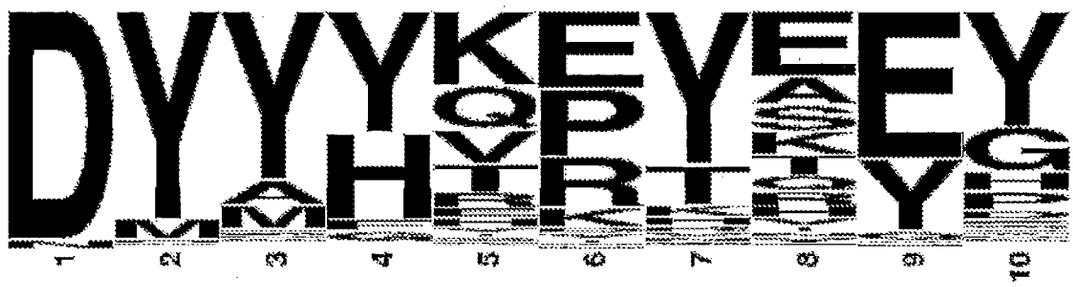


Figure 38



Figure 39

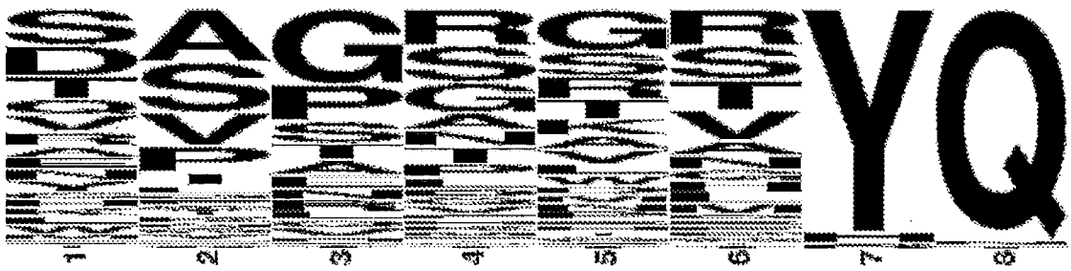


Figure 40



Figure 41



Figure 42



Figure 43

	a	b	c	d	e	f	g	h	i	j	k	l
CLONE NAME	A431 pEGFR ICW (nM)*	A431 pERK ICW (nM)*	H292 pEGFR ELISA (nM)*	H292 pIGFR ELISA (nM)*	De-grades EGFR	De-grades IGFR	EGFR KD (nM)	IGFR KD (nM)	EGF Blocking ELISA (nM)	Inhibition of Colony Forma-tion (nM)	Tm	% Mono-mer
E1-GS10-I1 pegylated	297	295	123	4	+	+	57.9	2.43	238	---	49	>95%
E3-GS10-I1 pegylated	42	40	10	6	++	++	10.4	0.74	89	---	52.5	>95%
E2-GS10-I1 pegylated	77	78	32	0.3	++	(-)	10.1	1.17	25	560	57.5	>95%
E4-GS10-I1 pegylated	12±0	12±2	1.3±0.5	0.4±0.2	(-)	(-)	4.77	0.77	19.5	5	55.5	>95%
E96-GS10-I1 pegylated	61±1	54±21	10±1	0.4	(-)	(-)	24.2	0.96	43.8	---	55	>95%
E5-GS10-I1 pegylated	44±1	47±7	12±4	0.4	+	+	12.4	1.16	119.3	---	54.5	>95%
E85-GS10-I1 pegylated	15±0	15±2	4±1	0.3	(-)	+	4.76	0.75	65.9	---	55.5	>95%
E90-GS10-I1 pegylated	65±0	63±9	10±1	0.4	---	---	13.5	1.5	69.1	---	49.5	>95%
E105-GS10-I1 pegylated	56±0	61±6	15±4	0.5	++	++	9.28	1.35	75	---	58.5	>95%
E105-GS10-I1 pegylated	61±11	49±17	16±6	0.5	---	---	7.65	1.19	93.8	---	56.5	>95%
I1-GS10-E5 pegylated	54±33	58±13	12±4	0.4±0.1	+	++	7.66	0.4	150.8	1	56	>95%
I1-GS10-E85 pegylated	22±15	23±4	8±3	0.7±0.5	(-)	(-)	5.97	0.43	37.8	---	58	>95%
I1-GS10-E4 pegylated	12±4	13±1	4±1	0.2	(-)	+	3.63	0.46	38.1	6	60	>95%
I1-GS10-E105 pegylated	53±9	48±3	13±3	0.5±0.2	++	++	4.28	0.37	61.2	---	59.5	>95%
I1-GS10-E112 pegylated	116	94	16	0.3	---	---	3.35	0.38	104.3	---	62.5	>95%
cetuximab	5±4	9±1	5±3	---	++	---	0.39	---	1	770	---	---
panitumumab	6±4	5±2	5±2	---	++	---	0.05	---	24.4	140	---	---
nimotuzumab	>3	>3	>3	---	+	---	1	---	13.6	---	---	---
I1	---	---	---	0.4±0.2	---	(-)	---	0.11	---	15,510	65.3	>95%

Figure 44

Dose	Molecule		HL_Lambda_z (hr)	Cmax (ug/mL)	AUCINF_obs (hr*ug/mL)	Cl_F_obs (mL/hr/kg)	Vz_F_obs (mL/kg)	MRTINF_obs (hr)
100 mg/kg	E4-GS10-I1 pegylated	N	3	3	3	3	3	3
		Mean	**18.5**	521.1	20811.4	4.8	128.3	34.1
		SD	2.6	75.7	2058.7	0.5	6.4	2.0
		Min	16.6	434.2	18824.8	4.4	122.4	31.8
		Max	21.5	573.0	22935.3	5.3	135.2	35.6
		CV%	14.0	14.5	9.9	9.8	5.0	6.0
	I1-GS10-E5 pegylated	N	3	3	3	3	3	3
		Mean	**20.9**	719.5	25730.1	3.9	117.4	33.0
		SD	2.3	90.4	2983.3	0.4	4.1	2.2
		Min	18.6	623.7	23362.5	3.4	114.9	30.6
		Max	23.2	803.4	29080.9	4.3	122.1	34.8
		CV%	11.0	12.6	11.6	11.1	3.5	6.7
	I1-GS10-E4 pegylated	N	3	3	3	3	3	3
		Mean	**15.2**	757.1	28344.0	3.6	77.7	34.5
		SD	0.6	202.9	2777.8	0.4	6.7	2.0
		Min	14.6	533.9	25411.7	3.2	70.3	32.4
		Max	15.9	930.4	30936.0	3.9	83.1	36.5
		CV%	4.1	26.8	9.8	10.0	8.6	5.9
10mg/kg	E4-GS10-I1 pegylated	N	3	3	3	3	3	3
		Mean	**12.7**	67.2	1721.2	6.0	108.4	19.6
		SD	1.4	12.9	336.7	1.3	15.1	0.9
		Min	11.6	52.5	1338.0	5.1	95.5	18.7
		Max	14.3	76.8	1969.5	7.5	125.0	20.6
		CV%	11.0	19.2	19.6	21.8	13.9	4.8
	I1-GS10-E5 pegylated	N	2	2	2	2	2	2
		Mean	**19.0**	80.9	2345.6	4.4	118.7	23.7
		SD	1.5	3.2	526.4	1.0	17.1	0.6
		Min	17.9	78.7	1973.4	3.7	106.6	23.3
		Max	20.1	83.2	2717.8	5.1	130.8	24.1
		CV%	8.2	3.9	22.4	22.4	14.4	2.5
	I1-GS10-E4 pegylated	N	3	3	3	3	3	3
		Mean	**12.1**	85.9	1857.1	5.6	95.5	19.6
		SD	1.6	15.4	420.2	1.1	9.7	0.9
		Min	10.7	69.6	1581.1	4.3	85.0	18.6
		Max	13.8	100.2	2340.7	6.3	104.1	20.4
		CV%	12.9	17.9	22.6	20.1	10.2	4.7

Figure 45

SEQ ID NO	Binder	% inhibition at 100nM	Amino Acid Sequence
219	E6	80.0	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPYDVYTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
220	E7	89.4	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPYDVHTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
221	E8	92.4	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPYDLTTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
222	E9	77.3	MGVSDVPRDLEVVAATPTSLLISWEANPSRYQYYRITYGETGGNSPVQEFTVPHDLNTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
223	E10	84.7	MGVSDVPRDLEVVAATPTSLLISWYPGSRTYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYY HPATYEHEYHAHPISINYRTEIDKPSQ
224	E11	83.7	MGVSDVPRDLEVVAATPTSLLISWTPANKSYQYYRITYGETGGNSPVQEFTVPYDGTTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHEYPISINYRTEIDKPSQ
225	E12	76.5	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPHDVYTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
226	E13	86.7	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPGQVYTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
227	E14	80.4	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPYDVTTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
228	E15	88.8	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPHDLRTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
229	E16	97.7	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPYDLVTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHESPISINYRTEIDKPSQ
230	E3	87.5	MGVSDVPRDLEVVAATPTSLLISWLPGKLRYQYYRITYGETGGNSPVQEFTVPHDLRTATISGLKPGVDYTITVYAVTNMM HVEYSEYPISINYRTEIDKPSQH
231	E1	85.9	MGVSDVPRDLEVVAATPTSLLISWVAGAEDYQYYRITYGETGGNSPVQEFTVPHDLVTATISGLKPGVDYTITVYAVTDMM HVEYTEHPISINYRTEIDKPSQ
232	E17	75.5	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPGMVHTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHESPISINYRTEIDKPSQ

Figure 45 Con't

SEQ ID NO	Binder	% inhibition at 100nM	Amino Acid Sequence
233	E18	91.1	MGVSDVPRDLEVVAATPTSLLISWFVTHVAYQYYRITYGETGGNSPVQEFTVPGGLSTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
234	E19	84.6	MGVSDVPRDLEVVAATPTSLLISWETESNAYQYYRITYGETGGNSPVQEFTVPGQIYTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
235	E20	80.2	MGVSDVPRDLEVVAATPTSLLISWMTSPSVYQYYRITYGETGGNSPVQEFTVPGPVQTATISGLKPGVDYTITVYAVTDYK EHQHAPHQYTAHPISINYRTEIDKPSQ
236	E2	80.5	MGVSDVPRDLEVVAATPTSLLISWDSGRGSYQYYRITYGETGGNSPVQEFTVPGPVHTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHESPISINYRTEIDKPSQ
237	E22	83.7	MGVSDVPRDLEVVAATPTSLLISWSTGRTTYQYYRITYGETGGNSPVQEFTVPHDLDTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
238	E23	81.1	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPYDVITATISGLKPGVDYTITVYAVTDMM HVEYAEYPISINYRTEIDKPSQ
239	E24	90.3	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPGQVPTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
240	E25	77.1	MGVSDVPRDLEVVAATPTSLLISWGYQSGGYTYYRITYGETGGNSPVQEFTVPHDLRTATISGLKPGVDYTITVYAVTDYA YKEYQEHPISINYRTEIDKPSQ
241	E26	75.4	MGVSDVPRDLEVVAATPTSLLISWWIGIPVYQYYRITYGETGGNSPVQEFTVPYDGKTATISGLKPGVDYTITVYAVTDMM HVEYAEYPISINYRTEIDKPSQ
242	E27	94.6	MGVSDVPRDLEVVAATPTSLLISWSKGSKSYQYYRITYGETGGNSPVQEFTVPYHVYTATISGLKPGVDYTITVYAVTDYY NPATYEYIYLTTPISINYRTEIDKPSQ
243	E28	85.3	MGVSDVPRDLEVVAATPTSLLISWNPGSKSYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDFY NPDTHEYLYNQYPISINYRTEIDKPSQ
244	E29	87.9	MGVSDVPRDLEVVAATPTSLLISWQPGTTHYQYYRITYGETGGNSPVQEFTVPYDLMTATISGLKPGVDYTITVYAVTDYY NPNTYEYIYLTTPISINYRTEIDKPSQ
245	E30	87.3	MGVSDVPRDLEVVAATPTSLLISWAIGTIVYQYYRITYGETGGNSPVQEFTVPAGVYTATISGLKPGVDYTITVYAVTDYY DWATHEYNYHTAPISINYRTEIDKPSQ
246	E31	75.8	MGVSDVPRDLEVVAATPTSLLISWTYNDGSYQYYRITYGETGGNSPVQEFTVPYAVYTATISGLKPGVDYTITVYAVTDFY NPATYEYIYHTTPISINYRTEIDKPSQ

Figure 45 Con't

SEQ ID NO	Binder	% inhibition at 100nM	Amino Acid Sequence
247	E32	86.0	MGVSDVPRDLEVVAATPTSLLISWVSLVGFYQYYRITYGETGGNSPVQEFTVPGGVHTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
248	E33	75.8	MGVSDVPRDLEVVAATPTSLLISWASRKEVYQYYRITYGETGGNSPVQEFTVPGWLNTATISGLKPGVDYTITVYAVTDYM HVEYAEYPISINYRTEIDKPSQ
249	E34	80.4	MGVSDVPRDLEVVAATPTSLLISWLAPFWRYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
250	E35	90.2	MGVSDVPRDLEVVAATPTSLLISWTPPGHQHQYYRITYGETGGNSPVQEFTVPGQVTTATISGLKPGVDYTITVYAVTDYY NPATHYYTYYTTPISINYRTEIDKPSQ
251	E36	81.3	MGVSDVPRDLEVVAATPTSLLISWESGSRTYQYYRITYGETGGNSPVQEFTVPGGVHTATISGLKTGVDYTITVYAVTDYK PHADGPHTYHEYPISINYRTEIDKPSQ
252	E37	80.8	MGVSDVPRDLEVVAATPTSLLISWERTSTHYQYYRITYGETGGNSPVQEFTVPGRVYTATISGLKPGVDYTITVYAVTDYY NPATHEYKYHQTPISINYRTEIDKPSQ
253	E38	89.8	MGVSDVPRDLEVVAATPTSLLISWNARTDAYQYYRITYGETGGNSPVQEFTVPRDLETATISGLKPGVDYTITVYAVTDYK PHADGPHTYQESPISINYRTEIDKPSQ
254	E39	76.7	MGVSDVPRDLEVVAATPTSLLISWQVSAFRYQYYRITYGETGGNSPVQEFTVPGMVSTATISGLKPGVDYTITVYAVTDYK PHADGPHTYSEYPISINYRTEIDKPSQ
255	E40	89.6	MGVSDVPRDLEVVAATPTSLLISWVLGRRVYQYYRITYGETGGNSPVQEFTVPGAVYTATISGLKPGVDYTITVYAVTDYF NPATHEYQYELTPISINYRTEIDKPSQ
256	E41	75.2	MGVSDVPRDLEVVAATPTSLLISWTPPNSGHNYYRITYGETGGNSPVQEFTVPHDLTTATISGLKPGVDYTITVYAVTDYY NPNTYEYTYQFTPISINYRTEIDKPSQ
257	E42	77.3	MGVSDVPRDLEVVAATPTSLLISWVVPNWMYQYYRITYGETGGNSPVQEFTVPGMLETATISGLKPGVDYTITVYAVTDYY NPTTYEYTYFTYPISINYRTEIDKPSQ
258	E43	75.0	MGVSDVPRDLEVVAATPTSLLISWSGGFMRYQYYRITYGETGGNSPVQEFTVPGQVYTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
259	E44	83.3	MGVSDVPRDLEVVAATPTSLLISWDSEGPSYQYYRITYGETGGNSPVQEFTVPYAVYTATISGLKPGVDYTITVYAVTDYY NPRTHELFFQQYPISINYRTEIDKPSQ
260	E45	80.4	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGEKGGNSPVQEFTVPHDLRTATISGLKPGVDYTITVYAVTDYY DPTSNLYNYNQTPISINYRTEIDKPSQ

Figure 45 Con't

SEQ ID NO	Binder	% inhibition at 100nM	Amino Acid Sequence
261	E46	77.0	MGVSDVPRDLEVVAATPTSLLISWQVGSVVYQYYRITYGETGGNSPVQEFTVPRDVLTATISGLKPGVDYTITVYAVTDYK PKPDGPHIYQAVPISINYRTEIDKPSQ
262	E47	76.9	MGVSDVPRDLEVVAATPTSLLISWNPASKDYQYYRITYGETGGNSPVQEFTVPGQVPTATISGLKPGVDYTITVYAVTDFY NPATHEYKYDSTPISINYRTEIDKPSQ
263	E48	88.6	MGVSDVPRDLEVVAATPTSLLISWRSSATAYQYYRITYGETGGNSPVQEFTVPGRVYTATISGLKPGVDYTITVYAVTDFF NWATHEYIYHSTPISINYRTEIDKPSQ
264	E49	83.5	MGVSDVPRDLEVVAATPTSLLISWHSGPREYQYYRITYGETGGNSPVQEFTVPGQVYTATISGLKPGVDYTITVYAVTDFF NPITHYYYYELTPISINYRTEIDKPSQ
265	E50	77.4	MGVSDVPRDLEVVAATPTSLLISWTVGLSVYQYYRITYGETGGNSPVQEFTVPGMVSTATISGLKPSVDYTITVYAVTDYK PHADGPHTYHEYPISINYRTEIDKPSQ
266	E51	82.8	MGVSDVPRDLEVVAATPTSLLISWGGHRAVYQYYRITYGETGGNSPVQEFTVPGAVYTATISGLKPGVDYTITVYAVTDYY NPDTHEYKYHQYPISINYRTEIDKPSQ
267	E52	75.3	MGVSDVPRDLEVVSATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYW FKEYREDPISINYRTEIDKPSQ
268	E53	79.8	MGVSDVPRDLEVVAATPTSLLISWSVGGMIYQYYRITYGETGGNSPVQEFTVPGMVTTATISGLKPGVDYTITVYAVTDYY NPATHEYKYHQTPISINYRTEIDKPSQ
113, wherein X = Ser	E5	99.1	MGVSDVPRDLEVVAATPTSLLISWWAPVDRYQYYRITYGETGGNSPVQEFTVPRDVYTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
269	E54	76.1	MGVSDVPRDLEVVAATPTSLLISWKASYTGYNYYRITYGETGGNSPVQEFTVPRDVMTATISGLKPGVDYTITVYAVTDFY NPDTHQYTYRRIPISINYRTEIDKPSQ
270	E55	99.1	MGVSDVPRDLEVVAATPTSLLISWSVGQVFYQYYRITYGETGGNSPVQEFTVPYDVYTATISGLKPGVDYTITVYAVTDYY NPATHEYKYHQTPISINYRTEIDKPSQ
271	E56	84.2	MGVSDVPRDLEVVAATPTSLLISWYSGDYHYQYYRITYGETGGNSPVQEFTVPHDLETATISGLKPGVDYTITVYAVTDYY NPATHYYKYEQTPISINYRTEIDKPSQ
272	E57	75.5	MGVSDVPRDLEVVAATPTSLLISWIVQGGRYQYYRITYGETGGNSPVQEFTVPGMVTTATISGLKPGVDYTITVYAVTDYY NPSTHEYKYHQTPISINYRTEIDKPSQ
273	E58	79.7	MGVSDVPRDLEVVAATPTSLLISWSAVRWRYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDFY NPRTHVYIYDQFPISINYRTEIDKPSQ

Figure 45 Con't

SEQ ID NO	Binder	% inhibition at 100nM	Amino Acid Sequence
274	E59	76.3	MGVSDVPRDLEVVAATPTSLLISWRARRLQYQYYRITYGETGGNSPVQEFTVPGMVTTATISGLKPGVDYTITVYAVTDFY NPATMEYTYQRTPISINYRTEIDKPSQ
275	E60	100.0	MGVSDVPRDLEVVAATPTSLLISWLQPLWRYQYYRITYGETGGNSPVQEFTVPGGLDTATISGLKPGVDYTITVYAVTDYK PHVDGPHAYHEYPISINYRTEIDKPSQ
276	E61	79.8	MGVSDVPRDLEVVAATPTSLLISWDASQGNYQYYRITYGETGGNSPVQEFTVPGAVKTATISGLKPGVDYTITVYAVTDFF NPATHEYIYHTTPISINYRTEIDKPSQ
277	E62	78.9	MGVSDVPRDLEVVAATPTSLLISWCLDGQLYQYYRITYGETGGNSPVQEFTVPGSIVTATISGLKPGVDYTITVYAVTDWY NLATHEYNYRVTPISINYRTEIDKPSQ
278	E63	76.2	MGVSDVPRDLEVVAATPTSLLISWDTSGASYQYYRITYGETGGNSPVQEFTVPYSVYTATISGLKPGVDYTITVYAVTDYY DPDSHYYNYNMVPISINYRTEIDKPSQ
279	E64	78.2	MGVSDVPRDLEVVAATPTSLLISWDSGNGTYQYYRITYGETGGNSPVQEFTVPYRVYTATISGLKPGVDYTITVYAVTDYY NPATHEYTYELRPISINYRTEIDKPSQ
280	E65	80.7	MGVSDVPRDLEVVATTPTSLLISWRPTSQVYQYYRITYGETGGNSPVQEFTVPYNVYTATISGLKPGVDYTITVYAVTDFF NYATHEYIYHTIPISINYRTEIDKPSQ
281	E66	75.0	MGVSDVPRDLEVVAATPTSLLISWKSYGSAYQYYRITYGETGGNSPVQEFTVPGDLQTATISGLKPGVDYTITVYAITDYY NPDTHEYKYHVSPISINYRTEIDKPSQ
282	E67	75.3	MGVSDVPRDLEVVAATPTSLLISWSSVMGLYQYYRITYGETGGNSPVQEFTVPYDVYTATISGLKPGVDYTITVYAVTDYY NPSTYEYKYNTTPISINYRTEIDKPSQ
283	E68	78.5	MGVSDVPRDLEVVAATPTSLLISWKTEPGRHQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDWY NLVSHEYVYHTTPISINYRTEIDKPSQ
284	E69	85.1	MGVSDVPRDLEVVAATPTSLLISWHAGMAVYQYYRITYGETGGNSPVQEFTVPGDVLTATISGLKPGVDYTITVYAVTDFF NPVTHEYMYHTIPISINYRTEIDKPSQ
285	E70	76.8	MGVSDVPRDLEVVAATPTSLLISWVSARGRYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYY NLETYEYHYYRTPISINYRTEIDKPSQ
286	E71	80.4	MGVSDVPRDLEVVAATPTSLLISWWFGTSSYQYYRITYGETGGNSPVQEFTVPGDLKTATISGLKPGVDYTITVYAVTDYF NPVTHEYEYHTTPISINYRTEIDKPSQ
287	E72	82.8	MGVSDVPRDLEVVAATPTSLLISWSATRTLYQYYRITYGETGGNSPVQEFTVPYDVHTATISGLKPGVDYTITVYAVTDYY NMVTYEYNYHLTPISINYRTEIDKPSQ

Figure 45 Con't

SEQ ID NO	Binder	% inhibition at 100nM	Amino Acid Sequence
288	E73	78.8	MGVSDVPRDLEVVVATPTSLLISWTKLLGGYQYYRITYGETGGNSPVQEFTVPGPVYTATISGLKPGVDYTITVYAVTDFF NPRTHEYQYHTTPISINYRTEIDKPSQ
289	E74	80.9	MGVSDVPRDLEVVAATPTSLLISWRASGGLYQYYRITYGETGGNSPVQEFTVPGSVNTATISGLKPGVDYTITVYAVTDFY NPATYEYIYHTTPISINYRTEIDKPSQ
290	E75	76.5	MGVSDVPRDLEVVAATPTSLLISWAAGRATYQYYRITYGETGGNSPVQEFTVPYDVTTATISGLKPGVDYTITVYAVTDFY NPATHEYYYETTPISINYRTEIDKPSQ
291	E76	79.0	MGVSDVPRDLEVVAATPTSLLISWYSQPLTYQYYRITYGETGGNSPVQEFTVPHDVNTATISGLKPGVDYTITVYAVTDFY NPETHEYTYHLTPISINYRTEIDKPSQ
292	E77	81.1	MGVSDVPRDLEVVAATPTSLLISWSSATRPYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDFF NPTTHEYYYHTTPISINYRTEIDKPSQ
293	E78	76.9	MGVSDVPRDLEVVAATPTSLLISWSVERSVYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYY NPSTHEYNYLTTPISINYRTEIDKPSQ
294	E79	99.2	MGVSDVPRDLEVVAATPTSLLISWQDTSSYHQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYF NPSTHEYIYRTIPISINYRTEIDKPSQ
295	E80	89.6	MGVSDVPRDLEVVAATPTSLLISWSSSHRRYQYYRITYGETGGNSPVQEFTVPGSVATATISGLKPGVDYTITVYAVTDYF NPDTHEYLYHATPISINYRTEIDKPSQ
296	E81	75.1	MGVSDVPRDLEVVAATPTSLLISWDNNSNSYQYYRITYGETGGNSPVQEFTVPYDLRTATISGLKPGVDYTITVYAVTDYK PHTEGEHTYHESPISINYRTEIDKPSQ
297	E82	77.2	MGVSDVPRDLEVVAATPTSLLISWRVLVDMYQYYRITYGETGGNSPVQEFTVPGGVLTATISGLKPGVDYTITVYAVTDYK PHVDGPHTYYESPISINYRTEIDKPSQ
298	E83	90.7	MGVSDVPRDLEVVAATPTSLLISWMFVGMSYQYYRITYGETGGNSPVQEFTVPYGVHTATISGLKPGVDYTITVYAVTDYF NPATHEYIYHVTPISINYRTEIDKPSQ
299	E84	86.5	MGVSDVPRDLEVVAATPTSLLISWTLHRKNYQYYRITYGETGGNSPVQEFTVPGGVVTATISGLKPGVDYTITVYAVTDYY NPATHEYDYRTTPISINYRTEIDKPSQ
300	E85	89.3	MGVSDVPRDLEVVAATPTSLLISWTQGSTHYQYYRITYGETGGNSPVQEFTVPGMVYTATISGLKPGVDYTITVYAVTDYF DRSTHEYKYRTTPISINYRTEIDKPSQ
Residues 1-108 of SEQ ID NO: 107,	E4	94.3	MGVSDVPRDLEVVAATPTSLLISWHERDGSRQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYF NPTTHEYIYQTTPISINYRTEIDKPSQ

Figure 45 Con't

SEQ ID NO	Binder	% inhibition at 100nM	Amino Acid Sequence
wherein X = Ser			
301	E86	84.7	MGVSDVPRDLEVVAATPTSLLISWDSGENNYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYY NPKTHEYNYLTIPISINYRTEIDKPSQ
302	E87	87.0	MGVSDVPRDLEVVAATPTSLLISWGSPLIEYQYYRITYGETGGNSPVQEFTVPGGLSTATISGLKPGVDYTITVYAVTDYF NPATHEYTYHVSPISINYRTEIDKPSQ
303	E88	89.3	MGVSDVPRDLEVVAATPTSLLISWSATNKTYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYF NPTTHEYIYQTTPISINYRTEIDKPSQ
304	E89	82.6	MGVSDVPRDLEVVAATPTSLLISWDDPAANRQYYRITYGETGGNSPVQEFTVPYDLRTATISGLKPGVDYTITVYAVTDYY NPATHQYKYSQSPISINYRTEIDKPSQ
305	E90	81.3	MGVSDVPRDLEVVAATPTSLLISWYWEGLPYQYYRITYGETGGNSPVQEFTVPRDVNTATISGLKPGVDYTITVYAVTDWY NPDTHEYIYHTIPISINYRTEIDKPSQ
306	E91	84.7	MGVSDVPRDLEVVAATPTSLLISWSAPWRTYQYYRITYGETGGNSPVQEFTVPYDVYTATISGLKPGVDYTITVYAVTDYL NPNTLEYTYQRIPISINYRTEIDKPSQ
307	E92	88.5	MGVSDVPRDLEVVAATPTSLLISWQAANHSYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDFF NPVTHEYKYRTIPISINYRTEIDKPSQ
308	E93	76.9	MGVSDVPRDLEVVAATPTSLLISWDSGRGSYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHEYPISINYRTEIDKPSQ
309	E94	78.7	MGVSDVPRDLEVVAATPTSLLISWNNGGRNYQYYRITYGETGGNSPVQEFTVPYDVYTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHEYPISINYRTEIDKPSQ
310	E95	98.0	MGVSDVPRDLEVVAATPTSLLISWVVPQGMYQYYRITYGETGGNSPVQEFTVPGGVSTATISGLKPGVDYTITVYAVTDYF NPATHEYNYHSIPISINYRTEIDKPSQ
311	E96	91.7	MGVSDVPRDLEVVAATPTSLLISWASNRGTYQYYRITYGETGGNSPVQEFTVPGGVSTATISGLKPGVDYTITVYAVTDAF NPTTHEYNYFTTPISINYRTEIDKPSQ
312	E97	89.3	MGVSDVPRDLEVVAATPTSLLISWLPGKLRYQYYRITYGETGGNSPVQEFTVPHDLRTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
313	E98	75.8	MGVSDVPRDLEVVAATPTSLLISWDAPTSRYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHEYPISINYRTEIDKPSQ

Figure 45 Con't

SEQ ID NO	Binder	% inhibition at 100nM	Amino Acid Sequence
314	E99	84.7	MGVSDVPRDLEVVAATPTSLLISWDAPTSRYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHEYPISINYRTEIDKPSQ
315	E100	83.3	MGVSDVPRDLEVVAATPTSLLISWTPANKSYQYYRITYGETGGNSPVQEFTVPHDLVTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHEYPISINYRTEIDKPSQ
316	E101	90.9	MGVSDVPRDLEVVAATPTSLLISWDAPAVTYQYYRITYGETGGNSPVQEFTVPHDLVTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
317	E102	80.0	MGVSDVPRDLEVVAATPTSLLISWTPANKSYQYYRITYGETGGNSPVQEFTVPHDLVTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHESPISINYRTEIDKPSQ
318	E103	76.3	MGVSDVPRDLEVVAATPTSLLISWTPANKSYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTNMM HVEYSEYPISINYRTEIDKPSQ
319	E104	89.3	MGVSDVPRDLEVVAATPTSLLISWDAGAVTYQYYRITYGETGGNSPVQEFTVPHDLVTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHEYPISINYRTEIDKPSQ
320	E105	87.0	MGVSDVPRDLEVVAATPTSLLISWDAPTSRYQYYRITYGETGGNSPVQEFTVPGGLSTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
321	E106	84.0	MGVSDVPRDLEVVAATPTSLLISWDAPAVTYQYYRITYGETGGNSPVQEFTVPYDVYTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHEYPISINYRTEIDKPSQ
322	E107	75.8	MGVSDVPRDLEVVAATPTSLLISWDSGRGSYQYYRITYGETGGNSPVQEFTVPYDVYTATISGLKPGVDYTITVYAVTDMM HVEYTEHPISINYRTEIDKPSQH
323	E108	80.0	MGVSDVPRDLEVVAATPTSLLISWDAPAVTYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
324	E109	90.9	MGVSDVPRDLEVVAATPTSLLISWDAPTSRYQYYRITYGETGGNSPVQEFTVPHDLVTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
325	E110	81.3	MGVSDVPRDLEVVAATPTSLLISWDAGAVTYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
326	E111	85.5	MGVSDVPRDLEVVAATPTSLLISWDAPTSRYQYYRITYGETGGNSPVQEFTVPHDLVTATISGLKPGVDYTITVYAVTNMM HVEYSEYPISINYRTEIDKPSQ
327	E112	86.2	MGVSDVPRDLEVVAATPTSLLISWDAGAVTYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHEYPISINYRTEIDKPSQ

Figure 46

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                21        30                  51  56                                  76        87
WT   EVVAATPTSLLI SWDAPAVTVR YYRITYGETGGNSPVQEFTV PGSKST ATISGLKPGVDYTITVYAV TGRGDSPASSK     P ISINYRT
I1   EVVAATPTSLLI SWSARLKVAR YYRITYGETGGNSPVQEFTV PKNVYT ATISGLKPGVDYTITVYAV TRFRDYQ        P ISINYRT
E1   EVVAATPTSLLI SWVAGAEDYQ YYRITYGETGGNSPVQEFTV PHDLVT ATISGLKPGVDYTITVYAV TDMMHVEYTEH    P ISINYRT
E2   EVVAATPTSLLI SWDSGRGSYQ YYRITYGETGGNSPVQEFTV PGPVHT ATISGLKPGVDYTITVYAV TDHKPHADGPHTYHESP ISINYRT
E3   EVVAATPTSLLI SWLPGKLRYQ YYRITYGETGGNSPVQEFTV PHDLRT ATISGLKPGVDYTITVYAV TNMMHVEYSEY    P ISINYRT
E4   EVVAATPTSLLI SWHERDGSRQ YYRITYGETGGNSPVQEFTV PGGVRT ATISGLKPGVDYTITVYAV TDYFNPTTHEYIYQTTP ISINYRT
E5   EVVAATPTSLLI SWWAPVDRYQ YYRITYGETGGNSPVQEFTV PRDVYT ATISGLKPGVDYTITVYAV TDYKPHADGPHTYHESP ISINYRT
E85  EVVAATPTSLLI SWTQGSTHYQ YYRITYGETGGNSPVQEFTV PGMVYT ATISGLKPGVDYTITVYAV TDYFDRSTHEYKYRTTP ISINYRT
E90  EVVAATPTSLLI SWYWEGLPYQ YYRITYGETGGNSPVQEFTV PRDVNT ATISGLKPGVDYTITVYAV TDWYNPDTHEYIYHTIP ISINYRT
E96  EVVAATPTSLLI SWASNRGTYQ YYRITYGETGGNSPVQEFTV PGGVST ATISGLKPGVDYTITVYAV TDAFNPTTHEYNYFTTP ISINYRT
E105 EVVAATPTSLLI SWDAPTSRYQ YYRITYGETGGNSPVQEFTV PGGLST ATISGLKPGVDYTITVYAV TDYKPHADGPHTYHESP ISINYRT
E112 EVVAATPTSLLI SWDAGAVTYQ YYRITYGETGGNSPVQEFTV PGGVRT ATISGLKPGVDYTITVYAV TDYKPHADGPHTYHEYP ISINYRT
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Figure 47

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
328	I1 (with Cys tail)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTGCGCGTCTG AAAGTTGCGCGATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTAAAAACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAGGTTCCGCGACTACCAG CCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCACCACCACCACCAC
329	E6	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
330	E7	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT CATACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
331	E8	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACCTG ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
332	E9	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGAAGCTAACCCT TCTCGTTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG AACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
333	E10	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTACCCAGGATCT CGCACCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACTACCATCCGGCT ACTTACGAACATGAATACCATGCTCATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
334	E11	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACCCCTGCTAAT AAATCTTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGGT ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
335	E12	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
336	E13	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCAGGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
337	E14	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
338	E15	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
339	E16	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
340	E3	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTTGCCGGGCAAG CTGAGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAACATGATGCATGTTGAA TACTCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
341	E1	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGTGGCCGGGGCG GAGGACTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACATGATGCATGTTGAA TACACTGAACATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
342	E17	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGGTT CACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
343	E18	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTTCGTGACGCAC GTCGCCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTCTG TCCACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
344	E19	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGAGACGGAGAGC AACGCGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCAGATC TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
345	E20	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGATGACGTCGCCC TCGGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCCGGTT CAGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACAAAGAACATCAG CATGCTCCGCATCAGTACACTGCTCATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
346	E2	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATTCAGGACGA GGTTCCTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCCGGTT CATACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
347	E22	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCAACAGGTCGC ACAACTTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
348	E23	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT ATCACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACATGATGCATGTTGAA TACGCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
349	E24	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCAGGTT CCAACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
350	E25	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGGCTACCAAAGT GGCGGCTATACCTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACGCTTACAAAGAA TACCAGGAACATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
351	E26	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTGGATCGGCATC CCGGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGGT AAAACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACATGATGCATGTTGAA TACGCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
352	E27	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTAAAGGTTCA AAATCTTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACCATGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTATAACCCGGCT ACTTACGAATACATATACCTTACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
353	E28	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAATCCCGGCTCC AAAAGCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTACAATCCGGAT ACTCATGAATACCTATACAATCAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
354	E29	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAACCCGGCACC ACACATTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACCTG ATGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGAAT ACTTATGAGTATATATACTTGACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
355	E30	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGCCATCGGCACC ATCGTCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGCTGGTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACGACTGGGCT ACTCATGAATACAATTACCACACCGCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
356	E31	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACTTATAATGAT GGCAGCTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGCTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTACAATCCGGCT ACATATGAATACATATATCACACGACACCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
357	E32	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGTCTCCCTCGTG GGCTTCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CATACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
358	E33	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGCCTCGAGGAAG GAGGTCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTTGGTTG AACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACATGCATGTTGAA TACGCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
359	E34	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTTGGCGCCCTTC TGGCGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
360	E35	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACACCACCAGGA CATCAACATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCAGGTT ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCAGCT ACTCACTATTACACTTATTATACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
361	E36	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGAGTCGGGGTCC AGGACGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CATACAGCTACCATCAGCGGCCTTAAAACTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
362	E37	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGAGAGGACCTCC ACCCACTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCGTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
363	E38	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAATGCTCGCACC GACGCTTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCGTGACCTG GAAACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCTCATGCG GACGGACCGCATACTTACCAAGAGTCGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
364	E39	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTGAGCGCG TTCCGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGGTT TCTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACTCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
365	E40	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGTGCTGGGCAGG AGGGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGCTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTCAACCCAGCT ACCCATGAATACCAATACGAGCTTACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
366	E41	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACTCCACCCAAT TCTGGTCATAATTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGAAT ACCTATGAATACACATATCAATTCACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
367	E42	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGTCGTCCCGAAC TGGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGCTG GAAACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTATAACCCGACT ACGTATGAATACACATACTTTACCTATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
368	E43	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCCGGCGGGTTC ATGCGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCAGGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
369	E44	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATTCCGAAGGT CCTTCTTATCAATATTACCGCATCACTTACGGCGAAAAAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGCTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGAGA ACGCATGAATTATTTTTCCAGCAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
370	E45	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACGACCCGACA TCTAATCTGTACAATTACAACCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
371	E46	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTGGGCTCG GTGGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCGTGACGTT CTGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGAAGCCT GACGGTCCACATATATACCAGGCAGTGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
372	E47	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAACCCTGCTTCT AAAGACTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCAGGTT CCGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTACAACCCGGCT ACTCATGAGTATAAATATGACTCGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
373	E48	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAGATCATCAGCA ACCGCCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCGTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTCAACTGGGCC ACTCATGAGTACATATACCACTCAACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
374	E49	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCATTCCGGTCCA CGAGAATATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCAGGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTCAACCCGATT ACACATTACTATTACTACGAGCTGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
375	E50	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACGGTGGGCCTG AGCGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGGTT TCTACAGCTACCATCAGCGGCCTTAAACCTAGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
376	E51	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGGGGGGCACCGG GCGGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGCTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACTACAACCCGGAT ACTCATGAATACAAATACCATCAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
377	E52	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTTCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACTGGTTCAAGGAA TACCGTGAAGACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
378	E53	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAGCGTCGGGGGC ATGATCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGGTT ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
379	E5	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTGGGCCCCCGTC GACCGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCGTGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
380	E5 (with Cys tail)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTGGGCCCCCGTC GACCGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCGTGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCACCACCAC CACCAC
381	E54	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAAAGCCAGCTAT ACCGGCTACAACTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCGTGACGTT ATGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTCTACAATCCGGAT ACTCATCAATACACATACCGTCGCATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
382	E55	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCGGTGGGCCAG GTCTTCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
383	E56	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTACTCTGGTGAT TACCATTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GAAACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGGCT ACTCATTACTACAAGTACGAGCAGACACCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
384	E57	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTTGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGATCGTCCAGGGG GGGCGCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGGTT ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCTTCA ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
385	E58	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCGGCCGTCCGC TGGCGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTACAACCCGCGT ACTCATGTATACATATACGATCAGTTCCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
386	E59	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAGGGCCAGGCGC TTGCAGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGGTT ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTACAACCCGGCT ACTATGGAGTACACATATCAGCGGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
387	E60	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTTGCAGCCCCTC TGGAGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTCTG GACACAGCTACCATCAGCGGACTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGTT GACGGTCCCCATGCTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
388	E61	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCCTCCCAG GGGAACTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGCTGTT AAAACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTCAACCCGGCT ACTCATGAATACATATACCATACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
389	E62	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTGCCTCGACGGG CAGTTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTTCTATC GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTGGTACAACCTCGCG ACTCATGAATACAACTACCGTGTGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
390	E63	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACACTTCAGGT GCTTCATATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACTCTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACGACCCTGAT TCGCATTATTACAACTACAATATGGTTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
391	E64	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATTCTGGTAAT GGTACTTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACCGTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGGCT ACTCACGAATATACATACGAGCTGCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
392	E65	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTACCACCCCCACCAGCCTGCTGATCAGCTGGCGGCCCACCAGC CAGGTCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACAACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTTAACTATGCT ACTCACGAATACATATACCATACCATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
393	E66	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAAGTCGTACGGG TCGGCCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGACCTG CAGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTATCACTGACTATTACAACCCGGAT ACACATGAGTATAAATACCATGTGTCGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
394	E67	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCGTCGGTGATG GGGTTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCTTCT ACTTATGAATACAAATACAATACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
495	E68	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAAAACAGAACCA GGCCGCCACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTGGTACAACCTGGTT TCTCATGAATACGTATACCATACTACCCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
395	E69	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCACGCCGGCATG GCGGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGACGTT CTGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTCAATCCGGTT ACTCATGAATACATGTATCATACGATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
396	E70	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGTGTCCGCGAGG GGGCGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCTAGAA ACTTATGAATATCATTACTATCGCACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
397	E71	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTGGTTCGGCACC TCGTCCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGACCTG AAAACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTTAACCCCGTT ACTCATGAATACGAATATCATACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
398	E72	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCCGCGACCCGG ACCCTGTACCAATATTACCGAATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT CATACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACATGGTT ACTTATGAATACAACTACCATCTTACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
399	E73	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGTTGCCACCCCCACCAGCCTGCTGATCAGCTGGACCAAGTTGTTG GGCGGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCCTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTCAACCCTCGT ACTCATGAATATCAATATCACACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
400	E74	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAGGGCGTCGGGC GGGCTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTTCTGTT AACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTACAACCCGGCT ACTTATGAGTACATATACCATACCACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
401	E75	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGCGGCCGGGCGC GCCACGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTACAACCCGGCT ACTCATGAATACTACTATGAGACCACGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
402	E76	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTACTCGCAGCCC TTGACGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACGTT AACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTCTACAACCCGGAG ACACATGAATACACTTACCACCTGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
403	E77	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAGTTCTGCAACA AGACCTTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTCAACCCGACT ACGCACGAATACTATTATCATACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
404	E78	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCCGTCGAGAGG TCCGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGTCT ACTCATGAATACAATTACCTCACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
405	E79	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAAGATACCTCC AGTTATCATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTCAACCCGTCT ACCCATGAATACATCTACCGTACCATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
406	E80	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTAGCTCTCAT CGCCGCTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTTCGGTT GCTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTCAACCCAGAC ACTCATGAATACCTATACCATGCCACCCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
407	E81	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATAATAATTCT AACTCATATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACCTG CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCTCATACT GAGGGTGAGCATACTTATCATGAATCGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
408	E82	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCGCGTGTTGGTC GACATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CTGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGTT GACGGGCCGCACACCTACTATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
409	E83	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGATGTTCGTGGGG ATGTCCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGGTGTT CATACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTCAACCCGGCT ACGCATGAATACATCTACCATGTGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
410	E84	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACGCTGCACCGG AAGAACTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGGCA ACTCATGAATACGACTACCGAACAACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
411	E85	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTTCTGATCAGCTGGACACAAGGCAGT ACTCATTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTCGACCGCTCT ACTCATGAGTATAAATACCGTACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
412	E4	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCACGAACGTGAC GGAAGTAGACAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTTAACCCGACT ACACATGAATACATATATCAGACAACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
413	E86	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACTCCGGTGAA AACAATTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGAAG ACTCATGAATATAATTATCTTACTATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
414	E87	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGGGAGCCCCTTG ATCGAGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTCTG TCTACAGCTACCATCAGCGGCCTCAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTCAACCCGGCT ACTCATGAATACACATACCATGTGAGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
415	E88	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTGCAACAAAC AAAACTTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTTAACCCGACT ACACATGAATACATATATCAGACAACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
416	E89	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATGACCCAGCT GCAAACCGACAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACCTG CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGGCT ACCCATCAATACAAATACTCTCAGAGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
417	E90	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTACTGGGAGGGG CTGCCCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCGTGACGTT AACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTGGTACAACCCCGAC ACCCATGAGTATATATACCATACGATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
418	E91	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAGCGCGCCGTGG CGGACCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTAAACCCTAAC ACGCTTGAATACACCTACCAGCGCATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
419	E92	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGCGGCCAAC CACTCGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTCAATCCTGTC ACTCATGAATACAAATACCGTACAATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
420	E93	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATTCAGGACGA GGTTCCTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCACGCT GACGGTCCGCACACTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
421	E94	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAATAACGGAGGA CGCAATTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCACGCT GACGGTCCGCACACTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
422	E95	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGTCGTGCCGCAG GGGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT TCTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTCAACCCGGCA ACCCATGAATACAATTATCATTCAATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
423	E96	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGCGAGCAACCGG GGGACGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT TCTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACGCTTTCAACCCAACT ACTCATGAATACAATTATTTTACAACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
424	E97	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTTGCCGGGCAAG CTGAGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
425	E98	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCAACC TCCCGCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
426	E99	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCAACC TCCCGCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCACGCT GACGGTCCGCACACTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
427	E100	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACCCCTGCTAAT AAATCTTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
428	E101	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCGGCT GTTACTTACCAGTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
429	E102	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACCCCTGCTAAT AAATCTTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
430	E103	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACCCCTGCTAAT AAATCTTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAACATGATGCATGTTGAA TACTCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
431	E104	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTGGTGCT GTTACTTACCAGTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
432	E105	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCAACC TCCCGCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTCTG TCCACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
433	E106	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCGGCT GTTACTTACCAGTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCACGCT GACGGTCCGCACACTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
434	E107	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATTCAGGACGA GGTTCCTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACATGATGCATGTTGAA TACACTGAACATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
435	E108	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCGGCT GTTACTTACCAGTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
436	E109	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCAACC TCCCGCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
437	E110	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTGGTGCT GTTACTTACCAGTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
438	E111	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCAACC TCCCGCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAACATGATGCATGTTGAA TACTCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC

Figure 47 Con't

SEQ ID NO	BINDER	NUCLEOTIDE SEQUENCE
439	E112	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTGGTGCT GTTACTTACCAGTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCACGCT GACGGTCCGCACACTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
440	E113	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTATCCTGGCCAA CCAACATATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCATTGTGCCTTACCTGGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACGCTTACAAAGAA TACTCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
441	E114	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAAAGTTCAACC AGCCAATATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

Figure 48

SEQ ID NO	Binder	DNA SEQ
442	E3-GS10-I1	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTTGCCGGGCA AGCTGAGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGA CCTGCGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAACATGATGCAT GTTGAATACTCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAAGGTAGCGGCTCTGGTTCCGGCAGCGGCT CCGGCAGCGGCTCTGGCAGCGGTTCTGGTTCCGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAG CCTGCTGATCAGCTGGTCTGCGCGTCTGAAAGTTGCGCGATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCT GTCCAGGAGTTCACTGTGCCTAAAAACGTTTACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTG TGTATGCTGTCACTAGGTTCCGCGACTACCAGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCA CCACCACCACCAC
443	I1-GS10-E3	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTGCGCGTC TGAAAGTTGCGCGATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTAAAAA CGTTTACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAGGTTCCGCGAC TACCAGCCAATTTCCATTAATTACCGCACAGAAATTGACAAAGGTAGCGGCTCTGGTTCCGGCAGCGGCTCCGGCAGCGGCT CTGGCAGCGGTTCTGGTTCCGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAG CTGGTTGCCGGGCAAGCTGAGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTC ACTGTGCCTCATGACCTGCGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCA CTAACATGATGCATGTTGAATACTCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCA CCACCACCACCAC
444	E1-GS10-I1	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGTGGCCGGGG CGGAGGACTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGA CCTGGTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACATGATGCAT GTTGAATACACTGAACATCCAATTTCCATTAATTACCGCACAGAAATTGACAAAGGTAGCGGCTCTGGTTCCGGCAGCGGCT CCGGCAGCGGCTCTGGCAGCGGTTCTGGTTCCGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAG CCTGCTGATCAGCTGGTCTGCGCGTCTGAAAGTTGCGCGATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCT GTCCAGGAGTTCACTGTGCCTAAAAACGTTTACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTG TGTATGCTGTCACTAGGTTCCGCGACTACCAGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCA CCACCACCACCAC

Figure 48 Con't

SEQ ID NO	Binder	DNA SEQ
445	I1-GS10-E1	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTGCGCGTC TGAAAGTTGCGCGATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTAAAAA CGTTTACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAGGTTCCGCGAC TACCAGCCAATTTCCATTAATTACCGCACAGAAATTGACAAAGGTAGCGGCTCTGGTTCCGGCAGCGGCTCCGGCAGCGGCT CTGGCAGCGGTTCTGGTTCCGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAG CTGGGTGGCCGGGGCGGAGGACTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTC ACTGTGCCTCATGACCTGGTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCA CTGACATGATGCATGTTGAATACACTGAACATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCA CCACCACCACCAC
446	E2-GS10-I1	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATTCAGGAC GAGGTTCCTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCC GGTTCATACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCG CATGCTGACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAAGGTAGCGGCTCTG GTTCCGGCAGCGGCTCCGGCAGCGGCTCTGGCAGCGGTTCTGGTTCCGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGC TGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTGCGCGTCTGAAAGTTGCGCGATATTACCGCATCACTTACGGCGAAACA GGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTAAAAACGTTTACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTG ATTATACCATCACTGTGTATGCTGTCACTAGGTTCCGCGACTACCAGCCAATTTCCATTAATTACCGCACAGAAATTGACAA ACCATGCCAGCACCACCACCACCACCAC
447	I1-GS10-E2	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTGCGCGTC TGAAAGTTGCGCGATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTAAAAA CGTTTACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAGGTTCCGCGAC TACCAGCCAATTTCCATTAATTACCGCACAGAAATTGACAAAGGTAGCGGCTCTGGTTCCGGCAGCGGCTCCGGCAGCGGCT CTGGCAGCGGTTCTGGTTCCGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAG CTGGGATTCAGGACGAGGTTCCTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTC ACTGTGCCTGGTCCGGTTCATACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCA CTGACCATAAACCGCATGCTGACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAA ACCATGCCAGCACCACCACCACCACCAC
448	E5-GS10-I1	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAGGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTTCTTGGTGGGCACCGG TTGATCGTTATCAGTATTATCGCATCACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCTCGCGA CGTTTATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTACGCCGTTACCGATTATAAACCG CATGCAGATGGTCCGCATACCTATCATGAAAGCCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCG GTTCAGGTAGCGGATCAGGTTCTGGTTCTGGTAGTGGTAGCGGCAGCGTTTCAGATGTGCCTCGCGACCTGGAAGTGGTGGC AGCCACACCGACTTCTCTGCTGATTAGCTGGTCTGCACGTCTGAAAGTTGCCCGTTATTACCGTATTACTTATGGCGAAACA GGCGGAAATAGCCCTGTGCAAGAATTTACCGTGCCGAAAAATGTGTACACAGCCACCATCTCTGGCCTGAAACCTGGCGTGG ACTACACAATCACAGTTTATGCAGTGACCCGTTTTCGTGATTATCAGCCGATCAGCATCAATTATCGTACAGAGATCGATAA ACCGTGCCAGCATCACCACCATCATCAC

Figure 48 Con't

SEQ ID NO	Binder	DNA SEQ
449	E85-GS10-I1	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAGGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTTCTTGGACCCAGGGTA GCACACATTATCAGTATTATCGCATCACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCTGGTAT GGTTTATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTACGCCGTTACCGATTATTTCGAT CGGTCCACCCATGAATATAAATATCGGACCACCCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCG GTTCAGGTAGCGGATCAGGTTCTGGTTCTGGTAGTGGTAGCGGCAGCGTTTCAGATGTGCCTCGCGACCTGGAAGTGGTGGC AGCCACACCGACTTCTCTGCTGATTAGCTGGTCTGCACGTCTGAAAGTTGCCCGTTATTACCGTATTACTTATGGCGAAACA GGCGGAAATAGCCCTGTGCAAGAATTTACCGTGCCGAAAAATGTGTACACAGCCACCATCTCTGGCCTGAAACCTGGCGTGG ACTACACAATCACAGTTTATGCAGTGACCCGTTTTCGTGATTATCAGCCGATCAGCATCAATTATCGTACAGAGATCGATAA ACCGTGCCAGCATCACCACCATCATCAC
450	E4-GS10-I1	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAGGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTTCTTGGCATGAACGTG ATGGTAGCCGTCAGTATTATCGCATCACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCTGGCGG TGTTCGTACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTACGCCGTTACCGATTATTTCAAT CCGACCACCCATGAATATATTTATCAGACCACCCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCG GTTCAGGTAGCGGATCAGGTTCTGGTTCTGGTAGTGGTAGCGGCAGCGTTTCAGATGTGCCTCGCGACCTGGAAGTGGTGGC AGCCACACCGACTTCTCTGCTGATTAGCTGGTCTGCACGTCTGAAAGTTGCCCGTTATTACCGTATTACTTATGGCGAAACA GGCGGAAATAGCCCTGTGCAAGAATTTACCGTGCCGAAAAATGTGTACACAGCCACCATCTCTGGCCTGAAACCTGGCGTGG ACTACACAATCACAGTTTATGCAGTGACCCGTTTTCGTGATTATCAGCCGATCAGCATCAATTATCGTACAGAGATCGATAA ACCGTGCCAGCATCACCACCATCATCAC
451	E90-GS10-I1	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAGGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTTCTTGGTATTGGGAAG GTCTGCCGTATCAGTATTATCGCATCACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTCACCGTTCCTCGCGA CGTTAATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTACGCCGTTACCGATTGGTACAAC CCTGATACCCATGAATATATTTATCATACCATTCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCG GTTCAGGTAGCGGATCAGGTTCTGGTTCTGGTAGTGGTAGCGGCAGCGTTTCAGATGTGCCTCGCGACCTGGAAGTGGTGGC AGCCACACCGACTTCTCTGCTGATTAGCTGGTCTGCACGTCTGAAAGTTGCCCGTTATTACCGTATTACTTATGGCGAAACA GGCGGAAATAGCCCTGTGCAAGAATTTACCGTGCCGAAAAATGTGTACACAGCCACCATCTCTGGCCTGAAACCTGGCGTGG ACTACACAATCACAGTTTATGCAGTGACCCGTTTTCGTGATTATCAGCCGATCAGCATCAATTATCGTACAGAGATCGATAA ACCGTGCCAGCATCACCACCATCATCAC
452	E96-GS10-I1	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAGGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTTCTTGGGCAAGCAATC GTGGCACCTATCAGTATTATCGCATCACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCTGGCGG TGTTTCTACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTACGCCGTTACCGATGCATTTAAT CCGACCACCCATGAATATAATTATTTTACCACCCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCG GTTCAGGTAGCGGATCAGGTTCTGGTTCTGGTAGTGGTAGCGGCAGCGTTTCAGATGTGCCTCGCGACCTGGAAGTGGTGGC AGCCACACCGACTTCTCTGCTGATTAGCTGGTCTGCACGTCTGAAAGTTGCCCGTTATTACCGTATTACTTATGGCGAAACA GGCGGAAATAGCCCTGTGCAAGAATTTACCGTGCCGAAAAATGTGTACACAGCCACCATCTCTGGCCTGAAACCTGGCGTGG ACTACACAATCACAGTTTATGCAGTGACCCGTTTTCGTGATTATCAGCCGATCAGCATCAATTATCGTACAGAGATCGATAA ACCGTGCCAGCATCACCACCATCATCAC

Figure 48 Con't

SEQ ID NO	Binder	DNA SEQ
453	E105-GS10-I1	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAGGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTTCTTGGGATGCACCGA CCTCTCGTTATCAGTATTATCGCATCACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCTGGCGG TCTGAGCACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTACGCCGTTACCGATTATAAACCG CATGCAGATGGTCCGCATACCTATCATGAAAGCCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCG GTTCAGGTAGCGGATCAGGTTCTGGTTCTGGTAGTGGTAGCGGCAGCGTTTCAGATGTGCCTCGCGACCTGGAAGTGGTGGC AGCCACACCGACTTCTCTGCTGATTAGCTGGTCTGCACGTCTGAAAGTTGCCCGTTATTACCGTATTACTTATGGCGAAACA GGCGGAAATAGCCCTGTGCAAGAATTTACCGTGCCGAAAAATGTGTACACAGCCACCATCTCTGGCCTGAAACCTGGCGTGG ACTACACAATCACAGTTTATGCAGTGACCCGTTTTCGTGATTATCAGCCGATCAGCATCAATTATCGTACAGAGATCGATAA ACCGTGCCAGCATCACCACCATCATCAC
454	E112-GS10-I1	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAGGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTTCTTGGGATGCAGGTG CAGTTACCTATCAGTATTATCGCATCACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCTGGCGG TGTTCGTACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTACGCCGTTACCGATTATAAACCG CATGCAGATGGTCCGCATACCTATCATGAATATCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCG GTTCAGGTAGCGGATCAGGTTCTGGTTCTGGTAGTGGTAGCGGCAGCGTTTCAGATGTGCCTCGCGACCTGGAAGTGGTGGC AGCCACACCGACTTCTCTGCTGATTAGCTGGTCTGCACGTCTGAAAGTTGCCCGTTATTACCGTATTACTTATGGCGAAACA GGCGGAAATAGCCCTGTGCAAGAATTTACCGTGCCGAAAAATGTGTACACAGCCACCATCTCTGGCCTGAAACCTGGCGTGG ACTACACAATCACAGTTTATGCAGTGACCCGTTTTCGTGATTATCAGCCGATCAGCATCAATTATCGTACAGAGATCGATAA ACCGTGCCAGCATCACCACCATCATCAC
455	I1-GS10-E5	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAAGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTAGCTGGTCTGCACGTC TGAAAGTTGCCCGTTATTATCGCATTACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCGAAAAA TGTTTATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTATGCAGTTACCCGTTTTCGTGAT TATCAGCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCGGTTCTGGTAGCGGTTCAGGTTCTGGTT CTGGTAGTGGTAGCGGCAGCGTTTCAGACGTGCCTCGTGATTTAGAAGTGGTGGCAGCCACACCGACCTCACTGCTGATTTC TTGGTGGGCACCGGTTGATCGTTATCAGTATTATCGCATCACATACGGCGAAACAGGCGGAAATAGCCCTGTGCAAGAATTC ACCGTACCGCGTGATGTGTATACCGCCACAATTTCTGGTTTAAAACCTGGCGTGGACTACACAATCACAGTTTATGCCGTGA CCGATTATAAACCGCATGCAGATGGTCCGCATACCTATCATGAAAGCCCGATCTCTATCAATTATCGCACAGAGATCGATAA ACCGTGTCAGCATCACCACCATCATCAC
456	I1-GS10-E85	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAAGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTAGCTGGTCTGCACGTC TGAAAGTTGCCCGTTATTATCGCATTACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCGAAAAA TGTTTATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTATGCAGTTACCCGTTTTCGTGAT TATCAGCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCGGTTCTGGTAGCGGTTCAGGTTCTGGTT CTGGTAGTGGTAGCGGCAGCGTTTCAGACGTGCCTCGTGATTTAGAAGTGGTGGCAGCCACACCGACCTCACTGCTGATTTC TTGGACCCAGGGTAGCACACATTATCAGTATTATCGCATCACATACGGCGAAACAGGCGGAAATAGCCCTGTGCAAGAATTC ACCGTACCGGGTATGGTGTATACCGCCACAATTTCTGGTTTAAAACCTGGCGTGGACTACACAATCACAGTTTATGCCGTGA CCGATTATTTCGATCGCAGCACCCATGAATATAAATATCGTACCACCCCGATCTCTATCAATTATCGCACAGAGATCGATAA ACCGTGTCAGCATCACCACCATCATCAC

Figure 48 Con't

SEQ ID NO	Binder	DNA SEQ
457	I1-GS10-E4	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAAGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTAGCTGGTCTGCACGTC TGAAAGTTGCCCGTTATTATCGCATTACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCGAAAAA TGTTTATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTATGCAGTTACCCGTTTTCGTGAT TATCAGCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCGGTTCTGGTAGCGGTTCAGGTTCTGGTT CTGGTAGTGGTAGCGGCAGCGTTTCAGACGTGCCTCGTGATTTAGAAGTGGTGGCAGCCACACCGACCTCACTGCTGATTTC TTGGCATGAACGTGATGGTAGCCGTCAGTATTATCGCATCACATACGGCGAAACAGGCGGAAATAGCCCTGTGCAAGAATTC ACCGTACCGGGTGGTGTTCGTACCGCCACAATTTCTGGTTTAAAACCTGGCGTGGACTACACAATCACAGTTTATGCCGTGA CCGATTATTTCAATCCGACCACCCACGAATATATTTATCAGACCACCCCGATCTCTATCAATTATCGCACAGAGATCGATAA ACCGTGTCAGCATCACCACCATCATCAC
458	I1-GS10-E105	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAAGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTAGCTGGTCTGCACGTC TGAAAGTTGCCCGTTATTATCGCATTACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCGAAAAA TGTTTATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTATGCAGTTACCCGTTTTCGTGAT TATCAGCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCGGTTCTGGTAGCGGTTCAGGTTCTGGTT CTGGTAGTGGTAGCGGCAGCGTTTCAGACGTGCCTCGTGATTTAGAAGTGGTGGCAGCCACACCGACCTCACTGCTGATTTC TTGGGATGCACCGACCAGCCGTTATCAGTATTATCGCATCACATACGGCGAAACAGGCGGAAATAGCCCTGTGCAAGAATTC ACCGTACCGGGTGGTCTGAGCACCGCCACAATTTCTGGTTTAAAACCTGGCGTGGACTACACAATCACAGTTTATGCCGTGA CCGATTATAAACCGCATGCAGATGGTCCGCATACCTATCATGAAAGCCCGATCTCTATCAATTATCGCACAGAGATCGATAA ACCGTGTCAGCATCACCACCATCATCAC
459	I1-GS10-E112	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAAGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTAGCTGGTCTGCACGTC TGAAAGTTGCCCGTTATTATCGCATTACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCGAAAAA TGTTTATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTATGCAGTTACCCGTTTTCGTGAT TATCAGCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCGGTTCTGGTAGCGGTTCAGGTTCTGGTT CTGGTAGTGGTAGCGGCAGCGTTTCAGACGTGCCTCGTGATTTAGAAGTGGTGGCAGCCACACCGACCTCACTGCTGATTTC TTGGGATGCCGGTGCAGTTACCTATCAGTATTATCGCATCACATACGGCGAAACAGGCGGAAATAGCCCTGTGCAAGAATTC ACCGTACCGGGTGGTGTTCGTACCGCCACAATTTCTGGTTTAAAACCTGGCGTGGACTACACAATCACAGTTTATGCCGTGA CCGATTATAAACCGCATGCAGATGGTCCGCATACCTATCATGAATATCCGATCTCTATCAATTATCGCACAGAGATCGATAA ACCGTGTCAGCATCACCACCATCATCAC
460	I1-GSGCGS8-E5	ATGGGCGTGAGTGATGTTCCGCGTGATCTGGAAGTGGTTGCAGCAACCCCGACGAGCCTGCTGATTAGCTGGTCTGCCCGCC TGAAAGTGGCACGTTATTACCGCATCACCTACGGCGAAACGGGCGGTAACTCTCCGGTTCAGGAATTTACCGTGCCGAAAAA TGTTTATACCGCAACGATTAGCGGCCTGAAACCGGGTGTGGATTATACCATCACGGTGTACGCGGTTACCCGTTTCCGCGAT TACCAGCCGATTAGCATCAACTATCGTACGGAAATTGAAAAAGGCTCTGGTTGCGGCAGTGGTAGCGGCTCTGGTAGTGGCA GCGGTTCTGGCAGTGGTAGCGTGTCTGACGTCCCGCGCGACCTGGAAGTTGTTGCAGCGACCCCGACCAGCCTGCTGATTAG TTGGTGGGCCCCGGTGGATCGTTACCAGTATTACCGCATCACCTATGGCGAAACCGGTGGTAACAGCCCGGTGCAAGAATTT ACCGTGCCGCGTGATGTTTATACCGCGACCATCTCTGGTCTGAAACCGGGCGTTGACTACACGATTACCGTTTACGCGGTTA CCGATTATAAACCGCATGCCGATGGTCCGCATACGTACCACGAAAGTCCGATTAGCATCAATTATCGGACCGAACATCACCA TCACCATCAC

Figure 48 Con't

SEQ ID NO	Binder	DNA SEQ
461	I1-GS10-E5-GSGC	ATGGGCGTGTCTGATGTTCCGCGTGATCTGGAAGTGGTTGCGGCCACCCCGACGAGTCTGCTGATTAGCTGGTCTGCCCGCC TGAAAGTGGCACGTTATTACCGCATCACCTACGGCGAAACGGGCGGTAACAGCCCGGTTCAGGAATTTACCGTGCCGAAAAA TGTTTATACCGCAACGATTTCTGGCCTGAAACCGGGTGTGGATTATACCATCACGGTGTACGCGGTTACCCGTTTCCGCGAT TACCAGCCGATTAGCATCAACTATCGTACGGAAATTGAAAAAGGCAGTGGTAGCGGCTCTGGTAGTGGCAGCGGTTCTGGCA GTGGTAGCGGCTCTGGTAGTGTAAGCGACGTCCCGCGCGATCTGGAAGTGGTTGCAGCGACCCCGACGAGCCTGCTGATTTC TTGGTGGGCCCCGGTGGATCGTTACCAGTATTACCGCATCACCTATGGCGAAACCGGTGGCAATTCTCCGGTGCAAGAATTC ACCGTGCCGCGTGATGTTTATACCGCGACGATTAGCGGTCTGAAACCGGGCGTTGACTACACGATTACCGTGTACGCGGTTA CCGATTATAAACCGCATGCCGATGGTCCGCATACGTACCACGAATCTCCGATTAGTATCAATTATCGGACCGAAGGCAGTGG TTGCCATCACCATCACCATCAC
462	I1(S62C)-GS10-E5	ATGGGCGTGAGTGATGTTCCGCGTGATCTGGAAGTGGTTGCAGCAACCCCGACGAGCCTGCTGATTAGCTGGTCTGCCCGCC TGAAAGTGGCACGTTATTACCGCATCACCTACGGCGAAACGGGCGGTAACAGCCCGGTTCAGGAATTTACCGTGCCGAAAAA TGTTTATACCGCAACGATTTGCGGCCTGAAACCGGGTGTGGATTATACCATCACGGTGTACGCGGTTACCCGTTTCCGCGAT TACCAGCCGATTAGCATCAACTATCGTACGGAAATTGAAAAAGGCAGTGGTAGCGGCTCTGGTAGTGGCAGCGGTTCTGGCA GTGGTAGCGGCTCTGGTAGTGTAAGCGACGTCCCGCGCGACCTGGAAGTTGTTGCAGCGACGCCGACGAGCCTGCTGATCTC TTGGTGGGCCCCGGTGGATCGTTACCAGTATTACCGCATCACCTATGGCGAAACCGGTGGTAACTCTCCGGTGCAAGAATTT ACCGTGCCGCGTGATGTTTATACCGCGACGATTTCTGGTCTGAAACCGGGCGTTGACTACACGATTACCGTTTACGCGGTTA CCGATTATAAACCGCATGCCGATGGTCCGCATACGTACCACGAATCTCCGATTAGTATCAATTATCGGACCGAACATCACCA TCACCATCAC
463	I1-GS10-E5(S62C)	ATGGGCGTGAGTGATGTTCCGCGTGATCTGGAAGTGGTTGCAGCAACCCCGACGAGCCTGCTGATTAGCTGGTCTGCCCGCC TGAAAGTGGCACGTTATTACCGCATCACCTACGGCGAAACGGGCGGTAACTCTCCGGTTCAGGAATTTACCGTGCCGAAAAA TGTTTATACCGCAACGATTAGCGGCCTGAAACCGGGTGTGGATTATACCATCACGGTGTACGCGGTTACCCGTTTCCGCGAT TACCAGCCGATTAGCATCAACTATCGTACGGAAATTGAAAAAGGCAGTGGTAGCGGCTCTGGTAGTGGCAGCGGTTCTGGCA GTGGTAGCGGCTCTGGTAGTGTAAGCGACGTCCCGCGCGACCTGGAAGTTGTTGCAGCGACGCCGACGAGCCTGCTGATCTC TTGGTGGGCCCCGGTGGATCGTTACCAGTATTACCGCATCACCTATGGCGAAACCGGTGGTAACAGCCCGGTGCAAGAATTT ACCGTGCCGCGTGATGTTTATACCGCGACGATTTGTGGTCTGAAACCGGGCGTTGACTACACGATTACCGTTTACGCGGTTA CCGATTATAAACCGCATGCCGATGGTCCGCATACGTACCACGAATCTCCGATTAGTATCAATTATCGGACCGAACATCACCA TCACCATCAC
464	I1(S91C)-GS10-E5	ATGGGCGTGAGTGATGTTCCGCGTGATCTGGAAGTGGTTGCAGCAACCCCGACGAGCCTGCTGATTAGCTGGTCTGCCCGCC TGAAAGTGGCACGTTATTACCGCATCACCTACGGCGAAACGGGCGGTAACTCTCCGGTTCAGGAATTTACCGTGCCGAAAAA TGTTTATACCGCAACGATTAGCGGCCTGAAACCGGGTGTGGATTATACCATCACGGTGTACGCGGTTACCCGTTTCCGCGAT TACCAGCCGATTTGCATCAACTATCGTACGGAAATTGAAAAAGGCAGTGGTAGCGGCTCTGGTAGTGGCAGCGGTTCTGGCA GTGGTAGCGGCTCTGGTAGTGTAAGCGACGTCCCGCGCGACCTGGAAGTTGTTGCAGCGACGCCGACGAGCCTGCTGATCTC TTGGTGGGCCCCGGTGGATCGTTACCAGTATTACCGCATCACCTATGGCGAAACCGGTGGTAACAGCCCGGTGCAAGAATTT ACCGTGCCGCGTGATGTTTATACCGCGACCATCTCTGGTCTGAAACCGGGCGTTGACTACACGATTACCGTTTACGCGGTTA CCGATTATAAACCGCATGCCGATGGTCCGCATACGTACCACGAATCTCCGATTAGTATCAATTATCGGACCGAACATCACCA TCACCATCAC

Figure 48 Con't

SEQ ID NO	Binder	DNA SEQ
465	I1-GS10-E5(S91C)	ATGGGCGTGAGCGATGTTCCGCGTGATCTGGAAGTGGTTGCAGCAACCCCGACCAGCCTGCTGATTAGCTGGTCTGCCCGCC TGAAAGTGGCACGTTATTACCGCATCACCTACGGCGAAACGGGCGGTAACAGTCCGGTTCAGGAATTTACCGTGCCGAAAAA TGTTTATACCGCAACGATTAGCGGCCTGAAACCGGGTGTGGATTATACCATCACGGTGTACGCGGTTACCCGTTTCCGCGAT TACCAGCCGATTAGCATCAACTATCGTACGGAAATTGAAAAAAGGCAGTGGTAGCGGCTCTGGTAGTGGCAGCGGTTCTGGCA GTGGTAGCGGCTCTGGTAGTGTAAGCGACGTCCCGCGCGACCTGGAAGTTGTTGCAGCGACCGCCAGCCTGCTGATCAG TTGGTGGGCCCCGGTGGATCGTTACCAGTATTACCGCATCACCTATGGCGAAACCGGTGGTAACAGCCCGGTGCAAGAATTC ACCGTGCCGCGTGATGTTTATACCGCGACCATCTCTGGTCTGAAACCGGGCGTTGACTACACGATTACCGTTTACGCGGTTA CCGATTATAAACCGCATGCCGATGGTCCGCATACGTACCACGAAAGCCCGATTTGCATCAATTATCGGACCGAACATCACCA TCACCATCAC

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<150> 61/178,279
<151> 2009-05-14

<150> 61/212,966
<151> 2009-04-17

<150> 61/200,282
<151> 2008-11-26

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<160> 495

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<210> 1
<211> 94
<212> PRT
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

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Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

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

Ser Pro Ala Ser Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 2
<211> 94
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Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

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

Ser Pro Ala Ser Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

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<211> 90
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<220>
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<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

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Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 4
<211> 105
<212> PRT
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<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 4
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Pro Ser Gln His His His His His His
100 105

<210> 5
<211> 99
<212> PRT
<213> Artificial Sequence

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

<400> 5
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His Lys Pro
65 70 75 80

His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr

<210> 6
<211> 114
<212> PRT
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<220>
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<400> 6
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr

1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His
100 105 110

His His

<210> 7
<211> 94
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<213> Artificial Sequence

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

<400> 7
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1 5 10 15

Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met Met His
65 70 75 80

Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 8
<211> 109
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<213> Artificial Sequence

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

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1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65 70 75 80

Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln His His His His His His
100 105

<210> 9
<211> 7
<212> PRT
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 9
Glu Ile Asp Lys Pro Ser Gln
1 5

<210> 10
<211> 7
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<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 10
Glu Ile Asp Lys Pro Cys Gln
1 5

<210> 11
<211> 20
<212> PRT
<213> Artificial Sequence

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

<400> 11
Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
1 5 10 15

Gly Ser Gly Ser
20

<210> 12
<211> 7
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<213> Artificial Sequence

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

<400> 12
Pro Ser Thr Ser Thr Ser Thr
1 5

<210> 13
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 13
Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
1 5 10

<210> 14
<211> 15
<212> PRT
<213> Artificial Sequence

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

<400> 14
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 15
<211> 20
<212> PRT
<213> Artificial Sequence

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

<400> 15
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser
20

<210> 16
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<221> source

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

<400> 16
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

<210> 17
<211> 15
<212> PRT
<213> Artificial Sequence

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

<400> 17
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly
1 5 10 15

<210> 18
<211> 7
<212> PRT
<213> Artificial Sequence

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

<400> 18
Gly Pro Gly Pro Gly Pro Gly
1 5

<210> 19
<211> 11
<212> PRT
<213> Artificial Sequence

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

<400> 19
Gly Pro Gly Pro Gly Pro Gly Pro Gly Pro Gly
1 5 10

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

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

<400> 20
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

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Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65                  70                  75                  80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
        115                 120                 125

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
    130                 135                 140

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

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

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
            180                 185                 190

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
        195                 200                 205

Ile Asn Tyr Arg Thr
    210

<210> 21
<211> 222
<212> PRT
<213> Artificial Sequence

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

<400> 21
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                   10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60
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Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

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

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp His Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 22
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 22
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

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

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp His Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His
210 215 220

His His His His
225

<210> 23
<211> 220
<212> PRT
<213> Artificial Sequence

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

<400> 23
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His Lys Pro
65 70 75 80

His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro
115 120 125

Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser
130 135 140

Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly
145 150 155 160

Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn
165 170 175

Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
180 185 190

Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 24
<211> 222
<212> PRT
<213> Artificial Sequence

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

<400> 24
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 25
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 25
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His
210 215 220

His His His His
225

<210> 26
<211> 208
<212> PRT
<213> Artificial Sequence

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

<400> 26
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
130 135 140

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

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
165 170 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
180 185 190

Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

<210> 27
<211> 217
<212> PRT
<213> Artificial Sequence

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

<400> 27
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Met Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 28
<211> 223
<212> PRT

<213> Artificial Sequence

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

<400> 28

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
        115                 120                 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp
    130                 135                 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145                 150                 155                 160

Val Gln Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser
                165                 170                 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
            180                 185                 190

Asp Met Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr
        195                 200                 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His His His
    210                 215                 220
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<210> 29
<211> 208
<212> PRT
<213> Artificial Sequence

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

<400> 29

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Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                  10                  15

Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met Met His
65                  70                  75                  80

Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile
                85                  90                  95

Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val
        115                 120                 125

Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu
    130                 135                 140

Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
145                 150                 155                 160

Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr
                165                 170                 175

Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
            180                 185                 190

Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
        195                 200                 205
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<210> 30
<211> 217
<212> PRT
<213> Artificial Sequence

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

<400> 30

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45
```

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65 70 75 80

Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu
115 120 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
130 135 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145 150 155 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
165 170 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
180 185 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 31
<211> 223
<212> PRT
<213> Artificial Sequence

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

<400> 31
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65 70 75 80

```
Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90                  95

Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu
        115                 120                 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
    130                 135                 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145                 150                 155                 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
                165                 170                 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
            180                 185                 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
        195                 200                 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His His His
    210                 215                 220


<210> 32
<211> 146
<212> PRT
<213> Artificial Sequence

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


<220>
<221> MOD_RES
<222> (21)..(40)
<223> Any amino acid

<220>
<221> misc_feature
<222> (21)..(40)
<223> /note="This region may encompass 1-20 residues"

<220>
<221> MOD_RES
<222> (61)..(80)
<223> Any amino acid

<220>
<221> misc_feature
<222> (61)..(80)
<223> /note="This region may encompass 1-20 residues"

<220>
<221> MOD_RES
<222> (100)..(139)
<223> Any amino acid

<220>
<221> misc_feature
<222> (100)..(139)
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<223> /note="This region may encompass 1-40 residues"

<400> 32
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu
35 40 45

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
85 90 95

Tyr Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr
130 135 140

Arg Thr
145

<210> 33
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 33
Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
1 5 10

<210> 34
<211> 18
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>

<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Any amino acid

<220>
<221> misc_feature
<222> (14)..(18)
<223> /note="This region may encompass 0-5 residues".

<400> 34
Xaa Xaa Xaa Xaa Xaa Val Ala Gly Ala Glu Asp Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 35
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 35
Pro His Asp Leu Val Thr
1 5

<210> 36
<211> 14
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (10)..(14)
<223> Any amino acid

<220>
<221> misc_feature
<222> (10)..(14)
<223> /note="This region may encompass 0-5 residues"

<400> 36
Xaa Xaa Xaa Xaa Xaa His Asp Leu Val Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 37

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

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

<400> 37
Thr Asp Met Met His Val Glu Tyr Thr Glu His Pro
1 5 10

<210> 38
<211> 20
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (16)..(20)
<223> Any amino acid

<220>
<221> misc_feature
<222> (16)..(20)
<223> /note="This region may encompass 0-5 residues"

<400> 38
Xaa Xaa Xaa Xaa Xaa Asp Met Met His Val Glu Tyr Thr Glu His Xaa
1 5 10 15

Xaa Xaa Xaa Xaa
20

<210> 39
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 39
Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
1 5 10

<210> 40
<211> 18
<212> PRT
<213> Artificial Sequence

<220>

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Any amino acid

<220>
<221> misc_feature
<222> (14)..(18)
<223> /note="This region may encompass 0-5 residues"

<400> 40
Xaa Xaa Xaa Xaa Xaa Asp Ser Gly Arg Gly Ser Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 41
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 41
Pro Gly Pro Val His Thr
1 5

<210> 42
<211> 14
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (10)..(14)
<223> Any amino acid

<220>
<221> misc_feature
<222> (10)..(14)
<223> /note="This region may encompass 0-5 residues"

<400> 42
Xaa Xaa Xaa Xaa Xaa Gly Pro Val His Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 43
<211> 17
<212> PRT
<213> Artificial Sequence

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

<400> 43
Thr Asp His Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser
1 5 10 15

Pro

<210> 44
<211> 24
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (20)..(24)
<223> Any amino acid

<220>
<221> misc_feature
<222> (20)..(24)
<223> /note="This region may encompass 0-5 residues"

<400> 44
Xaa Xaa Xaa Xaa Xaa Asp His Lys Pro His Ala Asp Gly Pro His Thr
1 5 10 15

Tyr His Glu Xaa Xaa Xaa Xaa Xaa
20

<210> 45
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

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

<400> 45
Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
1 5 10

<210> 46
<211> 17
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (13)..(17)
<223> Any amino acid

<220>
<221> misc_feature
<222> (13)..(17)
<223> /note="This region may encompass 0-5 residues"

<400> 46
Xaa Xaa Xaa Xaa Xaa Ser Ala Arg Leu Lys Val Ala Xaa Xaa Xaa Xaa
1 5 10 15

Xaa

<210> 47
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 47
Pro Lys Asn Val Tyr Thr
1 5

<210> 48
<211> 14
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (10)..(14)
<223> Any amino acid

<220>
<221> misc_feature
<222> (10)..(14)
<223> /note="This region may encompass 0-5 residues"

<400> 48
Xaa Xaa Xaa Xaa Xaa Lys Asn Val Tyr Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 49
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 49
Thr Arg Phe Arg Asp Tyr Gln Pro
1 5

<210> 50
<211> 16
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (12)..(16)
<223> Any amino acid

<220>
<221> misc_feature
<222> (12)..(16)
<223> /note="This region may encompass 0-5 residues"

<400> 50
Xaa Xaa Xaa Xaa Xaa Arg Phe Arg Asp Tyr Gln Xaa Xaa Xaa Xaa Xaa
1 5 10 15

<210> 51
<211> 3
<212> PRT
<213> Artificial Sequence

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

<400> 51
Gly Pro Gly
1

<210> 52
<211> 109
<212> PRT
<213> Artificial Sequence

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

<400> 52
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met
65 70 75 80

Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln His His His His His His
100 105

<210> 53
<211> 223
<212> PRT
<213> Artificial Sequence

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

<400> 53
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln

35 40 45

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met
65 70 75 80

Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu
115 120 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
130 135 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145 150 155 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
165 170 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
180 185 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Cys Gln His His His His His His
210 215 220

<210> 54
<211> 223
<212> PRT
<213> Artificial Sequence

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

<400> 54
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe

65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asn Met Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Cys Gln His His His His His His
210 215 220

<210> 55
<211> 223
<212> PRT
<213> Artificial Sequence

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

<400> 55
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65 70 75 80

Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser

100 105 110

Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu
115 120 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
130 135 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145 150 155 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
165 170 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
180 185 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Cys Gln His His His His His His
210 215 220

<210> 56
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 56
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu

130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 57
<211> 223
<212> PRT
<213> Artificial Sequence

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

<400> 57
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro

145 150 155 160

Val Gln Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Met Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Cys Gln His His His His His His
210 215 220

<210> 58
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 58
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

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

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr

180 185 190

Asp His Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 59
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 59
Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln
1 5 10

<210> 60
<211> 18
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Any amino acid

<220>
<221> misc_feature
<222> (14)..(18)
<223> /note="This region may encompass 0-5 residues"

<400> 60
Xaa Xaa Xaa Xaa Xaa Leu Pro Gly Lys Leu Arg Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 61
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 61
Pro His Asp Leu Arg Thr
1 5

<210> 62
<211> 14
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (10)..(14)
<223> Any amino acid

<220>
<221> misc_feature
<222> (10)..(14)
<223> /note="This region may encompass 0-5 residues"

<400> 62
Xaa Xaa Xaa Xaa Xaa His Asp Leu Arg Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 63
<211> 12
<212> PRT
<213> Artificial Sequence

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

<400> 63
Thr Asn Met Met His Val Glu Tyr Ser Glu Tyr Pro
1 5 10

<210> 64
<211> 20
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)

<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (16)..(20)
<223> Any amino acid

<220>
<221> misc_feature
<222> (16)..(20)
<223> /note="This region may encompass 0-5 residues"

<400> 64
Xaa Xaa Xaa Xaa Xaa Asn Met Met His Val Glu Tyr Ser Glu Tyr Xaa
1 5 10 15

Xaa Xaa Xaa Xaa
20

<210> 65
<211> 82
<212> PRT
<213> Artificial Sequence

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

<400> 65
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
1 5 10 15

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
65 70 75 80

Arg Thr

<210> 66
<211> 86
<212> PRT
<213> Artificial Sequence

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

<400> 66
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Val Ala
1 5 10 15

Gly Ala Glu Asp Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro His Asp Leu Val Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp Met Met His Val Glu Tyr Thr Glu His Pro Ile
65 70 75 80

Ser Ile Asn Tyr Arg Thr
85

<210> 67
<211> 91
<212> PRT
<213> Artificial Sequence

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

<400> 67
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser
1 5 10 15

Gly Arg Gly Ser Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Pro Val His Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp His Lys Pro His Ala Asp Gly Pro His Thr Tyr
65 70 75 80

His Glu Ser Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 68
<211> 86
<212> PRT
<213> Artificial Sequence

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

<400> 68
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro
1 5 10 15

Gly Lys Leu Arg Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro His Asp Leu Arg Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asn Met Met His Val Glu Tyr Ser Glu Tyr Pro Ile
65 70 75 80

Ser Ile Asn Tyr Arg Thr
85

<210> 69
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 69
Met Gly Val Ser Asp Val Pro Arg Asp Leu
1 5 10

<210> 70
<211> 9
<212> PRT
<213> Artificial Sequence

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

<400> 70
Gly Val Ser Asp Val Pro Arg Asp Leu
1 5

<210> 71
<211> 8
<212> PRT
<213> Artificial Sequence

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

<400> 71
Val Ser Asp Val Pro Arg Asp Leu
1 5

<210> 72
<211> 9
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(2)

<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(2)
<223> /note="This region may encompass 0-2 residues"

<400> 72
Xaa Xaa Ser Asp Val Pro Arg Asp Leu
1 5

<210> 73
<211> 8
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(2)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(2)
<223> /note="This region may encompass 0-2 residues"

<400> 73
Xaa Xaa Asp Val Pro Arg Asp Leu
1 5

<210> 74
<211> 7
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(2)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(2)
<223> /note="This region may encompass 0-2 residues"

<400> 74
Xaa Xaa Val Pro Arg Asp Leu
1 5

<210> 75
<211> 6
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(2)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(2)
<223> /note="This region may encompass 0-2 residues"

<400> 75
Xaa Xaa Pro Arg Asp Leu
1 5

<210> 76
<211> 5
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(2)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(2)
<223> /note="This region may encompass 0-2 residues"

<400> 76
Xaa Xaa Arg Asp Leu
1 5

<210> 77
<211> 4
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(2)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(2)
<223> /note="This region may encompass 0-2 residues"

<400> 77
Xaa Xaa Asp Leu
1

<210> 78
<211> 4
<212> PRT
<213> Artificial Sequence

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

peptide"

<400> 78
Glu Ile Asp Lys
1

<210> 79
<211> 5
<212> PRT
<213> Artificial Sequence

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

<400> 79
Glu Ile Asp Lys Pro
1 5

<210> 80
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 80
Glu Ile Asp Lys Pro Ser
1 5

<210> 81
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 81
Glu Ile Asp Lys Pro Cys
1 5

<210> 82
<211> 94
<212> PRT
<213> Artificial Sequence

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

<400> 82
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met Met His
65 70 75 80

Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 83
<211> 185
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (7)..(21)
<223> Any amino acid

<220>
<221> misc_feature
<222> (7)..(21)
<223> /note="This region may encompass 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3 or 1-2 residues"

<220>
<221> MOD_RES
<222> (26)..(35)
<223> Any amino acid

<220>
<221> misc_feature
<222> (26)..(35)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<220>
<221> MOD_RES
<222> (46)..(55)
<223> Any amino acid

<220>
<221> misc_feature
<222> (46)..(55)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<220>
<221> MOD_RES
<222> (64)..(83)
<223> Any amino acid

<220>
<221> misc_feature
<222> (64)..(83)
<223> /note="This region may encompass 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 or 6-7 residues"

<220>
<221> MOD_RES
<222> (89)..(98)
<223> Any amino acid

<220>

<221> misc_feature
<222> (89)..(98)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<220>
<221> MOD_RES
<222> (105)..(114)
<223> Any amino acid

<220>
<221> misc_feature
<222> (105)..(114)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<220>
<221> MOD_RES
<222> (118)..(137)
<223> Any amino acid

<220>
<221> misc_feature
<222> (118)..(137)
<223> /note="This region may encompass 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 or 6-7 residues"

<220>
<221> MOD_RES
<222> (147)..(156)
<223> Any amino acid

<220>
<221> misc_feature
<222> (147)..(156)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<220>
<221> MOD_RES
<222> (169)..(178)
<223> Any amino acid

<220>
<221> misc_feature
<222> (169)..(178)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<400> 83

```
Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1               5                  10                  15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30

Xaa Xaa Xaa Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln Xaa Xaa Xaa
        35                  40                  45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
    50                  55                  60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65                  70                  75                  80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                85                  90                  95
```

Xaa Xaa Pro His Asp Leu Val Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Met Met
145 150 155 160

His Val Glu Tyr Thr Glu His Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
165 170 175

Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185

<210> 84
<211> 190
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (7)..(21)
<223> Any amino acid

<220>
<221> misc_feature
<222> (7)..(21)
<223> /note="This region may encompass 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3 or 1-2 residues"

<220>
<221> MOD_RES
<222> (26)..(35)
<223> Any amino acid

<220>
<221> misc_feature
<222> (26)..(35)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<220>
<221> MOD_RES
<222> (46)..(55)
<223> Any amino acid

<220>
<221> misc_feature
<222> (46)..(55)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<220>
<221> MOD_RES
<222> (64)..(83)
<223> Any amino acid

<220>

<221> misc_feature
<222> (64)..(83)
<223> /note="This region may encompass 2-20, 2-15,
2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10,
6-8, 2-7, 5-7 or 6-7 residues"

<220>
<221> MOD_RES
<222> (89)..(98)
<223> Any amino acid

<220>
<221> misc_feature
<222> (89)..(98)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5
or 2-5 residues"

<220>
<221> MOD_RES
<222> (105)..(114)
<223> Any amino acid

<220>
<221> misc_feature
<222> (105)..(114)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5
or 2-5 residues"

<220>
<221> MOD_RES
<222> (118)..(137)
<223> Any amino acid

<220>
<221> misc_feature
<222> (118)..(137)
<223> /note="This region may encompass 2-20, 2-15,
2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10,
6-8, 2-7, 5-7 or 6-7 residues"

<220>
<221> MOD_RES
<222> (147)..(156)
<223> Any amino acid

<220>
<221> misc_feature
<222> (147)..(156)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5
or 2-5 residues"

<220>
<221> MOD_RES
<222> (174)..(183)
<223> Any amino acid

<220>
<221> misc_feature
<222> (174)..(183)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5
or 2-5 residues"

<400> 84

```
Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1               5                  10                  15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30

Xaa Xaa Xaa Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln Xaa Xaa Xaa
        35                  40                  45
```

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Gly Pro Val His Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp His Lys
145 150 155 160

Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Xaa Xaa Xaa
165 170 175

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185 190

<210> 85
<211> 185
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (7)..(21)
<223> Any amino acid

<220>
<221> misc_feature
<222> (7)..(21)
<223> /note="This region may encompass 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3 or 1-2 residues"

<220>
<221> MOD_RES
<222> (26)..(35)
<223> Any amino acid

<220>
<221> misc_feature
<222> (26)..(35)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<220>
<221> MOD_RES
<222> (46)..(55)
<223> Any amino acid

<220>
<221> misc_feature
<222> (46)..(55)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5
or 2-5 residues"

<220>
<221> MOD_RES
<222> (64)..(83)
<223> Any amino acid

<220>
<221> misc_feature
<222> (64)..(83)
<223> /note="This region may encompass 2-20, 2-15,
2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10,
6-8, 2-7, 5-7 or 6-7 residues"

<220>
<221> MOD_RES
<222> (89)..(98)
<223> Any amino acid

<220>
<221> misc_feature
<222> (89)..(98)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5
or 2-5 residues"

<220>
<221> MOD_RES
<222> (105)..(114)
<223> Any amino acid

<220>
<221> misc_feature
<222> (105)..(114)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5
or 2-5 residues"

<220>
<221> MOD_RES
<222> (118)..(137)
<223> Any amino acid

<220>
<221> misc_feature
<222> (118)..(137)
<223> /note="This region may encompass 2-20, 2-15,
2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10,
6-8, 2-7, 5-7 or 6-7 residues"

<220>
<221> MOD_RES
<222> (147)..(156)
<223> Any amino acid

<220>
<221> misc_feature
<222> (147)..(156)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5
or 2-5 residues"

<220>
<221> MOD_RES
<222> (169)..(178)
<223> Any amino acid

<220>
<221> misc_feature
<222> (169)..(178)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5
or 2-5 residues"

<400> 85

Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro His Asp Leu Arg Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asn Met Met
145 150 155 160

His Val Glu Tyr Ser Glu Tyr Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
165 170 175

Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185

<210> 86
<211> 181
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (7)..(21)
<223> Any amino acid

<220>
<221> misc_feature
<222> (7)..(21)
<223> /note="This region may encompass 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3 or 1-2 residues"

<220>
<221> MOD_RES
<222> (26)..(35)
<223> Any amino acid

<220>
<221> misc_feature
<222> (26)..(35)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5
or 2-5 residues"

<220>
<221> MOD_RES
<222> (46)..(55)
<223> Any amino acid

<220>
<221> misc_feature
<222> (46)..(55)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5
or 2-5 residues"

<220>
<221> MOD_RES
<222> (64)..(83)
<223> Any amino acid

<220>
<221> misc_feature
<222> (64)..(83)
<223> /note="This region may encompass 2-20, 2-15,
2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10,
6-8, 2-7, 5-7 or 6-7 residues"

<220>
<221> MOD_RES
<222> (89)..(98)
<223> Any amino acid

<220>
<221> misc_feature
<222> (89)..(98)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5
or 2-5 residues"

<220>
<221> MOD_RES
<222> (105)..(114)
<223> Any amino acid

<220>
<221> misc_feature
<222> (105)..(114)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5
or 2-5 residues"

<220>
<221> MOD_RES
<222> (118)..(137)
<223> Any amino acid

<220>
<221> misc_feature
<222> (118)..(137)
<223> /note="This region may encompass 2-20, 2-15,
2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10,
6-8, 2-7, 5-7 or 6-7 residues"

<220>
<221> MOD_RES
<222> (147)..(156)
<223> Any amino acid

<220>
<221> misc_feature
<222> (147)..(156)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5
or 2-5 residues"

<220>
<221> MOD_RES
<222> (165)..(174)
<223> Any amino acid

<220>
<221> misc_feature
<222> (165)..(174)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<400> 86
Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Lys Asn Val Tyr Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Arg Phe Arg
145 150 155 160

Asp Tyr Gln Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser
165 170 175

Ile Asn Tyr Arg Thr
180

<210> 87
<211> 215
<212> PRT
<213> Artificial Sequence

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

<400> 87
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met Met His
65 70 75 80

Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile
85 90 95

Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val
115 120 125

Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu
130 135 140

Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
145 150 155 160

Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr
165 170 175

Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
180 185 190

Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Cys Gln
210 215

<210> 88
<211> 215
<212> PRT
<213> Artificial Sequence

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

<400> 88
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln
130 135 140

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

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
165 170 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met
180 185 190

Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Cys Gln
210 215

<210> 89
<211> 215
<212> PRT
<213> Artificial Sequence

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

<400> 89
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met Met His
65 70 75 80

Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile
85 90 95

Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val
115 120 125

Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu
130 135 140

Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
145 150 155 160

Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr
165 170 175

Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
180 185 190

Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Cys Gln
210 215

<210> 90
<211> 220
<212> PRT
<213> Artificial Sequence

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

<400> 90
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His Lys Pro
65 70 75 80

His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro
115 120 125

Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser
130 135 140

Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly
145 150 155 160

Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn
165 170 175

Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
180 185 190

Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln
210 215 220

<210> 91
<211> 215
<212> PRT
<213> Artificial Sequence

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

<400> 91
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
130 135 140

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

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
165 170 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
180 185 190

Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Cys Gln
210 215

<210> 92
<211> 220
<212> PRT
<213> Artificial Sequence

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

<400> 92
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
130 135 140

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

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

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
180 185 190

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln
210 215 220

<210> 93
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 93
Pro Ala Pro Ala Pro Ala
1 5

<210> 94
<211> 12
<212> PRT
<213> Artificial Sequence

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

<400> 94
Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
1 5 10

<210> 95
<211> 18
<212> PRT
<213> Artificial Sequence

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

<400> 95
Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
1 5 10 15

Pro Ala

<210> 96
<211> 5
<212> PRT
<213> Artificial Sequence

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

<400> 96
Glu Gly Ser Gly Ser
1 5

<210> 97
<211> 5
<212> PRT
<213> Artificial Sequence

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

<400> 97
Glu Gly Ser Gly Cys
1 5

<210> 98
<211> 208
<212> PRT
<213> Artificial Sequence

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

<220>
<221> misc_feature
<222> (96)..(113)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (208)..(208)
<223> /replace="Cys"

<220>
<221> misc_feature
<222> (208)..(208)
<223> /note="Residue given in the sequence has no preference with respect to that in the annotation for said position"

<400> 98
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met Met His
65 70 75 80

Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr Glu Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro
100 105 110

Ala Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro
115 120 125

Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr
130 135 140

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

Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys
165 170 175

Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg
180 185 190

Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Gly Ser Gly Ser
195 200 205

<210> 99
<211> 208
<212> PRT
<213> Artificial Sequence

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

<220>
<221> misc_feature
<222> (92)..(109)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (208)..(208)
<223> /replace="Cys"

<220>
<221> misc_feature
<222> (208)..(208)
<223> /note="Residue given in the sequence has no preference with respect to that in the annotation for said position"

<400> 99
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp
100 105 110

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
115 120 125

Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln Tyr Tyr Arg Ile Thr
130 135 140

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
145 150 155 160

His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
165 170 175

Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met Met His Val Glu Tyr
180 185 190

Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr Glu Gly Ser Gly Ser
195 200 205

<210> 100
<211> 208
<212> PRT
<213> Artificial Sequence

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

<220>
<221> misc_feature
<222> (96)..(113)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (208)..(208)
<223> /replace="Cys"

<220>
<221> misc_feature
<222> (208)..(208)
<223> /note="Residue given in the sequence has no preference with respect to that in the annotation for said position"

<400> 100
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met Met His
65 70 75 80

Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr Glu Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro
100 105 110

Ala Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro
115 120 125

Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr
130 135 140

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

Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys
165 170 175

Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg
180 185 190

Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Gly Ser Gly Ser
195 200 205

<210> 101
<211> 213
<212> PRT
<213> Artificial Sequence

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

<220>
<221> misc_feature
<222> (101)..(118)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (213)..(213)
<223> /replace="Cys"

<220>
<221> misc_feature
<222> (213)..(213)
<223> /note="Residue given in the sequence has no preference with respect to that in the annotation for said position"

<400> 101
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

```
Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His Lys Pro
65                  70                  75                  80

His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn
                85                  90                  95

Tyr Arg Thr Glu Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
            100                 105                 110

Pro Ala Pro Ala Pro Ala Val Ser Asp Val Pro Arg Asp Leu Glu Val
        115                 120                 125

Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu
    130                 135                 140

Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
145                 150                 155                 160

Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr
                165                 170                 175

Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
            180                 185                 190

Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
        195                 200                 205

Glu Gly Ser Gly Ser
    210


<210> 102
<211> 208
<212> PRT
<213> Artificial Sequence

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


<220>
<221> misc_feature
<222> (92)..(109)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala"
      repeats"

<220>
<221> VARIANT
<222> (208)..(208)
<223> /replace="Cys"

<220>
<221> misc_feature
<222> (208)..(208)
<223> /note="Residue given in the sequence has no preference
      with respect to that in the annotation for said position"

<400> 102
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15
```

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp
100 105 110

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
115 120 125

Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln Tyr Tyr Arg Ile Thr
130 135 140

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
145 150 155 160

His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
165 170 175

Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met Met His Val Glu Tyr
180 185 190

Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr Glu Gly Ser Gly Ser
195 200 205

<210> 103
<211> 213
<212> PRT
<213> Artificial Sequence

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

<220>
<221> misc_feature
<222> (92)..(109)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (213)..(213)
<223> /replace="Cys"

<220>
<221> misc_feature
<222> (213)..(213)

<223> /note="Residue given in the sequence has no preference with respect to that in the annotation for said position"

<400> 103

```
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                  10                  15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65                  70                  75                  80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro
                85                  90                  95

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp
            100                 105                 110

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
        115                 120                 125

Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln Tyr Tyr Arg Ile Thr
    130                 135                 140

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
145                 150                 155                 160

Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
                165                 170                 175

Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His Lys Pro His Ala Asp
            180                 185                 190

Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn Tyr Arg Thr
        195                 200                 205

Glu Gly Ser Gly Ser
    210
```

<210> 104
<211> 215
<212> PRT
<213> Artificial Sequence

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

<400> 104

```
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                  10                  15
```

Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met Met His
65 70 75 80

Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile
85 90 95

Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val
115 120 125

Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu
130 135 140

Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
145 150 155 160

Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr
165 170 175

Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
180 185 190

Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 105
<211> 215
<212> PRT
<213> Artificial Sequence

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

<400> 105
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

```
Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65                  70                  75                  80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
        115                 120                 125

Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln
    130                 135                 140

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

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
                165                 170                 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met
            180                 185                 190

Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
        195                 200                 205

Glu Ile Asp Lys Pro Ser Gln
    210                 215


<210> 106
<211> 99
<212> PRT
<213> Artificial Sequence

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

<400> 106
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                   10                  15

Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Phe Asn
65                  70                  75                  80
```

Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr

<210> 107
<211> 114
<212> PRT
<213> Artificial Sequence

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

<400> 107
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His
100 105 110

His His

<210> 108
<211> 91
<212> PRT
<213> Artificial Sequence

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

<400> 108
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp His Glu
1 5 10 15

Arg Asp Gly Ser Arg Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Gly Val Arg Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val

50 55 60

Tyr Ala Val Thr Asp Tyr Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr
65 70 75 80

Gln Thr Thr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 109
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 109
Ser Trp His Glu Arg Asp Gly Ser Arg Gln
1 5 10

<210> 110
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 110
Pro Gly Gly Val Arg Thr
1 5

<210> 111
<211> 17
<212> PRT
<213> Artificial Sequence

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

<400> 111
Thr Asp Tyr Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr
1 5 10 15

Pro

<210> 112
<211> 99
<212> PRT
<213> Artificial Sequence

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

<400> 112
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Lys Pro
65 70 75 80

His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr

<210> 113
<211> 108
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (107)..(107)
<223> /replace="Cys"

<220>
<221> misc_feature
<222> (107)..(107)
<223> /note="Residue given in the sequence has no preference with respect to that in the annotation for said position"

<400> 113
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 114
<211> 91
<212> PRT
<213> Artificial Sequence

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

<400> 114
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala
1 5 10 15

Pro Val Asp Arg Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr
65 70 75 80

His Glu Ser Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 115
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 115
Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln
1 5 10

<210> 116
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 116
Pro Arg Asp Val Tyr Thr
1 5

<210> 117
<211> 17
<212> PRT
<213> Artificial Sequence

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

<400> 117
Thr Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser
1 5 10 15

Pro

<210> 118
<211> 213
<212> PRT
<213> Artificial Sequence

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

<400> 118
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Phe Asn
65 70 75 80

Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro
115 120 125

Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser
130 135 140

Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly
145 150 155 160

Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn
165 170 175

Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
180 185 190

Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr
210

<210> 119
<211> 220
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (219)..(219)
<223> /replace="Cys"

<220>
<221> misc_feature
<222> (219)..(219)
<223> /note="Residue given in the sequence has no preference with respect to that in the annotation for said position"

<400> 119
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Phe Asn
65 70 75 80

Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro
115 120 125

Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser
130 135 140

Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly
145 150 155 160

Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn
165 170 175

Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
180 185 190

Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser
195 200 205

```
Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
    210                 215                 220


<210> 120
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 120
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15


Pro Thr Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln
            20                  25                  30


Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45


Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60


Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65                  70                  75                  80


Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser
                85                  90                  95


Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
            100                 105                 110


Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
        115                 120                 125


Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
    130                 135                 140


Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145                 150                 155                 160


Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
                165                 170                 175


Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
            180                 185                 190


Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
        195                 200                 205


Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
    210                 215                 220


His His His His
225
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<210> 121
<211> 221
<212> PRT
<213> Artificial Sequence

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

<220>
<221> misc_feature
<222> (101)..(118)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<400> 121
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Phe Asn
65 70 75 80

Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr Glu Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
100 105 110

Pro Ala Pro Ala Pro Ala Val Ser Asp Val Pro Arg Asp Leu Glu Val
115 120 125

Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu
130 135 140

Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
145 150 155 160

Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr
165 170 175

Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
180 185 190

Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Cys Gln His His His His His His
210 215 220

<210> 122
<211> 213
<212> PRT
<213> Artificial Sequence

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

<400> 122
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln
130 135 140

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

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
165 170 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
180 185 190

Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr
210

<210> 123
<211> 220
<212> PRT
<213> Artificial Sequence

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

polypeptide"

<220>
<221> VARIANT
<222> (219)..(219)
<223> /replace="Cys"

<220>
<221> misc_feature
<222> (219)..(219)
<223> /note="Residue given in the sequence has no preference with respect to that in the annotation for said position"

<400> 123

```
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                  10                  15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65                  70                  75                  80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
        115                 120                 125

Pro Thr Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln
    130                 135                 140

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

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
                165                 170                 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
            180                 185                 190

Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser
        195                 200                 205

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
    210                 215                 220
```

<210> 124
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 124
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser
130 135 140

Arg Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 125
<211> 215
<212> PRT
<213> Artificial Sequence

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

polypeptide"

<220>
<221> misc_feature
<222> (92)..(109)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (214)..(214)
<223> /replace="Cys"

<220>
<221> misc_feature
<222> (214)..(214)
<223> /note="Residue given in the sequence has no preference with respect to that in the annotation for said position"

<400> 125
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp
100 105 110

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
115 120 125

Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln Tyr Tyr Arg Ile Thr
130 135 140

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
145 150 155 160

Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
165 170 175

Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Phe Asn Pro Thr Thr
180 185 190

His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 126
<211> 213
<212> PRT
<213> Artificial Sequence

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

<400> 126
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Lys Pro
65 70 75 80

His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro
115 120 125

Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser
130 135 140

Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly
145 150 155 160

Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn
165 170 175

Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
180 185 190

Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr
210

<210> 127
<211> 220
<212> PRT
<213> Artificial Sequence

<220>

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

<220>
<221> VARIANT
<222> (219)..(219)
<223> /replace="Cys"

<220>
<221> misc_feature
<222> (219)..(219)
<223> /note="Residue given in the sequence has no preference with respect to that in the annotation for said position"

<400> 127

```
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                  10                  15

Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Lys Pro
65                  70                  75                  80

His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn
                85                  90                  95

Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly
            100                 105                 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro
        115                 120                 125

Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser
    130                 135                 140

Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly
145                 150                 155                 160

Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn
                165                 170                 175

Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
            180                 185                 190

Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser
        195                 200                 205

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
    210                 215                 220
```

<210> 128
<211> 228

<212> PRT
<213> Artificial Sequence

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

<400> 128

```
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65                  70                  75                  80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
                85                  90                  95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
            100                 105                 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
        115                 120                 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
    130                 135                 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145                 150                 155                 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
                165                 170                 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
            180                 185                 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
    210                 215                 220

His His His His
225
```

<210> 129
<211> 215
<212> PRT
<213> Artificial Sequence

<220>

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

<220>
<221> misc_feature
<222> (101)..(118)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (214)..(214)
<223> /replace="Cys"

<220>
<221> misc_feature
<222> (214)..(214)
<223> /note="Residue given in the sequence has no preference with respect to that in the annotation for said position"

<400> 129

```
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                  10                  15

Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Lys Pro
65                  70                  75                  80

His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn
                85                  90                  95

Tyr Arg Thr Glu Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
            100                 105                 110

Pro Ala Pro Ala Pro Ala Val Ser Asp Val Pro Arg Asp Leu Glu Val
        115                 120                 125

Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu
    130                 135                 140

Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
145                 150                 155                 160

Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr
                165                 170                 175

Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
            180                 185                 190

Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
        195                 200                 205
```

Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 130
<211> 213
<212> PRT
<213> Artificial Sequence

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

<400> 130
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln
130 135 140

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

Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
165 170 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
180 185 190

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr
210

<210> 131
<211> 220
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (219)..(219)
<223> /replace="Cys"

<220>
<221> misc_feature
<222> (219)..(219)
<223> /note="Residue given in the sequence has no preference with respect to that in the annotation for said position"

<400> 131
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln
130 135 140

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

Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
165 170 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
180 185 190

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 132
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 132
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 133
<211> 217
<212> PRT
<213> Artificial Sequence

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

<220>
<221> misc_feature
<222> (94)..(111)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (216)..(216)
<223> /replace="Cys"

<220>
<221> misc_feature
<222> (216)..(216)
<223> /note="Residue given in the sequence has no preference with respect to that in the annotation for said position"

<400> 133
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

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

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val
100 105 110

Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser
115 120 125

Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln Tyr Tyr Arg
130 135 140

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

Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly
165 170 175

Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Lys Pro His
180 185 190

Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 134
<211> 18
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Any amino acid

<220>
<221> misc_feature
<222> (14)..(18)
<223> /note="This region may encompass 0-5 residues"

<400> 134
Xaa Xaa Xaa Xaa Xaa His Glu Arg Asp Gly Ser Arg Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 135
<211> 14
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (10)..(14)
<223> Any amino acid

<220>
<221> misc_feature
<222> (10)..(14)

<223> /note="This region may encompass 0-5 residues"

<400> 135
Xaa Xaa Xaa Xaa Xaa Gly Gly Val Arg Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 136
<211> 25
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (21)..(25)
<223> Any amino acid

<220>
<221> misc_feature
<222> (21)..(25)
<223> /note="This region may encompass 0-5 residues"

<400> 136
Xaa Xaa Xaa Xaa Xaa Asp Tyr Phe Asn Pro Thr Thr His Glu Tyr Ile
1 5 10 15

Tyr Gln Thr Thr Xaa Xaa Xaa Xaa Xaa
20 25

<210> 137
<211> 18
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Any amino acid

<220>
<221> misc_feature

<222> (14)..(18)
<223> /note="This region may encompass 0-5 residues"

<400> 137
Xaa Xaa Xaa Xaa Xaa Trp Ala Pro Val Asp Arg Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 138
<211> 14
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (10)..(14)
<223> Any amino acid

<220>
<221> misc_feature
<222> (10)..(14)
<223> /note="This region may encompass 0-5 residues"

<400> 138
Xaa Xaa Xaa Xaa Xaa Arg Asp Val Tyr Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 139
<211> 25
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (21)..(25)
<223> Any amino acid

<220>

<221> misc_feature
<222> (21)..(25)
<223> /note="This region may encompass 0-5 residues"

<400> 139
Xaa Xaa Xaa Xaa Xaa Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr
1 5 10 15

Tyr His Glu Ser Xaa Xaa Xaa Xaa Xaa
20 25

<210> 140
<211> 114
<212> PRT
<213> Artificial Sequence

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

<400> 140
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His
100 105 110

His His

<210> 141
<211> 91
<212> PRT
<213> Artificial Sequence

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

<400> 141
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln
1 5 10 15

Gly Ser Thr His Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Met Val Tyr Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp Tyr Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr
65 70 75 80

Arg Thr Thr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 142
<211> 108
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77"

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (102)..(108)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81"

<220>
<221> misc_feature
<222> (102)..(108)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 142
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 143
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 143
Ser Trp Thr Gln Gly Ser Thr His Tyr Gln
1 5 10

<210> 144
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 144
Pro Gly Met Val Tyr Thr
1 5

<210> 145
<211> 17
<212> PRT
<213> Artificial Sequence

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

<400> 145
Thr Asp Tyr Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr
1 5 10 15

Pro

<210> 146
<211> 18
<212> PRT
<213> Artificial Sequence

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

<220>
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<222> (1)..(5)
<223> Any amino acid

<220>
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<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Any amino acid

<220>
<221> misc_feature
<222> (14)..(18)
<223> /note="This region may encompass 0-5 residues"

<400> 146
Xaa Xaa Xaa Xaa Xaa Thr Gln Gly Ser Thr His Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 147
<211> 14
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
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<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (10)..(14)
<223> Any amino acid

<220>
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<222> (10)..(14)
<223> /note="This region may encompass 0-5 residues"

<400> 147
Xaa Xaa Xaa Xaa Xaa Gly Met Val Tyr Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 148
<211> 25
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
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<222> (1)..(5)

<223> /note="This region may encompass 0-5 residues"

<220>
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<222> (21)..(25)
<223> Any amino acid

<220>
<221> misc_feature
<222> (21)..(25)
<223> /note="This region may encompass 0-5 residues"

<400> 148
Xaa Xaa Xaa Xaa Xaa Asp Tyr Phe Asp Arg Ser Thr His Glu Tyr Lys
1 5 10 15

Tyr Arg Thr Thr Xaa Xaa Xaa Xaa Xaa
20 25

<210> 149
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 149
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 150
<211> 222
<212> PRT
<213> Artificial Sequence

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

<220>
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<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
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<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (216)..(222)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (216)..(222)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 150
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Ile Ser

85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 151
<211> 217
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
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<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> misc_feature
<222> (103)..(120)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (211)..(217)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (211)..(217)
<223> /note="Residues given in the sequence have no preference

with respect to those in the annotations for said positions"

<400> 151
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
100 105 110

Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp Val Pro Arg Asp Leu
115 120 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
130 135 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145 150 155 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
165 170 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
180 185 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 152
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 152
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg

20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 153
<211> 222
<212> PRT
<213> Artificial Sequence

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

<220>
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<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature

<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (216)..(222)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (216)..(222)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 153

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
        115                 120                 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His
    130                 135                 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145                 150                 155                 160

Val Gln Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser
                165                 170                 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
            180                 185                 190

Asp Tyr Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
    210                 215                 220
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<210> 154
<211> 217

<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> misc_feature
<222> (94)..(111)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (211)..(217)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (211)..(217)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 154
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

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

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val
100 105 110

Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser
115 120 125

Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His Tyr Gln Tyr Tyr Arg
130 135 140

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

Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly
                165                 170                 175

Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Phe Asp Arg
            180                 185                 190

Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Ile Ser Ile Asn Tyr
        195                 200                 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
    210                 215

<210> 155
<211> 114
<212> PRT
<213> Artificial Sequence

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

<400> 155
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                   10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65                  70                  75                  80

Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser
                85                  90                  95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His
            100                 105                 110

His His

<210> 156
<211> 91
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
      polypeptide"
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<400> 156
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp
1 5 10 15

Glu Gly Leu Pro Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Arg Asp Val Asn Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp Trp Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr
65 70 75 80

His Thr Ile Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 157
<211> 108
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77"

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (102)..(108)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81"

<220>
<221> misc_feature
<222> (102)..(108)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 157
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser Gly Leu

50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65 70 75 80

Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 158
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 158
Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln
1 5 10

<210> 159
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 159
Pro Arg Asp Val Asn Thr
1 5

<210> 160
<211> 17
<212> PRT
<213> Artificial Sequence

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

<400> 160
Thr Asp Trp Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile
1 5 10 15

Pro

<210> 161
<211> 18
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Any amino acid

<220>
<221> misc_feature
<222> (14)..(18)
<223> /note="This region may encompass 0-5 residues"

<400> 161
Xaa Xaa Xaa Xaa Xaa Tyr Trp Glu Gly Leu Pro Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 162
<211> 14
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (10)..(14)
<223> Any amino acid

<220>
<221> misc_feature
<222> (10)..(14)
<223> /note="This region may encompass 0-5 residues"

<400> 162
Xaa Xaa Xaa Xaa Xaa Arg Asp Val Asn Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 163
<211> 25
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (21)..(25)
<223> Any amino acid

<220>
<221> misc_feature
<222> (21)..(25)
<223> /note="This region may encompass 0-5 residues"

<400> 163
Xaa Xaa Xaa Xaa Xaa Asp Trp Tyr Asn Pro Asp Thr His Glu Tyr Ile
1 5 10 15

Tyr His Thr Ile Xaa Xaa Xaa Xaa Xaa
20 25

<210> 164
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 164
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65 70 75 80

Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

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Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145                 150                 155                 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
                165                 170                 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
            180                 185                 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
    210                 215                 220

His His His His
225
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<210> 165
<211> 222
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (216)..(222)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (216)..(222)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 165

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                   10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45
```

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Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65                  70                  75                  80

Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser
                85                  90                  95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
            100                 105                 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
        115                 120                 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
    130                 135                 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145                 150                 155                 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
                165                 170                 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
            180                 185                 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
    210                 215                 220


<210> 166
<211> 217
<212> PRT
<213> Artificial Sequence

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


<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO:
      72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75"
      or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference
      with respect to those in the annotations for said positions"

<220>
<221> misc_feature
<222> (103)..(120)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala"
      repeats"

<220>
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<221> VARIANT
<222> (211)..(217)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (211)..(217)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 166

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65                  70                  75                  80

Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser
                85                  90                  95

Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
            100                 105                 110

Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp Val Pro Arg Asp Leu
        115                 120                 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
    130                 135                 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145                 150                 155                 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
                165                 170                 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
            180                 185                 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
        195                 200                 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
    210                 215
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<210> 167
<211> 228
<212> PRT
<213> Artificial Sequence

<220>
<221> source

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

<400> 167

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
        115                 120                 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro
    130                 135                 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145                 150                 155                 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser
                165                 170                 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
            180                 185                 190

Asp Trp Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
    210                 215                 220

His His His His
225
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<210> 168
<211> 222
<212> PRT
<213> Artificial Sequence

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

<220>
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<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (216)..(222)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (216)..(222)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 168
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Trp Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro

195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 169
<211> 217
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> misc_feature
<222> (94)..(111)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (211)..(217)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (211)..(217)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 169
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

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

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val

100 105 110

Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser
115 120 125

Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln Tyr Tyr Arg
130 135 140

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

Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly
165 170 175

Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp Tyr Asn Pro
180 185 190

Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 170
<211> 114
<212> PRT
<213> Artificial Sequence

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

<400> 170
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ala
65 70 75 80

Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His
100 105 110

His His

<210> 171

<211> 91
<212> PRT
<213> Artificial Sequence

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

<400> 171
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser
1 5 10 15

Asn Arg Gly Thr Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Gly Val Ser Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp Ala Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr
65 70 75 80

Phe Thr Thr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 172
<211> 108
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77"

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (102)..(108)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81"

<220>
<221> misc_feature
<222> (102)..(108)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 172
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ala
65 70 75 80

Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 173
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 173
Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln
1 5 10

<210> 174
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 174
Pro Gly Gly Val Ser Thr
1 5

<210> 175
<211> 17
<212> PRT
<213> Artificial Sequence

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

<400> 175
Thr Asp Ala Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr
1 5 10 15

Pro

<210> 176
<211> 18

<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Any amino acid

<220>
<221> misc_feature
<222> (14)..(18)
<223> /note="This region may encompass 0-5 residues"

<400> 176
Xaa Xaa Xaa Xaa Xaa Ala Ser Asn Arg Gly Thr Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 177
<211> 14
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (10)..(14)
<223> Any amino acid

<220>
<221> misc_feature
<222> (10)..(14)
<223> /note="This region may encompass 0-5 residues"

<400> 177
Xaa Xaa Xaa Xaa Xaa Gly Gly Val Ser Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 178

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

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (21)..(25)
<223> Any amino acid

<220>
<221> misc_feature
<222> (21)..(25)
<223> /note="This region may encompass 0-5 residues"

<400> 178
Xaa Xaa Xaa Xaa Xaa Asp Ala Phe Asn Pro Thr Thr His Glu Tyr Asn
1 5 10 15

Tyr Phe Thr Thr Xaa Xaa Xaa Xaa Xaa
20 25

<210> 179
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 179
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ala
65 70 75 80

Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly

100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 180
<211> 222
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (216)..(222)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (216)..(222)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 180
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ala
65 70 75 80

Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 181
<211> 217
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference

with respect to those in the annotations for said positions"

<220>
<221> misc_feature
<222> (103)..(120)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala"
repeats"

<220>
<221> VARIANT
<222> (211)..(217)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO:
79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (211)..(217)
<223> /note="Residues given in the sequence have no preference
with respect to those in the annotations for said positions"

<400> 181

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ala
65                  70                  75                  80

Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro Ile Ser
                85                  90                  95

Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
            100                 105                 110

Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp Val Pro Arg Asp Leu
        115                 120                 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
    130                 135                 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145                 150                 155                 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
                165                 170                 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
            180                 185                 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
        195                 200                 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
    210                 215
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<210> 182
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 182
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Ala Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 183
<211> 222

<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (216)..(222)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (216)..(222)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 183
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Ala Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 184
<211> 217
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> misc_feature
<222> (94)..(111)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (211)..(217)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (211)..(217)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 184
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

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

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val
100 105 110

Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser
115 120 125

Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln Tyr Tyr Arg
130 135 140

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

Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly
165 170 175

Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ala Phe Asn Pro
180 185 190

Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 185
<211> 114
<212> PRT
<213> Artificial Sequence

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

<400> 185
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His
100 105 110

His His

<210> 186
<211> 91
<212> PRT
<213> Artificial Sequence

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

<400> 186
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala
1 5 10 15

Pro Thr Ser Arg Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Gly Leu Ser Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr
65 70 75 80

His Glu Ser Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 187
<211> 108
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77"

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (102)..(108)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81"

<220>
<221> misc_feature

<222> (102)..(108)
<223> /note="Residues given in the sequence have no preference
with respect to those in the annotations for said positions"

<400> 187
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 188
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 188
Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
1 5 10

<210> 189
<211> 6
<212> PRT
<213> Artificial Sequence

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

<400> 189
Pro Gly Gly Leu Ser Thr
1 5

<210> 190
<211> 18
<212> PRT
<213> Artificial Sequence

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

<220>

<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Any amino acid

<220>
<221> misc_feature
<222> (14)..(18)
<223> /note="This region may encompass 0-5 residues"

<400> 190
Xaa Xaa Xaa Xaa Xaa Asp Ala Pro Thr Ser Arg Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 191
<211> 14
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (10)..(14)
<223> Any amino acid

<220>
<221> misc_feature
<222> (10)..(14)
<223> /note="This region may encompass 0-5 residues"

<400> 191
Xaa Xaa Xaa Xaa Xaa Gly Gly Leu Ser Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 192
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 192

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65                  70                  75                  80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
                85                  90                  95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
            100                 105                 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
        115                 120                 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
    130                 135                 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145                 150                 155                 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
                165                 170                 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
            180                 185                 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
    210                 215                 220

His His His His
225


<210> 193
<211> 222
<212> PRT
<213> Artificial Sequence

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


<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO:
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72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (216)..(222)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (216)..(222)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 193

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65                  70                  75                  80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
                85                  90                  95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
            100                 105                 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
        115                 120                 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
    130                 135                 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145                 150                 155                 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
                165                 170                 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
            180                 185                 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
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210 215 220

<210> 194
<211> 217
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> misc_feature
<222> (103)..(120)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (211)..(217)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (211)..(217)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 194
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
100 105 110

Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp Val Pro Arg Asp Leu

115 120 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
130 135 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145 150 155 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
165 170 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
180 185 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 195
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 195
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro

145 150 155 160

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

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 196
<211> 222
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (216)..(222)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (216)..(222)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 196
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

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Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
        115                 120                 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg
    130                 135                 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145                 150                 155                 160

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

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
            180                 185                 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
    210                 215                 220


<210> 197
<211> 217
<212> PRT
<213> Artificial Sequence

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


<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO:
      72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75"
      or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference
      with respect to those in the annotations for said positions"

<220>
<221> misc_feature
<222> (94)..(111)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala"
      repeats"

<220>
<221> VARIANT
<222> (211)..(217)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO:
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79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (211)..(217)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 197
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

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

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val
100 105 110

Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser
115 120 125

Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln Tyr Tyr Arg
130 135 140

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

Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly
165 170 175

Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Lys Pro His
180 185 190

Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 198
<211> 114
<212> PRT
<213> Artificial Sequence

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

<400> 198
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His
100 105 110

His His

<210> 199
<211> 91
<212> PRT
<213> Artificial Sequence

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

<400> 199
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala
1 5 10 15

Gly Ala Val Thr Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Gly Val Arg Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr
65 70 75 80

His Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 200
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77"

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (102)..(108)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81"

<220>
<221> misc_feature
<222> (102)..(108)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 200
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 201
<211> 10
<212> PRT
<213> Artificial Sequence

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

<400> 201
Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
1 5 10

<210> 202
<211> 17

<212> PRT
<213> Artificial Sequence

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

<400> 202
Thr Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr
1 5 10 15

Pro

<210> 203
<211> 18
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature
<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Any amino acid

<220>
<221> misc_feature
<222> (14)..(18)
<223> /note="This region may encompass 0-5 residues"

<400> 203
Xaa Xaa Xaa Xaa Xaa Asp Ala Gly Ala Val Thr Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 204
<211> 25
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Any amino acid

<220>
<221> misc_feature

<222> (1)..(5)
<223> /note="This region may encompass 0-5 residues"

<220>
<221> MOD_RES
<222> (21)..(25)
<223> Any amino acid

<220>
<221> misc_feature
<222> (21)..(25)
<223> /note="This region may encompass 0-5 residues"

<400> 204
Xaa Xaa Xaa Xaa Xaa Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr
1 5 10 15

Tyr His Glu Tyr Xaa Xaa Xaa Xaa Xaa
20 25

<210> 205
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 205
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

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Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
            180                 185                 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
    210                 215                 220

His His His His
225
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<210> 206
<211> 222
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
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<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (216)..(222)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (216)..(222)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 206

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                   10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65                  70                  75                  80
```

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 207
<211> 217
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> misc_feature
<222> (103)..(120)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (211)..(217)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (211)..(217)

<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 207

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65                  70                  75                  80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
                85                  90                  95

Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
            100                 105                 110

Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp Val Pro Arg Asp Leu
        115                 120                 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
    130                 135                 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145                 150                 155                 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
                165                 170                 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
            180                 185                 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
        195                 200                 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
    210                 215
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<210> 208
<211> 228
<212> PRT
<213> Artificial Sequence

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

<400> 208

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15
```

```
Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
        115                 120                 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr
    130                 135                 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145                 150                 155                 160

Val Gln Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser
                165                 170                 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
            180                 185                 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
    210                 215                 220

His His His His
225
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<210> 209
<211> 222
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>

<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (216)..(222)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (216)..(222)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 209

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
        115                 120                 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr
    130                 135                 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145                 150                 155                 160

Val Gln Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser
                165                 170                 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
            180                 185                 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
    210                 215                 220
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<210> 210

<211> 217
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(10)
<223> /replace="SEQ ID NO: 70" or "SEQ ID NO: 71" or "SEQ ID NO: 72" or "SEQ ID NO: 73" or "SEQ ID NO: 74" or "SEQ ID NO: 75" or "SEQ ID NO: 76" or "SEQ ID NO: 77" or " "

<220>
<221> misc_feature
<222> (1)..(10)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> misc_feature
<222> (94)..(111)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<220>
<221> VARIANT
<222> (211)..(217)
<223> /replace="SEQ ID NO: 10" or "SEQ ID NO: 78" or "SEQ ID NO: 79" or "SEQ ID NO: 80" or "SEQ ID NO: 81" or " "

<220>
<221> misc_feature
<222> (211)..(217)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 210
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

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

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val
100 105 110

Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser
115 120 125

Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln Tyr Tyr Arg

130 135 140

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

Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly
165 170 175

Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Lys Pro His
180 185 190

Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 211
<211> 222
<212> PRT
<213> Artificial Sequence

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

<400> 211
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Glu Lys
85 90 95

Gly Ser Gly Cys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser

165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu His His His His His His
210 215 220

<210> 212
<211> 226
<212> PRT
<213> Artificial Sequence

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

<400> 212
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Glu Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro

195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Gly Ser Gly Cys His His His His
210 215 220

His His
225

<210> 213
<211> 222
<212> PRT
<213> Artificial Sequence

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

<400> 213
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Cys Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Glu Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu His His His His His His

210 215 220

<210> 214
<211> 222
<212> PRT
<213> Artificial Sequence

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

<400> 214
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Glu Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Cys
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu His His His His His His
210 215 220

<210> 215
<211> 222
<212> PRT
<213> Artificial Sequence

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

<400> 215
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

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

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu His His His His His His
210 215 220

<210> 216
<211> 222
<212> PRT
<213> Artificial Sequence

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

<400> 216
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

```
Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Glu Lys
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
        115                 120                 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg
    130                 135                 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145                 150                 155                 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser
                165                 170                 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
            180                 185                 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
        195                 200                 205

Ile Cys Ile Asn Tyr Arg Thr Glu His His His His His His
    210                 215                 220


<210> 217
<211> 4
<212> PRT
<213> Artificial Sequence

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

<400> 217
Glu Ile Glu Lys
1


<210> 218
<211> 20
<212> PRT
<213> Artificial Sequence

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

<400> 218
Gly Ser Gly Cys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
1 5 10 15

Gly Ser Gly Ser
20

<210> 219
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 219
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 220
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 220
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 221
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 221
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Leu Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 222
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 222
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Glu Ala Asn Pro Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln

35 40 45

Glu Phe Thr Val Pro His Asp Leu Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 223
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 223
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Pro Gly Ser Arg Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr His Pro Ala Thr Tyr Glu His Glu Tyr His Ala His Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 224
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 224
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Pro Ala Asn Lys Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Gly Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 225
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 225
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 226
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 226
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

```
Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Gly Gln Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65                  70                  75                  80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
                85                  90                  95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
            100                 105


<210> 227
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 227
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                   10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Tyr Asp Val Thr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65                  70                  75                  80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
                85                  90                  95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
            100                 105


<210> 228
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 228
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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 229
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 229
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 230
<211> 104
<212> PRT
<213> Artificial Sequence

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

polypeptide"

<400> 230
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met
65 70 75 80

Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln His
100

<210> 231
<211> 103
<212> PRT
<213> Artificial Sequence

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

<400> 231
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65 70 75 80

Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 232
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 232
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 233
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 233
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Phe Val Thr His Val Ala Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 234
<211> 108

<212> PRT
<213> Artificial Sequence

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

<400> 234
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Glu Thr Glu Ser Asn Ala Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gln Ile Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 235
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 235
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Met Thr Ser Pro Ser Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Pro Val Gln Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Glu His Gln His Ala Pro His Gln Tyr Thr Ala His Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 236
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 236
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 237
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 237
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Thr Gly Arg Thr Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Asp Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 238
<211> 103
<212> PRT
<213> Artificial Sequence

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

<400> 238
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Ile Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65 70 75 80

Met His Val Glu Tyr Ala Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 239
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 239
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gln Val Pro Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser

85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 240
<211> 103
<212> PRT
<213> Artificial Sequence

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

<400> 240
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gly Tyr Gln Ser Gly Gly Tyr Thr
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Ala Tyr Lys Glu Tyr Gln Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 241
<211> 103
<212> PRT
<213> Artificial Sequence

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

<400> 241
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Trp Ile Gly Ile Pro Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Gly Lys Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65 70 75 80

Met His Val Glu Tyr Ala Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 242
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 242
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Lys Gly Ser Lys Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

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

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr Tyr Glu Tyr Ile Tyr Leu Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 243
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 243
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asn Pro Gly Ser Lys Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Asp Thr His Glu Tyr Leu Tyr Asn Gln Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 244
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 244
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Pro Gly Thr Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Leu Met Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Asn Thr Tyr Glu Tyr Ile Tyr Leu Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 245
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 245
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ile Gly Thr Ile Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Ala Gly Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asp Trp Ala Thr His Glu Tyr Asn Tyr His Thr Ala Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 246
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 246
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Tyr Asn Asp Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Ala Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Ala Thr Tyr Glu Tyr Ile Tyr His Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 247
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 247
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Ser Leu Val Gly Phe Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln

35 40 45

Glu Phe Thr Val Pro Gly Gly Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 248
<211> 103
<212> PRT
<213> Artificial Sequence

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

<400> 248
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Arg Lys Glu Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Trp Leu Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Met His Val Glu Tyr Ala Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 249
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 249
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Leu Ala Pro Phe Trp Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 250
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 250
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Pro Pro Gly His Gln His Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gln Val Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Tyr Tyr Thr Tyr Tyr Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 251
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 251
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Glu Ser Gly Ser Arg Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Thr Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 252
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 252
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Glu Arg Thr Ser Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

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

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 253
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 253

Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asn Ala Arg Thr Asp Ala Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Leu Glu Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr Gln Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 254
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 254
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Ser Ala Phe Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr Ser Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 255
<211> 108
<212> PRT
<213> Artificial Sequence

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

polypeptide"

<400> 255
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Leu Gly Arg Arg Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Ala Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Ala Thr His Glu Tyr Gln Tyr Glu Leu Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 256
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 256
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Pro Pro Asn Ser Gly His Asn
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Asn Thr Tyr Glu Tyr Thr Tyr Gln Phe Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 257
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 257
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Val Pro Asn Trp Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Leu Glu Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Thr Thr Tyr Glu Tyr Thr Tyr Phe Thr Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 258
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 258
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Gly Gly Phe Met Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gln Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 259
<211> 108

<212> PRT
<213> Artificial Sequence

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

<400> 259
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Glu Gly Pro Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Ala Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Arg Thr His Glu Leu Phe Phe Gln Gln Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 260
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 260
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Lys Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asp Pro Thr Ser Asn Leu Tyr Asn Tyr Asn Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 261
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 261
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Gly Ser Val Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Val Leu Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro Lys Pro Asp Gly Pro His Ile Tyr Gln Ala Val Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 262
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 262
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asn Pro Ala Ser Lys Asp Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gln Val Pro Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr Asp Ser Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 263
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 263
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Arg Ser Ser Ala Thr Ala Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

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

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Trp Ala Thr His Glu Tyr Ile Tyr His Ser Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 264
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 264
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp His Ser Gly Pro Arg Glu Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gln Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Pro Ile Thr His Tyr Tyr Tyr Tyr Glu Leu Thr Pro Ile Ser

85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 265
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 265
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Val Gly Leu Ser Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Ser Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 266
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 266
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gly Gly His Arg Ala Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Ala Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Asp Thr His Glu Tyr Lys Tyr His Gln Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 267
<211> 103
<212> PRT
<213> Artificial Sequence

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

<400> 267
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ser Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Trp Phe Lys Glu Tyr Arg Glu Asp Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 268
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 268
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Val Gly Gly Met Ile Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 269
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 269
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Lys Ala Ser Tyr Thr Gly Tyr Asn
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Val Met Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Asp Thr His Gln Tyr Thr Tyr Arg Arg Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 270
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 270
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Val Gly Gln Val Phe Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 271
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 271
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Ser Gly Asp Tyr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Glu Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Tyr Tyr Lys Tyr Glu Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 272
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 272
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ile Val Gln Gly Gly Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln

35 40 45

Glu Phe Thr Val Pro Gly Met Val Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ser Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 273
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 273
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Val Arg Trp Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Arg Thr His Val Tyr Ile Tyr Asp Gln Phe Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 274
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 274
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Arg Ala Arg Arg Leu Gln Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Ala Thr Met Glu Tyr Thr Tyr Gln Arg Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 275
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 275
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Leu Gln Pro Leu Trp Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Leu Asp Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Val Asp Gly Pro His Ala Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 276
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 276
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Ser Gln Gly Asn Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Ala Val Lys Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Pro Ala Thr His Glu Tyr Ile Tyr His Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 277
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 277
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Cys Leu Asp Gly Gln Leu Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Ser Ile Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65 70 75 80

Tyr Asn Leu Ala Thr His Glu Tyr Asn Tyr Arg Val Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 278
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 278

Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Thr Ser Gly Ala Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Ser Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asp Pro Asp Ser His Tyr Tyr Asn Tyr Asn Met Val Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 279
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 279
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Asn Gly Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

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

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Thr Tyr Glu Leu Arg Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 280
<211> 108
<212> PRT
<213> Artificial Sequence

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

polypeptide"

<400> 280
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Thr Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Arg Pro Thr Ser Gln Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Tyr Ala Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 281
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 281
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Lys Ser Tyr Gly Ser Ala Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Asp Leu Gln Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Ile Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Asp Thr His Glu Tyr Lys Tyr His Val Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 282
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 282
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ser Val Met Gly Leu Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ser Thr Tyr Glu Tyr Lys Tyr Asn Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 283
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 283
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Lys Thr Glu Pro Gly Arg His Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65 70 75 80

Tyr Asn Leu Val Ser His Glu Tyr Val Tyr His Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 284
<211> 108

<212> PRT
<213> Artificial Sequence

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

<400> 284
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp His Ala Gly Met Ala Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Asp Val Leu Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Pro Val Thr His Glu Tyr Met Tyr His Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 285
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 285
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Ser Ala Arg Gly Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Leu Glu Thr Tyr Glu Tyr His Tyr Tyr Arg Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 286
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 286
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Trp Phe Gly Thr Ser Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Asp Leu Lys Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Val Thr His Glu Tyr Glu Tyr His Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 287
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 287
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Thr Arg Thr Leu Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Met Val Thr Tyr Glu Tyr Asn Tyr His Leu Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 288
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 288
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Val Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Lys Leu Leu Gly Gly Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Pro Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Pro Arg Thr His Glu Tyr Gln Tyr His Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 289
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 289
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Arg Ala Ser Gly Gly Leu Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Ser Val Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Ala Thr Tyr Glu Tyr Ile Tyr His Thr Thr Pro Ile Ser

85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 290
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 290
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ala Gly Arg Ala Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Tyr Tyr Glu Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 291
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 291
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Ser Gln Pro Leu Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Val Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Glu Thr His Glu Tyr Thr Tyr His Leu Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 292
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 292
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ser Ala Thr Arg Pro Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Pro Thr Thr His Glu Tyr Tyr Tyr His Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 293
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 293
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Val Glu Arg Ser Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ser Thr His Glu Tyr Asn Tyr Leu Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 294
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 294
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Asp Thr Ser Ser Tyr His Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Ser Thr His Glu Tyr Ile Tyr Arg Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 295
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 295
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ser Ser His Arg Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Ser Val Ala Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Asp Thr His Glu Tyr Leu Tyr His Ala Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 296
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 296
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Asn Asn Ser Asn Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Thr Glu Gly Glu His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 297
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 297
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Arg Val Leu Val Asp Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln

35 40 45

Glu Phe Thr Val Pro Gly Gly Val Leu Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Val Asp Gly Pro His Thr Tyr Tyr Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 298
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 298
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Met Phe Val Gly Met Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

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

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Ala Thr His Glu Tyr Ile Tyr His Val Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 299
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 299
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Leu His Arg Lys Asn Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Asp Tyr Arg Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 300
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 300
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 301
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 301
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Glu Asn Asn Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Lys Thr His Glu Tyr Asn Tyr Leu Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 302
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 302
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gly Ser Pro Leu Ile Glu Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Ala Thr His Glu Tyr Thr Tyr His Val Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 303
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 303

Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Thr Asn Lys Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 304
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 304
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Asp Pro Ala Ala Asn Arg Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Gln Tyr Lys Tyr Ser Gln Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 305
<211> 108
<212> PRT
<213> Artificial Sequence

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

polypeptide"

<400> 305
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65 70 75 80

Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 306
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 306
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Pro Trp Arg Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Leu Asn Pro Asn Thr Leu Glu Tyr Thr Tyr Gln Arg Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 307
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 307
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Ala Ala Asn His Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Pro Val Thr His Glu Tyr Lys Tyr Arg Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 308
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 308
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 309
<211> 108

<212> PRT
<213> Artificial Sequence

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

<400> 309
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asn Asn Gly Gly Arg Asn Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 310
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 310
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Val Pro Gln Gly Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Ala Thr His Glu Tyr Asn Tyr His Ser Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 311
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 311
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ala
65 70 75 80

Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 312
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 312
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 313
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 313
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 314
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 314
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser

85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 315
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 315
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Pro Ala Asn Lys Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 316
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 316
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 317
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 317
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Pro Ala Asn Lys Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 318
<211> 103
<212> PRT
<213> Artificial Sequence

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

<400> 318
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Pro Ala Asn Lys Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met
65 70 75 80

Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 319
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 319
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 320
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 320
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 321
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 321
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 322
<211> 104
<212> PRT
<213> Artificial Sequence

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

<400> 322
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln

35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65 70 75 80

Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln His
100

<210> 323
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 323
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 324
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 324
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 325
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 325
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 326
<211> 103
<212> PRT
<213> Artificial Sequence

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

<400> 326
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met
65 70 75 80

Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 327
<211> 108
<212> PRT
<213> Artificial Sequence

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

<400> 327
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 328
<211> 315
<212> DNA
<213> Artificial Sequence

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

<400> 328

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acaggaggca atagccctgt ccaggagttc actgtgccta aaaacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactaggttc 240

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<210> 329
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<213> Artificial Sequence

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

<400> 329
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atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 330
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<213> Artificial Sequence

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

<400> 330
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atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 331
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<213> Artificial Sequence

<220>
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atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

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<220>
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atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

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<210> 333
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<213> Artificial Sequence

<220>
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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgaccat 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 335
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<213> Artificial Sequence

<220>
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atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 336
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<213> Artificial Sequence

<220>
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<400> 336
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atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 337
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acaggaggca atagccctgt ccaggagttc actgtgcctt acgacgttac tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 338
<211> 342
<212> DNA
<213> Artificial Sequence

<220>
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<400> 338
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acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctgcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 339
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<213> Artificial Sequence

<220>
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<400> 339
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acaggaggca atagccctgt ccaggagttc actgtgcctt acgacctggt tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgaccat 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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<213> Artificial Sequence

<220>
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<400> 340
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acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctgcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactaacatg 240

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ccatcccagc accatcacca ccaccac 327

<210> 341
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<213> Artificial Sequence

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<400> 341
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acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctggt tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacatg 240

atgcatgttg aatacactga acatccaatt tccattaatt accgcacaga aattgacaaa 300

ccatcccagc accatcacca ccaccac 327

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acaggaggca atagccctgt ccaggagttc actgtgcctg gtatggttca cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgaccat 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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<213> Artificial Sequence

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acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtctgtc cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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<213> Artificial Sequence

<220>
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acaggaggca atagccctgt ccaggagttc actgtgcctg gtccggttca gacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactac 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 346
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 346
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ctgatcagct gggattcagg acgaggttcc tatcaatatt accgcatcac ttacggcgaa 120

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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<213> Artificial Sequence

<220>
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<400> 347
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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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<213> Artificial Sequence

<220>
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<400> 348
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acaggaggca atagccctgt ccaggagttc actgtgcctt acgacgttat cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacatg 240

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ccatcccagc accatcacca ccaccac 327

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<213> Artificial Sequence

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

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acaggaggca atagccctgt ccaggagttc actgtgcctg gtcaggttcc aacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

tacaacccgg ctactcatga atacaaatac catcagactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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<213> Artificial Sequence

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atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactac 240

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ccatcccagc accatcacca ccaccac 327

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<213> Artificial Sequence

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<213> Artificial Sequence

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ctgatcagct ggaatcccgg ctccaaaagc taccaatatt accgcatcac ttacggcgaa 120

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atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttt 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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<213> Artificial Sequence

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acaggaggca atagccctgt ccaggagttc actgtgcctg ctggtgttta cacagctacc 180

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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<211> 342
<212> DNA
<213> Artificial Sequence

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

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acaggaggca atagccctgt ccaggagttc actgtgcctt acgctgttta cacagctacc 180

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 357
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 357
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acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttca tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 358
<211> 327
<212> DNA
<213> Artificial Sequence

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

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acaggaggca atagccctgt ccaggagttc actgtgcctg gttggttgaa cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactac 240

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ccatcccagc accatcacca ccaccac 327

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<213> Artificial Sequence

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acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatctc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 360
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 360
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggacaccacc aggacatcaa catcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtcaggttac tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tacaacccag ctactcacta ttacacttat tatacgactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 361
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 361
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggagtcggg gtccaggacg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttca tacagctacc 180

atcagcggcc ttaaaactgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatatc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 362
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 362
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggagaggac ctccacccac taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtcgtgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactac 240

tacaacccgg ctactcatga atacaaatac catcagactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 363
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 363
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggaatgctcg caccgacgct tatcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc gtgacctgga aacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaacctcatg cggacggacc gcatacttac caagagtcgc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 364
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 364
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggcaggtgag cgcgttccgg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtatggtttc tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ctgacggtcc gcatacttac tctgaatacc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 365
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 365
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggtgctggg caggagggtg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtgctgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

ttcaacccag ctacccatga ataccaatac gagcttactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 366
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 366
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggactccacc caattctggt cataattatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctgac tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tacaacccga atacctatga atacacatat caattcactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 367
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 367
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggtcgtccc gaactggatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtatgctgga aacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tataacccga ctacgtatga atacacatac tttacctatc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 368
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 368
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggtccggcgg gttcatgcgg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtcaggttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatctc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 369
<211> 342

<212> DNA
<213> Artificial Sequence

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

<400> 369
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggattccga aggtccttct tatcaatatt accgcatcac ttacggcgaa 120

aaaggaggca atagccctgt ccaggagttc actgtgcctt acgctgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tacaacccga gaacgcatga attatttttc cagcaatatc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 370
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 370
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggcaggttcc gcgtccgatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctgcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tacgacccga catctaatct gtacaattac aaccagactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 371
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 371
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggcaggtggg ctcggtggtg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc gtgacgttct gacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgaagc ctgacggtcc acatatatac caggcagtgc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 372
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 372
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggaaccctgc ttctaaagac tatcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtcaggttcc gacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttt 240

tacaacccgg ctactcatga gtataaatat gactcgactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 373
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 373
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggagatcatc agcaaccgcc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtcgtgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttt 240

ttcaactggg ccactcatga gtacatatac cactcaactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 374
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 374
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggcattccgg tccacgagaa tatcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtcaggttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttt 240

ttcaacccga ttacacatta ctattactac gagctgactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 375
<211> 342
<212> DNA
<213> Artificial Sequence

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

polynucleotide"

<400> 375
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggacggtggg cctgagcgtg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtatggtttc tacagctacc 180

atcagcggcc ttaaacctag cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatatc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 376
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 376
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggggggggca ccgggcggtg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtgctgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactac 240

tacaacccgg atactcatga atacaaatac catcaatatc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 377
<211> 327
<212> DNA
<213> Artificial Sequence

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

<400> 377
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttt ctgccacccc caccagcctg 60

ctgatcagct ggcaggttcc gcgtccgatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactac 240

tggttcaagg aataccgtga agacccaatt tccattaatt accgcacaga aattgacaaa 300

ccatcccagc accatcacca ccaccac 327

<210> 378
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 378

atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggagcgtcgg gggcatgatc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtatggttac tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactac 240

tacaacccgg ctactcatga atacaaatac catcagactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 379
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 379
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggtgggcccc cgtcgaccgg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc gtgacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatctc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 380
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 380
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggtgggcccc cgtcgaccgg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc gtgacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatctc caatttccat taattaccgc 300

acagaaattg acaaaccatg ccagcaccac caccaccacc ac 342

<210> 381
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 381
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggaaagccag ctataccggc tacaactatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc gtgacgttat gacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttc 240

tacaatccgg atactcatca atacacatac cgtcgcattc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 382
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 382
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggtcggtggg ccaggtcttc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactac 240

tacaacccgg ctactcatga atacaaatac catcagactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 383
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 383
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggtactctgg tgattaccat taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctgga aacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tacaacccgg ctactcatta ctacaagtac gagcagacac caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 384
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 384
atgggagttt ctgatgtgcc gcgcgacctg gaagttgttg ctgccacccc caccagcctg 60

ctgatcagct ggatcgtcca ggggggggcgc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtatggttac tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tacaaccctt caactcatga atacaaatac catcagactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 385
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 385
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggtcggccgt ccgctggcgg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttt 240

tacaacccgc gtactcatgt atacatatac gatcagttcc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 386
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 386
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggagggccag gcgcttgcag taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtatggttac tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttt 240

tacaacccgg ctactatgga gtacacatat cagcggactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 387
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 387
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggttgcagcc cctctggagg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtctgga cacagctacc 180

atcagcggac ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ttgacggtcc ccatgcttac catgaatatc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 388
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 388
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggacgcctc ccaggggaac taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtgctgttaa aacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttt 240

ttcaacccgg ctactcatga atacatatac catacgactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 389
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 389
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggtgcctcga cgggcagttg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gttctatcgt tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactgg 240

tacaacctcg cgactcatga atacaactac cgtgtgactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 390
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 390
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggacacttc aggtgcttca tatcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt actctgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tacgaccctg attcgcatta ttacaactac aatatggttc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 391
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 391
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ctgatcagct gggattctgg taatggtact tatcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt accgtgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tacaacccgg ctactcacga atatacatac gagctgcgtc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 392
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 392
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctaccacccc caccagcctg 60

ctgatcagct ggcggcccac cagccaggtc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acaacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttt 240

tttaactatg ctactcacga atacatatac cataccattc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 393
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 393
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ctgatcagct ggaagtcgta cgggtcggcc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtgacctgca gacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctat cactgactat 240

tacaacccgg atacacatga gtataaatac catgtgtcgc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 394
<211> 342

<212> DNA
<213> Artificial Sequence

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

<400> 394
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ctgatcagct ggtcgtcggt gatggggttg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tacaaccctt ctacttatga atacaaatac aatacgactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 395
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 395
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ctgatcagct ggcacgccgg catggcggtg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtgacgttct gacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttt 240

ttcaatccgg ttactcatga atacatgtat catacgattc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 396
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 396
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggtgtccgc gaggggcgg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tacaacctag aaacttatga atatcattac tatcgcactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 397
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 397
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ctgatcagct ggtggttcgg cacctcgtcc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtgacctgaa aacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tttaaccccg ttactcatga atacgaatat catacgactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 398
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 398
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggtccgcgac ccggaccctg taccaatatt accgaatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacgttca tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tacaacatgg ttacttatga atacaactac catcttactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 399
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 399
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ttgccacccc caccagcctg 60

ctgatcagct ggaccaagtt gttgggcggg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtcctgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttt 240

ttcaaccctc gtactcatga atatcaatat cacacgactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 400
<211> 342
<212> DNA
<213> Artificial Sequence

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

polynucleotide"

<400> 400
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ctgatcagct ggagggcgtc gggcgggctg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gttctgttaa cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttt 240

tacaacccgg ctacttatga gtacatatac cataccactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 401
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 401
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ctgatcagct gggcggccgg gcgcgccacg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacgttac tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttt 240

tacaacccgg ctactcatga atactactat gagaccacgc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 402
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 402
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ctgatcagct ggtactcgca gcccttgacg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacgttaa cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttc 240

tacaacccgg agacacatga atacacttac cacctgactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 403
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 403

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ctgatcagct ggagttctgc aacaagacct taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttt 240

ttcaacccga ctacgcacga atactattat catacgactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 404
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 404
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ctgatcagct ggtccgtcga gaggtccgtg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tacaacccgt ctactcatga atacaattac ctcacgactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 405
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 405
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ctgatcagct ggcaagatac ctccagttat catcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

ttcaacccgt ctacccatga atacatctac cgtaccattc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 406
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 406
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggtctagctc tcatcgccgc tatcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gttcggttgc tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

ttcaacccag acactcatga atacctatac catgccaccc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 407
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 407
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggataataa ttctaactca tatcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacctgcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaacctcata ctgagggtga gcatacttat catgaatcgc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 408
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 408
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggcgcgtgtt ggtcgacatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttct gacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ttgacgggcc gcacacctac tatgaatctc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 409
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 409
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggatgttcgt ggggatgtcc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acggtgttca tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

ttcaacccgg ctacgcatga atacatctac catgtgactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 410
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 410
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggacgctgca ccggaagaac taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttgt tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tacaacccgg caactcatga atacgactac cgaacaactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 411
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 411
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctt 60

ctgatcagct ggacacaagg cagtactcat taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtatggttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

ttcgaccgct ctactcatga gtataaatac cgtacgactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 412
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 412
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggcacgaacg tgacggaagt agacaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

tttaacccga ctacacatga atacatatat cagacaactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 413
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 413
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggactccgg tgaaaacaat taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 414
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 414
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ctgatcagct gggggagccc cttgatcgag taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtctgtc tacagctacc 180

atcagcggcc tcaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

ttcaacccgg ctactcatga atacacatac catgtgagtc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 415
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 415
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggtctgcaac aaacaaaact taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

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tttaacccga ctacacatga atacatatat cagacaactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 416
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 416
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggatgaccc agctgcaaac cgacaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacctgcg tacagctacc 180

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tacaacccgg ctacccatca atacaaatac tctcagagtc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 417
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 417
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ctgatcagct ggtactggga ggggctgccc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc gtgacgttaa cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactgg 240

tacaaccccg acacccatga gtatatatac catacgattc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 418
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 418
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggagcgcgcc gtggcggacc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

ttaaacccta acacgcttga atacacctac cagcgcattc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 419
<211> 342

<212> DNA
<213> Artificial Sequence

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

<400> 419
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggcaggcggc caaccactcg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacttt 240

ttcaatcctg tcactcatga atacaaatac cgtacaattc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 420
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 420
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggattcagg acgaggttcc tatcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcacg ctgacggtcc gcacacttac catgaatatc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 421
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 421
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggaataacgg aggacgcaat tatcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcacg ctgacggtcc gcacacttac catgaatatc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 422
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 422
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggtcgtgcc gcaggggatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgtttc tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

ttcaacccgg caacccatga atacaattat cattcaattc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 423
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 423
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggcgagcaa ccgggggacg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgtttc tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacgct 240

ttcaacccaa ctactcatga atacaattat tttacaactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 424
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 424
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggttgccggg caagctgagg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctgcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatctc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 425
<211> 342
<212> DNA
<213> Artificial Sequence

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

polynucleotide"

<400> 425
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggacgctcc aacctcccgc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgaccat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatacc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 426
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 426
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggacgctcc aacctcccgc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcacg ctgacggtcc gcacacttac catgaatatc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 427
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 427
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggacccctgc taataaatct taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctggt tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgaccat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatacc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 428
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 428

atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggacgctcc ggctgttact taccagtatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctggt tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatctc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 429
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 429
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggacccctgc taataaatct taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctggt tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgaccat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatctc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 430
<211> 327
<212> DNA
<213> Artificial Sequence

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

<400> 430
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggacccctgc taataaatct taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactaacatg 240

atgcatgttg aatactctga atacccaatt tccattaatt accgcacaga aattgacaaa 300

ccatcccagc accatcacca ccaccac 327

<210> 431
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 431
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggacgctgg tgctgttact taccagtatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctggt tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgaccat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatacc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 432
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 432
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggacgctcc aacctcccgc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtctgtc cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatctc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 433
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 433
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggacgctcc ggctgttact taccagtatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcacg ctgacggtcc gcacacttac catgaatatc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 434
<211> 327
<212> DNA
<213> Artificial Sequence

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

<400> 434
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggattcagg acgaggttcc tatcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacatg 240

atgcatgttg aatacactga acatccaatt tccattaatt accgcacaga aattgacaaa 300

ccatcccagc accatcacca ccaccac 327

<210> 435
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 435
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggacgctcc ggctgttact taccagtatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatctc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 436
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 436
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggacgctcc aacctcccgc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctggt tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatctc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 437
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 437
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggacgctgg tgctgttact taccagtatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatctc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 438
<211> 327
<212> DNA
<213> Artificial Sequence

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

<400> 438
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggacgctcc aacctcccgc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctggt tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactaacatg 240

atgcatgttg aatactctga atacccaatt tccattaatt accgcacaga aattgacaaa 300

ccatcccagc accatcacca ccaccac 327

<210> 439
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 439
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggacgctgg tgctgttact taccagtatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

aaaccgcacg ctgacggtcc gcacacttac catgaatatc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 440
<211> 327
<212> DNA
<213> Artificial Sequence

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

<400> 440
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggtatcctgg ccaaccaaca tatcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc attgtgcctt acctggttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactac 240

gcttacaaag aatactctga atacccaatt tccattaatt accgcacaga aattgacaaa 300

ccatcccagc accatcacca ccaccac 327

<210> 441
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 441
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggcaaagttc aaccagccaa tatcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgaccat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatctc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 442
<211> 669
<212> DNA
<213> Artificial Sequence

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

<400> 442
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggttgccggg caagctgagg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctgcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactaacatg 240

atgcatgttg aatactctga atacccaatt tccattaatt accgcacaga aattgacaaa 300

ggtagcggct ctggttccgg cagcggctcc ggcagcggct ctggcagcgg ttctggttcc 360

gtttctgatg tgccgcgcga cctggaagtg gttgctgcca cccccaccag cctgctgatc 420

agctggtctg cgcgtctgaa agttgcgcga tattaccgca tcacttacgg cgaaacagga 480

ggcaatagcc ctgtccagga gttcactgtg cctaaaaacg tttacacagc taccatcagc 540

ggccttaaac ctggcgttga ttataccatc actgtgtatg ctgtcactag gttccgcgac 600

taccagccaa tttccattaa ttaccgcaca gaaattgaca aaccatgcca gcaccaccac 660

caccaccac 669

<210> 443
<211> 669
<212> DNA
<213> Artificial Sequence

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

<400> 443
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggtctgcgcg tctgaaagtt gcgcgatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgccta aaaacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactaggttc 240

cgcgactacc agccaatttc cattaattac cgcacagaaa ttgacaaagg tagcggctct 300

ggttccggca gcggctccgg cagcggctct ggcagcggtt ctggttccgt ttctgatgtg 360

ccgcgcgacc tggaagtggt tgctgccacc cccaccagcc tgctgatcag ctggttgccg 420

ggcaagctga ggtaccaata ttaccgcatc acttacggcg aaacaggagg caatagccct 480

gtccaggagt tcactgtgcc tcatgacctg cgtacagcta ccatcagcgg ccttaaacct 540

ggcgttgatt ataccatcac tgtgtatgct gtcactaaca tgatgcatgt tgaatactct 600

gaatacccaa tttccattaa ttaccgcaca gaaattgaca aaccatgcca gcaccaccac 660

caccaccac 669

<210> 444
<211> 669
<212> DNA
<213> Artificial Sequence

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

<400> 444
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggtggccgg ggcggaggac taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctggt tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacatg 240

atgcatgttg aatacactga acatccaatt tccattaatt accgcacaga aattgacaaa 300

ggtagcggct ctggttccgg cagcggctcc ggcagcggct ctggcagcgg ttctggttcc 360

gtttctgatg tgccgcgcga cctggaagtg gttgctgcca cccccaccag cctgctgatc 420

agctggtctg cgcgtctgaa agttgcgcga tattaccgca tcacttacgg cgaaacagga 480

ggcaatagcc ctgtccagga gttcactgtg cctaaaaacg tttacacagc taccatcagc 540

ggccttaaac ctggcgttga ttataccatc actgtgtatg ctgtcactag gttccgcgac 600

taccagccaa tttccattaa ttaccgcaca gaaattgaca aaccatgcca gcaccaccac 660

caccaccac 669

<210> 445
<211> 669
<212> DNA
<213> Artificial Sequence

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

<400> 445
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggtctgcgcg tctgaaagtt gcgcgatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgccta aaaacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactaggttc 240

cgcgactacc agccaatttc cattaattac cgcacagaaa ttgacaaagg tagcggctct 300

ggttccggca gcggctccgg cagcggctct ggcagcggtt ctggttccgt ttctgatgtg 360

ccgcgcgacc tggaagtggt tgctgccacc cccaccagcc tgctgatcag ctgggtggcc 420

ggggcggagg actaccaata ttaccgcatc acttacggcg aaacaggagg caatagccct 480

gtccaggagt tcactgtgcc tcatgacctg gttacagcta ccatcagcgg ccttaaacct 540

ggcgttgatt ataccatcac tgtgtatgct gtcactgaca tgatgcatgt tgaatacact 600

gaacatccaa tttccattaa ttaccgcaca gaaattgaca aaccatgcca gcaccaccac 660

caccaccac 669

<210> 446
<211> 684
<212> DNA
<213> Artificial Sequence

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

<400> 446
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct gggattcagg acgaggttcc tatcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtccggttca tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgaccat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatctc caatttccat taattaccgc 300

acagaaattg acaaaggtag cggctctggt tccggcagcg gctccggcag cggctctggc 360

agcggttctg gttccgtttc tgatgtgccg cgcgacctgg aagtggttgc tgccaccccc 420

accagcctgc tgatcagctg gtctgcgcgt ctgaaagttg cgcgatatta ccgcatcact 480

tacggcgaaa caggaggcaa tagccctgtc caggagttca ctgtgcctaa aaacgtttac 540

acagctacca tcagcggcct taaacctggc gttgattata ccatcactgt gtatgctgtc 600

actaggttcc gcgactacca gccaatttcc attaattacc gcacagaaat tgacaaacca 660

tgccagcacc accaccacca ccac 684

<210> 447
<211> 684
<212> DNA
<213> Artificial Sequence

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

<400> 447
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggtctgcgcg tctgaaagtt gcgcgatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgccta aaaacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactaggttc 240

cgcgactacc agccaatttc cattaattac cgcacagaaa ttgacaaagg tagcggctct 300

ggttccggca gcggctccgg cagcggctct ggcagcggtt ctggttccgt ttctgatgtg 360

ccgcgcgacc tggaagtggt tgctgccacc cccaccagcc tgctgatcag ctgggattca 420

ggacgaggtt cctatcaata ttaccgcatc acttacggcg aaacaggagg caatagccct 480

gtccaggagt tcactgtgcc tggtccggtt catacagcta ccatcagcgg ccttaaacct 540

ggcgttgatt ataccatcac tgtgtatgct gtcactgacc ataaaccgca tgctgacggt 600

ccgcatactt accatgaatc tccaatttcc attaattacc gcacagaaat tgacaaacca 660

tgccagcacc accaccacca ccac 684

<210> 448
<211> 684
<212> DNA
<213> Artificial Sequence

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

<400> 448
atgggtgttt ctgatgttcc gcgtgatctg gaggttgttg cagcaacccc gaccagcctg 60

ctgatttctt ggtgggcacc ggttgatcgt tatcagtatt atcgcatcac ctatggtgaa 120

accggtggta attctccggt tcaggaattt accgttcctc gcgacgttta taccgcaacc 180

attagcggtc tgaaaccggg tgttgattac accattaccg tttacgccgt taccgattat 240

aaaccgcatg cagatggtcc gcatacctat catgaaagcc cgattagcat taactatcgc 300

accgaaattg ataaaggtag cggtagcggt tcaggtagcg gatcaggttc tggttctggt 360

agtggtagcg gcagcgtttc agatgtgcct cgcgacctgg aagtggtggc agccacaccg 420

acttctctgc tgattagctg gtctgcacgt ctgaaagttg cccgttatta ccgtattact 480

tatggcgaaa caggcggaaa tagccctgtg caagaattta ccgtgccgaa aaatgtgtac 540

acagccacca tctctggcct gaaacctggc gtggactaca caatcacagt ttatgcagtg 600

acccgttttc gtgattatca gccgatcagc atcaattatc gtacagagat cgataaaccg 660

tgccagcatc accaccatca tcac 684

<210> 449
<211> 684
<212> DNA
<213> Artificial Sequence

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

<400> 449
atgggtgttt ctgatgttcc gcgtgatctg gaggttgttg cagcaacccc gaccagcctg 60

ctgatttctt ggacccaggg tagcacacat tatcagtatt atcgcatcac ctatggtgaa 120

accggtggta attctccggt tcaggaattt accgttcctg gtatggttta taccgcaacc 180

attagcggtc tgaaaccggg tgttgattac accattaccg tttacgccgt taccgattat 240

ttcgatcggt ccacccatga atataaatat cggaccaccc cgattagcat taactatcgc 300

accgaaattg ataaaggtag cggtagcggt tcaggtagcg gatcaggttc tggttctggt 360

agtggtagcg gcagcgtttc agatgtgcct cgcgacctgg aagtggtggc agccacaccg 420

acttctctgc tgattagctg gtctgcacgt ctgaaagttg cccgttatta ccgtattact 480

tatggcgaaa caggcggaaa tagccctgtg caagaattta ccgtgccgaa aaatgtgtac 540

acagccacca tctctggcct gaaacctggc gtggactaca caatcacagt ttatgcagtg 600

acccgttttc gtgattatca gccgatcagc atcaattatc gtacagagat cgataaaccg 660

tgccagcatc accaccatca tcac 684

<210> 450
<211> 684
<212> DNA
<213> Artificial Sequence

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

<400> 450
atgggtgttt ctgatgttcc gcgtgatctg gaggttgttg cagcaacccc gaccagcctg 60

ctgatttctt ggcatgaacg tgatggtagc cgtcagtatt atcgcatcac ctatggtgaa 120

accggtggta attctccggt tcaggaattt accgttcctg gcggtgttcg taccgcaacc 180

attagcggtc tgaaaccggg tgttgattac accattaccg tttacgccgt taccgattat 240

ttcaatccga ccacccatga atatatttat cagaccaccc cgattagcat taactatcgc 300

accgaaattg ataaaggtag cggtagcggt tcaggtagcg gatcaggttc tggttctggt 360

agtggtagcg gcagcgtttc agatgtgcct cgcgacctgg aagtggtggc agccacaccg 420

acttctctgc tgattagctg gtctgcacgt ctgaaagttg cccgttatta ccgtattact 480

tatggcgaaa caggcggaaa tagccctgtg caagaattta ccgtgccgaa aaatgtgtac 540

acagccacca tctctggcct gaaacctggc gtggactaca caatcacagt ttatgcagtg 600

acccgttttc gtgattatca gccgatcagc atcaattatc gtacagagat cgataaaccg 660

tgccagcatc accaccatca tcac 684

<210> 451
<211> 684
<212> DNA
<213> Artificial Sequence

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

<400> 451
atgggtgttt ctgatgttcc gcgtgatctg gaggttgttg cagcaacccc gaccagcctg 60

ctgatttctt ggtattggga aggtctgccg tatcagtatt atcgcatcac ctatggtgaa 120

accggtggta attctccggt tcaggaattc accgttcctc gcgacgttaa taccgcaacc 180

attagcggtc tgaaaccggg tgttgattac accattaccg tttacgccgt taccgattgg 240

tacaaccctg atacccatga atatatttat cataccattc cgattagcat taactatcgc 300

accgaaattg ataaaggtag cggtagcggt tcaggtagcg gatcaggttc tggttctggt 360

agtggtagcg gcagcgtttc agatgtgcct cgcgacctgg aagtggtggc agccacaccg 420

acttctctgc tgattagctg gtctgcacgt ctgaaagttg cccgttatta ccgtattact 480

tatggcgaaa caggcggaaa tagccctgtg caagaattta ccgtgccgaa aaatgtgtac 540

acagccacca tctctggcct gaaacctggc gtggactaca caatcacagt ttatgcagtg 600

acccgttttc gtgattatca gccgatcagc atcaattatc gtacagagat cgataaaccg 660

tgccagcatc accaccatca tcac 684

<210> 452
<211> 684
<212> DNA
<213> Artificial Sequence

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

<400> 452
atgggtgttt ctgatgttcc gcgtgatctg gaggttgttg cagcaacccc gaccagcctg 60

ctgatttctt gggcaagcaa tcgtggcacc tatcagtatt atcgcatcac ctatggtgaa 120

accggtggta attctccggt tcaggaattt accgttcctg gcggtgtttc taccgcaacc 180

attagcggtc tgaaaccggg tgttgattac accattaccg tttacgccgt taccgatgca 240

tttaatccga ccacccatga atataattat tttaccaccc cgattagcat taactatcgc 300

accgaaattg ataaaggtag cggtagcggt tcaggtagcg gatcaggttc tggttctggt 360

agtggtagcg gcagcgtttc agatgtgcct cgcgacctgg aagtggtggc agccacaccg 420

acttctctgc tgattagctg gtctgcacgt ctgaaagttg cccgttatta ccgtattact 480

tatggcgaaa caggcggaaa tagccctgtg caagaattta ccgtgccgaa aaatgtgtac 540

acagccacca tctctggcct gaaacctggc gtggactaca caatcacagt ttatgcagtg 600

acccgttttc gtgattatca gccgatcagc atcaattatc gtacagagat cgataaaccg 660

tgccagcatc accaccatca tcac 684

<210> 453
<211> 684
<212> DNA
<213> Artificial Sequence

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

<400> 453
atgggtgttt ctgatgttcc gcgtgatctg gaggttgttg cagcaacccc gaccagcctg 60

ctgatttctt gggatgcacc gacctctcgt tatcagtatt atcgcatcac ctatggtgaa 120

accggtggta attctccggt tcaggaattt accgttcctg gcggtctgag caccgcaacc 180

attagcggtc tgaaaccggg tgttgattac accattaccg tttacgccgt taccgattat 240

aaaccgcatg cagatggtcc gcatacctat catgaaagcc cgattagcat taactatcgc 300

accgaaattg ataaaggtag cggtagcggt tcaggtagcg gatcaggttc tggttctggt 360

agtggtagcg gcagcgtttc agatgtgcct cgcgacctgg aagtggtggc agccacaccg 420

acttctctgc tgattagctg gtctgcacgt ctgaaagttg cccgttatta ccgtattact 480

tatggcgaaa caggcggaaa tagccctgtg caagaattta ccgtgccgaa aaatgtgtac 540

acagccacca tctctggcct gaaacctggc gtggactaca caatcacagt ttatgcagtg 600

acccgttttc gtgattatca gccgatcagc atcaattatc gtacagagat cgataaaccg 660

tgccagcatc accaccatca tcac 684

<210> 454
<211> 684
<212> DNA
<213> Artificial Sequence

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

<400> 454
atgggtgttt ctgatgttcc gcgtgatctg gaggttgttg cagcaacccc gaccagcctg 60

ctgatttctt gggatgcagg tgcagttacc tatcagtatt atcgcatcac ctatggtgaa 120

accggtggta attctccggt tcaggaattt accgttcctg gcggtgttcg taccgcaacc 180

attagcggtc tgaaaccggg tgttgattac accattaccg tttacgccgt taccgattat 240

aaaccgcatg cagatggtcc gcatacctat catgaatatc cgattagcat taactatcgc 300

accgaaattg ataaaggtag cggtagcggt tcaggtagcg gatcaggttc tggttctggt 360

agtggtagcg gcagcgtttc agatgtgcct cgcgacctgg aagtggtggc agccacaccg 420

acttctctgc tgattagctg gtctgcacgt ctgaaagttg cccgttatta ccgtattact 480

tatggcgaaa caggcggaaa tagccctgtg caagaattta ccgtgccgaa aaatgtgtac 540

acagccacca tctctggcct gaaacctggc gtggactaca caatcacagt ttatgcagtg 600

acccgttttc gtgattatca gccgatcagc atcaattatc gtacagagat cgataaaccg 660

tgccagcatc accaccatca tcac 684

<210> 455
<211> 684
<212> DNA
<213> Artificial Sequence

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

<400> 455
atgggtgttt ctgatgttcc gcgtgatctg gaagttgttg cagcaacccc gaccagcctg 60

ctgattagct ggtctgcacg tctgaaagtt gcccgttatt atcgcattac ctatggtgaa 120

accggtggta attctccggt tcaggaattt accgttccga aaaatgttta taccgcaacc 180

attagcggtc tgaaaccggg tgttgattac accattaccg tttatgcagt tacccgtttt 240

cgtgattatc agccgattag cattaactat cgcaccgaaa ttgataaagg tagcggtagc 300

ggttctggta gcggttcagg ttctggttct ggtagtggta gcggcagcgt ttcagacgtg 360

cctcgtgatt tagaagtggt ggcagccaca ccgacctcac tgctgatttc ttggtgggca 420

ccggttgatc gttatcagta ttatcgcatc acatacggcg aaacaggcgg aaatagccct 480

gtgcaagaat tcaccgtacc gcgtgatgtg tataccgcca caatttctgg tttaaaacct 540

ggcgtggact acacaatcac agtttatgcc gtgaccgatt ataaaccgca tgcagatggt 600

ccgcatacct atcatgaaag cccgatctct atcaattatc gcacagagat cgataaaccg 660

tgtcagcatc accaccatca tcac 684

<210> 456
<211> 684
<212> DNA
<213> Artificial Sequence

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

<400> 456
atgggtgttt ctgatgttcc gcgtgatctg gaagttgttg cagcaacccc gaccagcctg 60

ctgattagct ggtctgcacg tctgaaagtt gcccgttatt atcgcattac ctatggtgaa 120

accggtggta attctccggt tcaggaattt accgttccga aaaatgttta taccgcaacc 180

attagcggtc tgaaaccggg tgttgattac accattaccg tttatgcagt tacccgtttt 240

cgtgattatc agccgattag cattaactat cgcaccgaaa ttgataaagg tagcggtagc 300

ggttctggta gcggttcagg ttctggttct ggtagtggta gcggcagcgt ttcagacgtg 360

cctcgtgatt tagaagtggt ggcagccaca ccgacctcac tgctgatttc ttggacccag 420

ggtagcacac attatcagta ttatcgcatc acatacggcg aaacaggcgg aaatagccct 480

gtgcaagaat tcaccgtacc gggtatggtg tataccgcca caatttctgg tttaaaacct 540

ggcgtggact acacaatcac agtttatgcc gtgaccgatt atttcgatcg cagcacccat 600

gaatataaat atcgtaccac cccgatctct atcaattatc gcacagagat cgataaaccg 660

tgtcagcatc accaccatca tcac 684

<210> 457
<211> 684
<212> DNA
<213> Artificial Sequence

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

<400> 457
atgggtgttt ctgatgttcc gcgtgatctg gaagttgttg cagcaacccc gaccagcctg 60

ctgattagct ggtctgcacg tctgaaagtt gcccgttatt atcgcattac ctatggtgaa 120

accggtggta attctccggt tcaggaattt accgttccga aaaatgttta taccgcaacc 180

attagcggtc tgaaaccggg tgttgattac accattaccg tttatgcagt tacccgtttt 240

cgtgattatc agccgattag cattaactat cgcaccgaaa ttgataaagg tagcggtagc 300

ggttctggta gcggttcagg ttctggttct ggtagtggta gcggcagcgt ttcagacgtg 360

cctcgtgatt tagaagtggt ggcagccaca ccgacctcac tgctgatttc ttggcatgaa 420

cgtgatggta gccgtcagta ttatcgcatc acatacggcg aaacaggcgg aaatagccct 480

gtgcaagaat tcaccgtacc gggtggtgtt cgtaccgcca caatttctgg tttaaaacct 540

ggcgtggact acacaatcac agtttatgcc gtgaccgatt atttcaatcc gaccacccac 600

gaatatattt atcagaccac cccgatctct atcaattatc gcacagagat cgataaaccg 660

tgtcagcatc accaccatca tcac 684

<210> 458
<211> 684
<212> DNA
<213> Artificial Sequence

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

<400> 458
atgggtgttt ctgatgttcc gcgtgatctg gaagttgttg cagcaacccc gaccagcctg 60

ctgattagct ggtctgcacg tctgaaagtt gcccgttatt atcgcattac ctatggtgaa 120

accggtggta attctccggt tcaggaattt accgttccga aaaatgttta taccgcaacc 180

attagcggtc tgaaaccggg tgttgattac accattaccg tttatgcagt tacccgtttt 240

cgtgattatc agccgattag cattaactat cgcaccgaaa ttgataaagg tagcggtagc 300

ggttctggta gcggttcagg ttctggttct ggtagtggta gcggcagcgt ttcagacgtg 360

cctcgtgatt tagaagtggt ggcagccaca ccgacctcac tgctgatttc ttgggatgca 420

ccgaccagcc gttatcagta ttatcgcatc acatacggcg aaacaggcgg aaatagccct 480

gtgcaagaat tcaccgtacc gggtggtctg agcaccgcca caatttctgg tttaaaacct 540

ggcgtggact acacaatcac agtttatgcc gtgaccgatt ataaaccgca tgcagatggt 600

ccgcatacct atcatgaaag cccgatctct atcaattatc gcacagagat cgataaaccg 660

tgtcagcatc accaccatca tcac 684

<210> 459
<211> 684
<212> DNA
<213> Artificial Sequence

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

<400> 459
atgggtgttt ctgatgttcc gcgtgatctg gaagttgttg cagcaacccc gaccagcctg 60

ctgattagct ggtctgcacg tctgaaagtt gcccgttatt atcgcattac ctatggtgaa 120

accggtggta attctccggt tcaggaattt accgttccga aaaatgttta taccgcaacc 180

attagcggtc tgaaaccggg tgttgattac accattaccg tttatgcagt tacccgtttt 240

cgtgattatc agccgattag cattaactat cgcaccgaaa ttgataaagg tagcggtagc 300

ggttctggta gcggttcagg ttctggttct ggtagtggta gcggcagcgt ttcagacgtg 360

cctcgtgatt tagaagtggt ggcagccaca ccgacctcac tgctgatttc ttgggatgcc 420

ggtgcagtta cctatcagta ttatcgcatc acatacggcg aaacaggcgg aaatagccct 480

gtgcaagaat tcaccgtacc gggtggtgtt cgtaccgcca caatttctgg tttaaaacct 540

ggcgtggact acacaatcac agtttatgcc gtgaccgatt ataaaccgca tgcagatggt 600

ccgcatacct atcatgaata tccgatctct atcaattatc gcacagagat cgataaaccg 660

tgtcagcatc accaccatca tcac 684

<210> 460
<211> 666

<212> DNA
<213> Artificial Sequence

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

<400> 460
atgggcgtga gtgatgttcc gcgtgatctg gaagtggttg cagcaacccc gacgagcctg 60

ctgattagct ggtctgcccg cctgaaagtg gcacgttatt accgcatcac ctacggcgaa 120

acgggcggta actctccggt tcaggaattt accgtgccga aaaatgttta taccgcaacg 180

attagcggcc tgaaaccggg tgtggattat accatcacgg tgtacgcggt tacccgtttc 240

cgcgattacc agccgattag catcaactat cgtacggaaa ttgaaaaagg ctctggttgc 300

ggcagtggta gcggctctgg tagtggcagc ggttctggca gtggtagcgt gtctgacgtc 360

ccgcgcgacc tggaagttgt tgcagcgacc ccgaccagcc tgctgattag ttggtgggcc 420

ccggtggatc gttaccagta ttaccgcatc acctatggcg aaaccggtgg taacagcccg 480

gtgcaagaat ttaccgtgcc gcgtgatgtt tataccgcga ccatctctgg tctgaaaccg 540

ggcgttgact acacgattac cgtttacgcg gttaccgatt ataaaccgca tgccgatggt 600

ccgcatacgt accacgaaag tccgattagc atcaattatc ggaccgaaca tcaccatcac 660

catcac 666

<210> 461
<211> 678
<212> DNA
<213> Artificial Sequence

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

<400> 461
atgggcgtgt ctgatgttcc gcgtgatctg gaagtggttg cggccacccc gacgagtctg 60

ctgattagct ggtctgcccg cctgaaagtg gcacgttatt accgcatcac ctacggcgaa 120

acgggcggta acagcccggt tcaggaattt accgtgccga aaaatgttta taccgcaacg 180

atttctggcc tgaaaccggg tgtggattat accatcacgg tgtacgcggt tacccgtttc 240

cgcgattacc agccgattag catcaactat cgtacggaaa ttgaaaaagg cagtggtagc 300

ggctctggta gtggcagcgg ttctggcagt ggtagcggct ctggtagtgt aagcgacgtc 360

ccgcgcgatc tggaagtggt tgcagcgacc ccgacgagcc tgctgatttc ttggtgggcc 420

ccggtggatc gttaccagta ttaccgcatc acctatggcg aaaccggtgg caattctccg 480

gtgcaagaat tcaccgtgcc gcgtgatgtt tataccgcga cgattagcgg tctgaaaccg 540

ggcgttgact acacgattac cgtgtacgcg gttaccgatt ataaaccgca tgccgatggt 600

ccgcatacgt accacgaatc tccgattagt atcaattatc ggaccgaagg cagtggttgc 660

catcaccatc accatcac 678

<210> 462
<211> 666
<212> DNA
<213> Artificial Sequence

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

<400> 462
atgggcgtga gtgatgttcc gcgtgatctg gaagtggttg cagcaacccc gacgagcctg 60

ctgattagct ggtctgcccg cctgaaagtg gcacgttatt accgcatcac ctacggcgaa 120

acgggcggta acagcccggt tcaggaattt accgtgccga aaaatgttta taccgcaacg 180

atttgcggcc tgaaaccggg tgtggattat accatcacgg tgtacgcggt tacccgtttc 240

cgcgattacc agccgattag catcaactat cgtacggaaa ttgaaaaagg cagtggtagc 300

ggctctggta gtggcagcgg ttctggcagt ggtagcggct ctggtagtgt aagcgacgtc 360

ccgcgcgacc tggaagttgt tgcagcgacg ccgacgagcc tgctgatctc ttggtgggcc 420

ccggtggatc gttaccagta ttaccgcatc acctatggcg aaaccggtgg taactctccg 480

gtgcaagaat ttaccgtgcc gcgtgatgtt tataccgcga cgatttctgg tctgaaaccg 540

ggcgttgact acacgattac cgtttacgcg gttaccgatt ataaaccgca tgccgatggt 600

ccgcatacgt accacgaatc tccgattagt atcaattatc ggaccgaaca tcaccatcac 660

catcac 666

<210> 463
<211> 666
<212> DNA
<213> Artificial Sequence

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

<400> 463
atgggcgtga gtgatgttcc gcgtgatctg gaagtggttg cagcaacccc gacgagcctg 60

ctgattagct ggtctgcccg cctgaaagtg gcacgttatt accgcatcac ctacggcgaa 120

acgggcggta actctccggt tcaggaattt accgtgccga aaaatgttta taccgcaacg 180

attagcggcc tgaaaccggg tgtggattat accatcacgg tgtacgcggt tacccgtttc 240

cgcgattacc agccgattag catcaactat cgtacggaaa ttgaaaaagg cagtggtagc 300

ggctctggta gtggcagcgg ttctggcagt ggtagcggct ctggtagtgt aagcgacgtc 360

ccgcgcgacc tggaagttgt tgcagcgacg ccgacgagcc tgctgatctc ttggtgggcc 420

ccggtggatc gttaccagta ttaccgcatc acctatggcg aaaccggtgg taacagcccg 480

gtgcaagaat ttaccgtgcc gcgtgatgtt tataccgcga cgatttgtgg tctgaaaccg 540

ggcgttgact acacgattac cgtttacgcg gttaccgatt ataaaccgca tgccgatggt 600

ccgcatacgt accacgaatc tccgattagt atcaattatc ggaccgaaca tcaccatcac 660

catcac 666

<210> 464
<211> 666
<212> DNA
<213> Artificial Sequence

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

polynucleotide"

<400> 464
atgggcgtga gtgatgttcc gcgtgatctg gaagtggttg cagcaacccc gacgagcctg 60

ctgattagct ggtctgcccg cctgaaagtg gcacgttatt accgcatcac ctacggcgaa 120

acgggcggta actctccggt tcaggaattt accgtgccga aaaatgttta taccgcaacg 180

attagcggcc tgaaaccggg tgtggattat accatcacgg tgtacgcggt tacccgtttc 240

cgcgattacc agccgatttg catcaactat cgtacggaaa ttgaaaaagg cagtggtagc 300

ggctctggta gtggcagcgg ttctggcagt ggtagcggct ctggtagtgt aagcgacgtc 360

ccgcgcgacc tggaagttgt tgcagcgacg ccgacgagcc tgctgatctc ttggtgggcc 420

ccggtggatc gttaccagta ttaccgcatc acctatggcg aaaccggtgg taacagcccg 480

gtgcaagaat ttaccgtgcc gcgtgatgtt tataccgcga ccatctctgg tctgaaaccg 540

ggcgttgact acacgattac cgtttacgcg gttaccgatt ataaaccgca tgccgatggt 600

ccgcatacgt accacgaatc tccgattagt atcaattatc ggaccgaaca tcaccatcac 660

catcac 666

<210> 465
<211> 666
<212> DNA
<213> Artificial Sequence

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

<400> 465
atgggcgtga gcgatgttcc gcgtgatctg gaagtggttg cagcaacccc gaccagcctg 60

ctgattagct ggtctgcccg cctgaaagtg gcacgttatt accgcatcac ctacggcgaa 120

acgggcggta acagtccggt tcaggaattt accgtgccga aaaatgttta taccgcaacg 180

attagcggcc tgaaaccggg tgtggattat accatcacgg tgtacgcggt tacccgtttc 240

cgcgattacc agccgattag catcaactat cgtacggaaa ttgaaaaagg cagtggtagc 300

ggctctggta gtggcagcgg ttctggcagt ggtagcggct ctggtagtgt aagcgacgtc 360

ccgcgcgacc tggaagttgt tgcagcgacg ccgaccagcc tgctgatcag ttggtgggcc 420

ccggtggatc gttaccagta ttaccgcatc acctatggcg aaaccggtgg taacagcccg 480

gtgcaagaat tcaccgtgcc gcgtgatgtt tataccgcga ccatctctgg tctgaaaccg 540

ggcgttgact acacgattac cgtttacgcg gttaccgatt ataaaccgca tgccgatggt 600

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Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30

Xaa Xaa Xaa Ser Trp His Glu Arg Asp Gly Ser Arg Gln Xaa Xaa Xaa
        35                  40                  45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
    50                  55                  60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65                  70                  75                  80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                85                  90                  95

Xaa Xaa Pro Gly Gly Val Arg Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            100                 105                 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        115                 120                 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
    130                 135                 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Tyr Phe
145                 150                 155                 160

Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
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1               5                  10                  15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30

Xaa Xaa Xaa Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln Xaa Xaa Xaa
        35                  40                  45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
    50                  55                  60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65                  70                  75                  80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                85                  90                  95

Xaa Xaa Pro Arg Asp Val Tyr Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            100                 105                 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        115                 120                 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
    130                 135                 140
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Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Tyr Lys
145 150 155 160

Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Xaa Xaa Xaa
165 170 175

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185 190

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Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Thr Gln Gly Ser Thr His Tyr Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Gly Met Val Tyr Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Tyr Phe
145 150 155 160

Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Xaa Xaa Xaa
165 170 175

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185 190

<210> 469
<211> 190
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<213> Artificial Sequence

<220>
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Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30

Xaa Xaa Xaa Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln Xaa Xaa Xaa
        35                  40                  45
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Arg Asp Val Asn Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Trp Tyr
145 150 155 160

Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185 190

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20 25 30

Xaa Xaa Xaa Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Gly Gly Val Ser Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Ala Phe
145 150 155 160

Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
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<210> 471
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or 2-5 residues"

<400> 471
Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Gly Gly Leu Ser Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Tyr Lys
145 150 155 160

Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Xaa Xaa Xaa
165 170 175

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185 190

<210> 472
<211> 190
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (7)..(21)

<223> Any amino acid

<220>
<221> misc_feature
<222> (7)..(21)
<223> /note="This region may encompass 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3 or 1-2 residues"

<220>
<221> MOD_RES
<222> (26)..(35)
<223> Any amino acid

<220>
<221> misc_feature
<222> (26)..(35)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<220>
<221> MOD_RES
<222> (46)..(55)
<223> Any amino acid

<220>
<221> misc_feature
<222> (46)..(55)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<220>
<221> MOD_RES
<222> (64)..(83)
<223> Any amino acid

<220>
<221> misc_feature
<222> (64)..(83)
<223> /note="This region may encompass 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 or 6-7 residues"

<220>
<221> MOD_RES
<222> (89)..(98)
<223> Any amino acid

<220>
<221> misc_feature
<222> (89)..(98)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<220>
<221> MOD_RES
<222> (105)..(114)
<223> Any amino acid

<220>
<221> misc_feature
<222> (105)..(114)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<220>
<221> MOD_RES
<222> (118)..(137)
<223> Any amino acid

<220>
<221> misc_feature
<222> (118)..(137)
<223> /note="This region may encompass 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10,

6-8, 2-7, 5-7 or 6-7 residues"

<220>
<221> MOD_RES
<222> (147)..(156)
<223> Any amino acid

<220>
<221> misc_feature
<222> (147)..(156)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<220>
<221> MOD_RES
<222> (174)..(183)
<223> Any amino acid

<220>
<221> misc_feature
<222> (174)..(183)
<223> /note="This region may encompass 0-10, 0-5, 1-10, 1-5 or 2-5 residues"

<400> 472
Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Gly Gly Val Arg Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Tyr Lys
145 150 155 160

Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Xaa Xaa Xaa
165 170 175

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185 190

<210> 473
<211> 10

<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (3)..(3)
<223> /replace="Tyr"

<220>
<221> misc_feature
<222> (3)..(3)
<223> /note="Residue given in the sequence has no preference with respect to the residue in the annotation for said position"

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Any amino acid

<400> 473
Asp Tyr Ala Gly Lys Pro Tyr Xaa Glu Tyr
1 5 10

<210> 474
<211> 10
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (3)..(3)
<223> /replace="Tyr"

<220>
<221> misc_feature
<222> (3)..(3)
<223> /note="Residue given in the sequence has no preference with respect to the residue in the annotation for said position"

<220>
<221> MOD_RES
<222> (5)..(5)
<223> /replace="Arg" or "Gln" or "Thr"

<220>
<221> misc_feature
<222> (5)..(5)
<223> /note="Residue given in the sequence has no preference with respect to those in the annotation for said position"

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Any amino acid

<400> 474
Asp Tyr Ala Tyr Lys Pro Tyr Xaa Glu Tyr
1 5 10

<210> 475
<211> 10

<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(1)
<223> /replace="Asn"

<220>
<221> misc_feature
<222> (1)..(1)
<223> /note="Residue given in the sequence has no preference with respect to the residue in the annotation for said position"

<220>
<221> VARIANT
<222> (3)..(3)
<223> /replace="Tyr"

<220>
<221> misc_feature
<222> (3)..(3)
<223> /note="Residue given in the sequence has no preference with respect to the residue in the annotation for said position"

<220>
<221> VARIANT
<222> (4)..(4)
<223> /replace="Phe"

<220>
<221> VARIANT
<222> (4)..(4)
<223> /note="Residue given in the sequence has no preference with respect to the residue in the annotation for said position"

<220>
<221> VARIANT
<222> (5)..(5)
<223> /replace="Arg" or "Gln" or "Thr"

<220>
<221> misc_feature
<222> (5)..(5)
<223> /note="Residue given in the sequence has no preference with respect to those in the annotation for said position"

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Any amino acid

<220>
<221> VARIANT
<222> (10)..(10)
<223> /replace="His"

<220>
<221> misc_feature
<222> (10)..(10)
<223> /note="Residue given in the sequence has no preference with respect to the residue in the annotation for said position"

<400> 475
Asp Tyr Ala Tyr Lys Glu Tyr Xaa Glu Tyr
1 5 10

<210> 476

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

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

<220>
<221> VARIANT
<222> (4)..(4)
<223> /replace="Tyr"

<220>
<221> misc_feature
<222> (4)..(4)
<223> /note="Residue given in the sequence has no preference with respect to the residue in the annotation for said position"

<220>
<221> MOD_RES
<222> (5)..(5)
<223> Any amino acid

<220>
<221> VARIANT
<222> (6)..(6)
<223> /replace="Lys"

<220>
<221> misc_feature
<222> (6)..(6)
<223> /note="Residue given in the sequence has no preference with respect to the residue in the annotation for said position"

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Any amino acid

<220>
<221> VARIANT
<222> (8)..(8)
<223> /replace="Thr"

<220>
<221> misc_feature
<222> (8)..(8)
<223> /note="Residue given in the sequence has no preference with respect to the residue in the annotation for said position"

<220>
<221> MOD_RES
<222> (10)..(10)
<223> Any amino acid

<400> 476
Asp Tyr Tyr His Xaa Arg Xaa Glu Tyr Xaa
1 5 10

<210> 477
<211> 10
<212> PRT
<213> Artificial Sequence

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

<220>

<221> VARIANT
<222> (4)..(4)
<223> /replace="Tyr"

<220>
<221> VARIANT
<222> (5)..(5)
<223> /replace="His" or "Gln"

<220>
<221> VARIANT
<222> (6)..(6)
<223> /replace="Lys"

<220>
<221> misc_feature
<222> (4)..(6)
<223> /note="Residues given in the sequence have no preference
with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (8)..(8)
<223> /replace="Thr"

<220>
<221> misc_feature
<222> (8)..(8)
<223> /note="Residue given in the sequence has no preference with
respect to the residue in the annotation for said position"

<220>
<221> VARIANT
<222> (10)..(10)
<223> /replace="Pro"

<220>
<221> misc_feature
<222> (10)..(10)
<223> /note="Residue given in the sequence has no preference with
respect to the residue in the annotation for said position"

<400> 477
Asp Tyr Tyr His Lys Arg Thr Glu Tyr Gly
1 5 10

<210> 478
<211> 10
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (1)..(1)
<223> /replace="Asn"

<220>
<221> misc_feature
<222> (1)..(1)
<223> /note="Residue given in the sequence has no preference with
respect to the residue in the annotation for said position"

<220>
<221> VARIANT
<222> (6)..(6)
<223> /replace="Asp"

<220>

<221> misc_feature
<222> (6)..(6)
<223> /note="Residue given in the sequence has no preference with respect to the residue in the annotation for said position"

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Any amino acid

<400> 478
Asp Met Met His Val Glu Tyr Xaa Glu Tyr
1 5 10

<210> 479
<211> 10
<212> PRT
<213> Artificial Sequence

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

<220>
<221> MOD_RES
<222> (5)..(6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Any amino acid

<400> 479
Asp Tyr Met His Xaa Xaa Tyr Xaa Glu Tyr
1 5 10

<210> 480
<211> 10
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (2)..(2)
<223> /replace="Tyr"

<220>
<221> misc_feature
<222> (2)..(2)
<223> /note="Residue given in the sequence has no preference with respect to the residue in the annotation for said position"

<220>
<221> MOD_RES
<222> (5)..(5)
<223> Any amino acid

<220>
<221> VARIANT
<222> (6)..(6)
<223> /replace="Arg"

<220>
<221> misc_feature

<222> (6)..(6)
<223> /note="Residue given in the sequence has no preference with respect to the residue in the annotation for said position"

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Any amino acid

<220>
<221> VARIANT
<222> (8)..(8)
<223> /replace="Ile" or "Leu" or "Met"

<220>
<221> misc_feature
<222> (8)..(8)
<223> /note="Residue given in the sequence has no preference with respect to those in the annotation for said position"

<400> 480
Asp Met Tyr His Xaa Lys Xaa Val Tyr Gly
1 5 10

<210> 481
<211> 15
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (2)..(3)
<223> /replace="Phe"

<220>
<221> misc_feature
<222> (2)..(3)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (11)..(11)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (13)..(15)
<223> Any amino acid

<400> 481
Asp Tyr Tyr Asn Pro Xaa Thr His Glu Tyr Xaa Tyr Xaa Xaa Xaa
1 5 10 15

<210> 482
<211> 15
<212> PRT
<213> Artificial Sequence

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

peptide"

<220>
<221> VARIANT
<222> (2)..(3)
<223> /replace="Phe"

<220>
<221> misc_feature
<222> (2)..(3)
<223> /note="Residues given in the sequence have no preference
with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (5)..(5)
<223> /replace="Leu"

<220>
<221> misc_feature
<222> (5)..(5)
<223> /note="Residue given in the sequence has no preference with
respect to the residue in the annotation for said position"

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Any amino acid

<220>
<221> VARIANT
<222> (7)..(7)
<223> /replace="Ser"

<220>
<221> misc_feature
<222> (7)..(7)
<223> /note="Residue given in the sequence has no preference with
respect to the residue in the annotation for said position"

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (11)..(11)
<223> Any amino acid

<220>
<221> MOD_RES
<222> (13)..(15)
<223> Any amino acid

<400> 482
Asp Tyr Tyr Asp Pro Xaa Thr His Xaa Tyr Xaa Tyr Xaa Xaa Xaa
1 5 10 15

<210> 483
<211> 15
<212> PRT
<213> Artificial Sequence

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

<220>
<221> VARIANT
<222> (2)..(2)

<223> /replace="Phe"

<220>
<221> VARIANT
<222> (3)..(3)
<223> /replace="Arg"

<220>
<221> misc_feature
<222> (2)..(3)
<223> /note="Residues given in the sequence have no preference
with respect to those in the annotations for said positions"

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Any amino acid

<220>
<221> VARIANT
<222> (11)..(11)
<223> /replace="Ile"

<220>
<221> misc_feature
<222> (11)..(11)
<223> /note="Residue given in the sequence has no preference with
respect to the residue in the annotation for said position"

<220>
<221> MOD_RES
<222> (13)..(13)
<223> Any amino acid

<220>
<221> VARIANT
<222> (15)..(15)
<223> /replace="Tyr"

<220>
<221> misc_feature
<222> (15)..(15)
<223> /note="Residue given in the sequence has no preference with
respect to the residue in the annotation for said position"

<400> 483
Asp Tyr Lys Pro His Xaa Asp Gly Pro His Thr Tyr Xaa Glu Ser
1 5 10 15

<210> 484
<211> 95
<212> PRT
<213> Artificial Sequence

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

<400> 484
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln Arg Tyr
20 25 30

Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu
35 40 45

Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys
50 55 60

Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Met
65 70 75 80

His Ser Glu Tyr Arg Gln Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

<210> 485
<211> 94
<212> PRT
<213> Artificial Sequence

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

<400> 485
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Met His
65 70 75 80

Ser Glu Tyr Arg Gln Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 486
<211> 102
<212> PRT
<213> Artificial Sequence

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

<400> 486
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln Arg Tyr
20 25 30

Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu
35 40 45

Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys
50 55 60

Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Met
65 70 75 80

His Ser Glu Tyr Arg Gln Tyr Pro Ile Ser Ile Asn Tyr Arg Thr Glu
85 90 95

Ile Asp Lys Pro Cys Gln
100

<210> 487
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic 6xHis tag"

<400> 487
His His His His His His
1 5

<210> 488
<211> 18
<212> PRT
<213> Artificial Sequence

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

<220>
<221> misc_feature
<222> (96)..(113)
<223> /note="This region may encompass 3, 6, or 9 "Pro-Ala" repeats"

<400> 488
Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
1 5 10 15

Pro Ala

<210> 489
<211> 4
<212> PRT
<213> Artificial Sequence

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

<400> 489
Gly Ser Gly Cys
1

<210> 490
<211> 109
<212> PRT
<213> Artificial Sequence

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

<400> 490

Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Met His Ser Glu Tyr Arg Gln Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln His His His His His His
100 105

<210> 491
<211> 19
<212> PRT
<213> Artificial Sequence

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

<400> 491
Phe Lys Gly Asp Ser Phe Thr Arg Thr Pro Pro Leu Asp Pro Arg Glu
1 5 10 15

Leu Glu Ile

<210> 492
<211> 100
<212> PRT
<213> Artificial Sequence

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

<400> 492
Glu Glu Lys Lys Val Cys Gln Gly Thr Ser Asn Lys Leu Thr Gln Leu
1 5 10 15

Gly Thr Phe Glu Asp His Phe Leu Ser Leu Gln Arg Met Phe Asn Asn
20 25 30

Cys Glu Val Val Leu Gly Asn Leu Glu Ile Thr Tyr Val Gln Arg Asn
35 40 45

Tyr Asp Leu Ser Phe Leu Lys Thr Ile Gln Glu Val Ala Gly Tyr Val
50 55 60

Leu Ile Ala Leu Asn Thr Val Glu Arg Ile Pro Leu Glu Asn Leu Gln

65 70 75 80

Ile Ile Arg Gly Asn Met Tyr Tyr Glu Asn Ser Tyr Ala Leu Ala Val
85 90 95

Leu Ser Asn Tyr
100

<210> 493
<211> 12
<212> PRT
<213> Artificial Sequence

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

<400> 493
Ile Gln Cys Ala His Tyr Ile Asp Gly Pro His Cys
1 5 10

<210> 494
<211> 16
<212> PRT
<213> Artificial Sequence

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

<400> 494
Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
1 5 10 15

<210> 495
<211> 342
<212> DNA
<213> Artificial Sequence

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

<400> 495
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggaaaacaga accaggccgc caccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactgg 240

tacaacctgg tttctcatga atacgtatac catactaccc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

MOLECULAS BIESPECIFICAS DE UNION A EGFR/IGFIR

Listado de secuencias

La presente solicitud contiene un Listado de Secuencias que ha sido presentado por medio de EFS-Web y se incorpora en la presente por referencia en su totalidad. Dicha copia en ASCII, creada el 23 de noviembre de 2009, se llama COTH52WO.txt, y pesa 552,529 bytes.

Solicitudes relacionadas

Esta solicitud reivindica el derecho de prioridad de las Solicitudes de Patente Provisional de Estados Unidos N° 61/200.164, presentada el 24 de noviembre de 2008; 61/200.282, presentada el 26 de noviembre de 2008; 61/212.966, presentada el 17 de abril de 2009; 61/178.279, presentada el 14 de mayo de 2009; y 61/227.330, presentada el 21 de julio de 2009, incorporándose en la presente memoria como referencia en su totalidad dichas solicitudes.

Campo de la invención

La presente invención se refiere a dominios de unión a EGFR y a moléculas biespecíficas que comprenden un domino de unión a EGFR y un dominio de unión a IGFIR distinto para el uso en aplicaciones de diagnóstico, investigación y terapéuticas. La invención se refiere además a células que comprenden tales proteínas, a polinucleótidos que codifican tales proteínas o fragmentos de las mismas y a vectores que

comprenden los polinucleótidos que codifican las proteínas innovadoras. Ejemplos de dominios de unión a EGFR y moléculas biespecíficas incluyen dímeros de proteína similar a anticuerpo basados en el décimo dominio de fibronectina de tipo III.

Introducción

La activación de la señalización del receptor tirosina cinasa es fundamental para el desarrollo del cáncer (véase, por ejemplo, Grimberg A. Cancer Biol Ther. 2003 2(6): 630-5 y Mendelsohn J. J Clin Oncol. 2003 21(14): 2787-99). Los receptores tirosina cinasa tienen una estructura de dominio conservado que incluye un dominio extracelular, un domino transmembrana y un dominio tirosina cinasa intracelular. El dominio extracelular se puede unir a un ligando, tal como un factor de crecimiento de polipéptidos o a una molécula asociada a membrana celular. Típicamente, la unión a ligando o la dimerización inducida por unión a ligando de receptores tirosina cinasa activa el dominio tirosina cinasa catalítico intracelular del receptor y la transducción de señal posterior.

Los ejemplos de receptores tirosina cinasa incluyen, pero sin limitación, receptores ERBB (por ejemplo, EGFR, ERBB2, ERBB3, ERBB4), receptores de hepatocelular productor de eritropoyetina (EPH), receptores de factor de crecimiento de fibroblastos (FGF) (por ejemplo, FGFR1, FGFR2,

FGFR3, FGFR4, FGFR5), receptores de factor de crecimiento derivado de plaquetas (PDGF) (por ejemplo, PDGFR-A, PDGFR-B), receptores de factor de crecimiento endotelial vascular (VEGF) (por ejemplo, VEGFR1/FLT1, VEGFR2/FLK1, VEGF3), receptores tirosina cinasa con dominios similares a inmunoglobulina y similares a EGF (TIE), receptores de factor de crecimiento similar a insulina (IGF) (por ejemplo, INS-R, IGFIR, IR-R), receptores de Domino de Discoidina (DD), receptor para c-Met (MET), receptor de origen nantés (RON); también como conocido como receptor estimulador de macrófagos 1, tirosina cinasa relacionada con fins 3 Flt3 (Flt3), receptor de factor estimulador de colonias 1 (CSF1), receptor cinasa relacionado con adhesión (por ejemplo, Axl), receptor para c-kit (KIT) y receptores relacionados con el receptor de insulina (IRR).

La inhibición de receptores tirosina cinasa ha surgido como una estrategia de tratamiento eficaz para ciertas neoplasias humanas (para una revisión, véase Roussidis AE, In Vivo. 2002 16(6): 459-69). Aunque la monoterapia dirigida inicialmente puede ser eficaz para tratar cáncer, a menudo viene seguida de la resistencia terapéutica, posiblemente como resultado de regulación positiva de otras cascadas de señalización (véase, por ejemplo, Nahta R y col., Breast Cancer Res. 2006 8(6): 215 y Horn L y col., Clin Lung Cancer. 2007 8: S68-73). Por

consiguiente, existe una necesidad de desarrollar terapéuticos para cáncer mejorados.

Breve descripción de la invención

En un aspecto, la solicitud proporciona décimos dominios de fibronectina de tipo III ($^{10}Fn_3$) de unión a EGFR que tienen nuevas secuencias. También se proporcionan $^{10}Fn_3$ de unión a EGFR que tienen una secuencia consenso. Estos $^{10}Fn_3$ de unión a EGFR pueden ser monoméricos o pueden incluirse como parte de una proteína de fusión.

En otro aspecto, la solicitud proporciona moléculas biespecíficas que se unen a EGFR y a IGFIR, denominadas en este documento "agentes de unión a E/I". Los agentes de unión a E/I incluidos en la invención incluyen anticuerpos biespecíficos y dímeros de proteínas de armazón de unión a ligando (por ejemplo, tendamistato, affibody, dominio de fibronectina de tipo III, anticalina, tetranectina y anquirina). Cuando se construyen como una única cadena polipeptídica, los agentes de unión a E/I se pueden construir en cualquier orientación, por ejemplo, del N-terminal al C-terminal en la disposición E-I o en la disposición I-E.

En un aspecto, se proporcionan dímeros de proteína similar a anticuerpo que comprenden un $^{10}Fn3$ de unión a EGFR unido covalentemente o no covalentemente con un $^{10}Fn3$ de unión a IGFIR. El $^{10}Fn3$ se une a su diana (EGFR o IGFIR) con una K_D menor de 500 nM. Cada uno de los $^{10}Fn3$ individuales tiene

independientemente una secuencia de aminoácidos que es idéntica al menos en el 70, 80, 85, 90, 95, 98 o el 100% a la SEC ID N°: 32, en la que n es un número entero de 1-20, o es un número entero de 1-20 y p es un número entero de 1-40. En algunas modalidades, n es un número entero de 8-12, o es un número entero de 4-8 y p es un número entero de 4-28. En algunas modalidades, n es 10, o es 6 y p es 12.

En algunas modalidades, los dímeros de proteína similar a anticuerpo comprenden ^{10}Fn3 de unión a IGFIR unido covalentemente con ^{10}Fn3 de unión a EGFR a través de un adaptador polipeptídico o un resto de polietilenglicol. En algunas modalidades, el dímero de proteína similar a anticuerpo comprende una secuencia de aminoácidos idéntica al menos en el 80, 90, 95 o el 100% a una cualquiera de las SEC ID N°: 20-31, 53-58, 87-92, 98-105, 118-133, 149-154, 164-169, 179-184, 192-197, 205-210 y 211-216.

En algunas modalidades, el agente de unión a E/I comprende una secuencia de aminoácidos que tiene una cualquiera de las SEC ID N°: 20-31, 53-58, 87-92, 98-105, 118-133, 149-154, 164-169, 179-184, 192-197, 205-210 y 211-216, donde (i) el ^{10}Fn3 de unión a EGFR y/o el ^{10}Fn3 de unión a IGF-IR comprende un armazón de ^{10}Fn3 que tiene de 0 a 20, de 0 a 15, de 0 a 10, de 0 a 8, de 0 a 6, de 0 a 5, de 0 a 4, de 0 a 3, de 0 a 2 o de 0 a 1 sustituciones, sustituciones conservativas, deleciones o adiciones con respecto a los

aminoácidos del armazón correspondiente de la SEC ID N°: 1, y/o (ii) el ^{10}Fn3 de unión a EGFR tiene de 0 a 15, de 0 a 10, de 0 a 8, de 0 a 6, de 0 a 5, de 0 a 4, de 0 a 3, de 0 a 2 o de 0 a 1 sustituciones, sustituciones conservativas, deleciones o adiciones con respecto a la secuencias de bucle correspondientes de una cualquiera de las SEC ID N°: 5-8, 52, 66-68, 106-108, 112-114, 140-142, 155-157, 170-172, 182, 185-187, 198-200 ó 219-327 y/o el ^{10}Fn3 de unión a IGF-IR tiene de 0 a 15, de 0 a 10, de 0 a 8, de 0 a 6, de 0 a 5, de 0 a 4, de 0 a 3, de 0 a 2 o de 0 a 1 sustituciones, sustituciones conservativas, deleciones o adiciones con respecto a las secuencias de bucle correspondientes de la SEC ID N°: 3.

En un aspecto, se proporcionan composiciones farmacéuticamente aceptables que comprenden un dímero de proteína similar a anticuerpo como se describe en este documento y un vehículo farmacéuticamente aceptable, donde la composición está esencialmente libre de pirógenos.

En un aspecto adicional se proporcionan procedimientos para tratar trastornos hiperproliferativos, tales como cáncer, en un sujeto, que comprenden administrar a un sujeto que lo necesite una cantidad terapéuticamente eficaz de una composición farmacéuticamente aceptable que comprende un dímero de proteína similar a anticuerpo como se describe en este documento.

En otro aspecto, la solicitud proporciona un ácido

nucleico que codifica un dímero de proteína similar a anticuerpo como se describe en este documento. También se proporciona un vector que comprende un ácido nucleico que codifica un dímero de proteína similar a anticuerpo como se describe en este documento. Los vectores adecuados incluyen, por ejemplo, vectores de expresión. También se proporcionan células huésped que comprenden un vector de ácido nucleico, o vector de expresión, que comprende un ácido nucleico que codifica un dímero de proteína similar a anticuerpo como se describe en este documento. Las células huésped adecuadas incluyen células huésped procariotas y eucariotas. Ejemplos de células procariotas son células bacterianas, tales como *E. coli*. Ejemplos de células eucariotas son células de mamífero, tales como células CHO. También se proporcionan procedimientos para producir un dímero de proteína similar a anticuerpo como se describe en este documento, que comprenden cultivar una célula huésped que comprende un vector de ácido nucleico, o vector de expresión, que comprende un ácido nucleico que codifica el dímero de proteína similar a anticuerpo y recuperar el dímero de proteína similar a anticuerpo expresado del cultivo.

Breve descripción de las figuras

Figura 1. Análisis SDS-PAGE de I1-GS10-E2. Las muestras de la lisis de sedimento de células bacterianas HMS174(DE3) de las que se expresó I1-GS10-E2 y se purificó

por una columna de cromatografía HisTrap se procesaron en un minigel NuPAGE al 4-12% y se tiñeron con Naranja Sypro y se visualizaron con una cámara STORM. Patrones de peso molecular Mark 12 (Carril 1); Lisado-soluble (Carril 2); Lisado-insoluble (Carril 3); carga de HisTrap (Carril 4); HisTrap no unido (Carril 5); Eluato de HisTrap Combinado (Carril 6); Dializado en NaOAc 50 mM, NaCl 150 mM, pH 4.5 (Carril 7); Dializado en PBS (Carril 8); Dializado en Tris, NaCl 150 mM, pH 8.5 (Carril 9).

Figura 2. A. Análisis SEC de I1-GS10-E2 purificado a media escala. 22 µg de I1-GS10-E2 purificado en HisTrap dializado en PBS, pH 7.4 se cargaron en una Columna de SEC Superdex 200 10/30 (GE Healthcare) con una fase móvil de $NaPO_4$ 100 mM, $NaSO_4$ 100 mM, NaCl 150 mM, pH 6.8 y se midieron usando A280. I1-GS10-E2 eluyó predominantemente como una única especie monomérica a un intervalo de peso molecular de aproximadamente 24.6 kDa frente a patrones de Filtración en Gel globulares (BioRad). B. análisis SEC de E2-GS10-I1.

Figura 3. A. Se realizó Calorimetría de Exploración Diferencial (DSC) de I1-GS10-E2 purificado a media escala en PBS se realizó para determinar la T_m. Se exploró una solución de 1 mg/ml de I1-GS10-E2 de 5°C a 95°C a una velocidad de 1 grado por minuto bajo una presión de 303.98 kPa (3 atm). El dato se analizó frente a un

procesamiento de control del amortiguador PBS. B. análisis DSC de E2-GS10-I1.

Figura 4. Inhibición de actividad de IGFR en células H292. Las células se estimularon con 100 ng/ml de IGF-1 y 100 ng/ml de EGF y se trataron con preparaciones de HTPP de • I1, □ E1 o Δ E1-GS10-I1. La fosforilación de IGFIR en la tirosina 1131 se determinó por ELISA.

Figura 5. Inhibición de actividad de EGFR en células H292. Las células se estimularon con 100 ng/ml de IGF-1 y 100 ng/ml de EGF y se trataron con preparaciones de HTPP de • I1, □ E1 o Δ E1-GS10-I1. La fosforilación de EGFR en la tirosina 1068 se determinó por ELISA.

Figura 6. Inhibición de fosforilación de AKT en células H292. Las células se estimularon con 100 ng/ml de IGF-1 y 100 ng/ml de EGF y se trataron con preparaciones de HTPP de • I1, □ E1 o Δ E1-GS10-I1. La fosforilación de AKT en la serina 473 se determinó por ELISA.

Figura 7. Inhibición de proliferación de células RH41. Las células se trataron con preparaciones de HTPP de • I1, □ E1 o Δ E1-GS10-I1 y se determinó el porcentaje de inhibición de proliferación.

Figura 8. Inhibición de proliferación de células H292. Las células se trataron con preparaciones de HTPP de • I1, □ E1 o Δ E1-GS10-I1 HTPP y se determinó el porcentaje de inhibición de proliferación.

Figura 9. Resume valores de CI50 en ensayos funcionales basados en células para mononectinas de EGFR aisladas, agentes de unión a E/I basados en ^{10}Fn3 con serina en la posición C-terminal sin PEG añadido y agentes de unión a E/I basados en ^{10}Fn3 con cisteína en la posición C-terminal conjugados con un PEG ramificado de 40 kDa. Se muestran los datos representativos.

Figura 10. Análisis de inmunotransferencia de agentes de unión a E/I basados en ^{10}Fn3 PEGilados con E2 en las posiciones N-terminal y C-terminal. A pesar de que ambas construcciones demuestran actividad comparable en el ensayo de células H292 para inhibir EGFR, el agente de unión a E/I basado en ^{10}Fn3 con E2 en la posición C-terminal no degradó EGFR mientras que el agente de unión a E/I basado en ^{10}Fn3 con E2 en la posición N-terminal sí. Ambas construcciones muestran degradación de IGFR de muy débil a ninguna en esta línea celular. Se incluyó β-actina para demostrar carga igual a lo largo de todos los carriles. También se examinó el estado de fosforilación de EGFR, ERK y Shc.

Figura 11. Inhibición de fosforilación de EGFR estimulada por EGF en células H292. Ambas construcciones demostraron actividad comparable en el ensayo de células H292 para inhibir EGFR. E2-GS10-I1 (con PEG) (o), I1-GS10-E2 (con PEG) (□), panitumumab (----).

Figura 12. Resultados de estudios de xenoinjerto

de tumor. Figura 12A: Actividad anti-tumoral preclínica en el modelo de xenoinjerto de tumor humano H292. Los tamaños medios de tumor calculados de grupos de 8 ratones se muestran en mg para animales de control (■), E3-GS10-I1 (con PEG) dosificado a 100 mg/kg (o), E2-GS10-I1 (con PEG) dosificado a 100 mg/kg (□), panitumumab dosificado a 1 mg/ratón (▫) o 0.1 mg/ratón (▫). La letra a en el eje x indica dosis de agentes de unión a E/I administrados y la p indica dosis de panitumumab administradas. Figura 12B: Se muestra el cambio de peso promedio para cada grupo a lo largo del curso del estudio. Los símbolos son como se describe en la leyenda de la Figura 12A.

Figura 13. Efectos farmacodinámicos en el modelo de xenoinjerto de tumor NSCLC H292. Los niveles de los analitos indicados se determinaron en lisados de tumor como se describe en el Ejemplo 12. (A) fosfo-EGFR, (B) fosfo-ErbB2, (C) fosfo-IGFR y (D) EGFR total. Barras con cuadros = panitumumab, barras vacías = E2-GS10-I1 (con PEG), barras sombreadas = E3-GS10-I1 (con PEG).

Figura 14. Análisis de Western Blot de células MCF7r comparadas con células parentales MCF7.

Figura 15. Estudios de xenoinjerto de tumor humano MCF7 (Panel A) y MCF7r (Panel B) en ratones desnudos. Se muestra el tamaño tumoral medio para los dos estudios calculado a partir de 8 ratones por grupo.

Figura 16. Estudios de xenoinjerto de tumor humano GEO en ratones desnudos.

Figura 17. Estudios de xenoinjerto de tumor humano H292 en ratones desnudos.

Figura 18. Ensayo de formación de colonias con células de NSCLC H292. A. Se muestran datos representativos a partir de una sola placa. B. Se muestra la CI50 de un agente de unión a E/I basado en ^{10}Fn3 con barras de error calculadas a partir de mediciones por triplicado.

Figura 19. Ensayo de mapeo de epítopos. En el panel A se muestra la localización de la unión a epítopo para diversos anticuerpos de unión a EGFR. En el Ejemplo 18, Tabla 11, se proporciona una descripción de los anticuerpos. La columna izquierda de la tabla 11 proporciona un número para cada anticuerpo anti-EGFR que se correlaciona con los anticuerpos numerados mostrados en el panel A. El panel B muestra un ejemplo de ensayo de localización de epítopo como se describe en el Ejemplo 18.

Figura 20. En el análisis DSC del agente de unión a E/I basado en ^{10}Fn3, I1-GS10-E5 pegilado, medido con un intervalo de exploración de 15-95°C a una concentración de proteína de 1 mg/ml en PBS, produjo una medición de Tm de 55.2°C

Figura 21. Evaluación de agentes de unión a E/I basados en ^{10}Fn3 con respecto a la inhibición de la

fosforilación por AKT en células H292 medida por ELISA. El I1-GS10-E5-pegilado (o) fue más potente que I1-pegilado solo (■) o E5-pegilado solo (▲) para el bloqueo de la fosforilación por AKT estimulada por IGF1.

Figura 22. Evaluación de agentes de unión a E/I basados en ^{10}Fn3 con respecto a la inhibición de la proliferación celular en células H292. I1-GS10-E5-pegilado (□) fue más potente que I1-pegilado solo (▲) y E5-pegilado solo (●) tuvo únicamente efectos débiles para inhibir el crecimiento de células H292. Los ensayos se realizaron por triplicado. Se muestran datos representativos.

Figura 23. Evaluación de agentes de unión a E/I basados en ^{10}Fn3 con respecto a la inhibición de la proliferación celular en células RH41. I1-GS10-E5-pegilado (□) fue ligeramente más potente que I1-pegilado solo (▲) y E5-pegilado solo (●) o panitumumab (línea de trazos) casi no tuvieron efecto para inhibir el crecimiento de células RH41. Los ensayos se realizaron por triplicado. Se muestran datos representativos.

Figura 24. Inhibición de la señalización estimulada por ligando por agentes de unión basados en ^{10}Fn3 (pegilados). Efecto del agente de unión a E/I basado en ^{10}Fn3 (I1-GS10-E5 pegilado) sobre la activación del receptor y la señalización celular en células DiFi, H292 o BxPC3. Las células se privaron de suero y se trataron durante 2 horas

con agentes de unión basados en ^{10}Fn3 1 μM antes de la estimulación con EGF, IGF1 o una combinación de EGF + IGF1. Se sondó con GAPDH para ilustrar la misma carga en todas las calles.

Figura 25. Inhibición de la señalización estimulada por ligando en células H292 por agentes de unión basados en ^{10}Fn3 (no pegilados). Efecto de agente de unión a E/I basado en ^{10}Fn3 (E2-GS10-I1) sobre la activación del receptor y la señalización celular en células H292. Las células se privaron de suero y se trataron durante 2 horas con agentes de unión basados en ^{10}Fn3 1 μM antes de la estimulación con EGF, IGF1 o una combinación de EGF + IGF1. Se sondó con GAPDH para ilustrar la misma carga en todas las calles.

Figura 26. Estudios de unión competitiva con agentes de unión a E/I basados en ^{10}Fn3. A. El agente de unión a EGFR basado en ^{10}Fn3 no compite por la unión de los anticuerpos contra EGFR a EGFR. La inyección inicial del agente de unión a EGFR basado en ^{10}Fn3 muestra unión a EGFR en la superficie del chip. Una segunda inyección de agente de unión a EGFR basado en ^{10}Fn3 mezclada con una cantidad igual de cetuximab, panitumumab o nimotuzumab no muestra competición por la unión de anticuerpos a EGFR por el agente de unión a EGFR basado en ^{10}Fn3. B. El agente de unión a E/I basado en ^{10}Fn3 puede unirse a EGFR e IGF-IR simultáneamente.

La inyección inicial del agente de unión a E/I basado en ^{10}Fn3 muestra unión a EGFR inmovilizado en la superficie del chip. Una segunda inyección del agente de unión a E/I basado en ^{10}Fn3 a IGF-IR soluble muestra la unión de sIGF-IR a otro extremo del agente de unión a E/I basado en ^{10}Fn3 inmovilizado.

Figura 27. Niveles plasmáticos de TGFα 4 horas después de la última dosis de estudios de xenoinjerto. En muestras plasmáticas tomadas al final del tratamiento a partir de los estudios de xenoinjerto de BxPC3, GEO y H441 descritos en la Tabla 24, se analizaron los niveles circulantes de TGFα.

Figura 28. Niveles plasmáticos de TGFα e IGF1 en ratones desnudos que no llevan tumores después de la dosificación con I1-GS10-E5 pegilado. A ratones que no llevaban tumores se les administró una sola dosis de agente de unión a I1-GS10-E5 pegilado basado en ^{10}Fn3 y se analizaron los niveles circulantes de TGFα e IGF1.

Figura 29. Estudio de xenoinjerto de H292 usando agentes de unión a E/I basados en 10Fn3 en comparación con panitumumab. Los xenoinjertos de H292 se dejaron sin tratar (■) o se dosificaron tres veces por semana con agentes de unión basados en ^{10}Fn3 formulados en PBS con las construcciones individuales descritas en la Figura o se dosificaron cada tres días i.p. con panitumumab a 1 mg/ratón

(o) o 0.1 mg/ratón (□). Las dosis reales de agentes de unión basados en ^{10}Fn3 y panitumumab (▲) se indican en el eje x, indicando las dosis de panitumumab más próximas al eje x por debajo de los triángulos dosis de agentes de unión basados en ^{10}Fn3.

Figura 30. Perfil de parámetros farmacocinéticos de E2-GS10-I1 pegilado en ratones.

Figura 31. Comparación de semivida a 100 mg/kg y 10 mg/kg IP, y 10 mg/kg y 64 mg/kg SC en diversos agentes de unión a E/I basados en ^{10}Fn3.

Figura 32. Eficacia antitumoral de E2-GS10-I1 pegilado en el modelo de RH41.

Figura 33. Medición de puntos finales farmacodinámicos en tumores. Al final del tratamiento, se extrajeron los tumores 4 horas después de la dosis final a partir del modelo de xenoinjerto de DiFi (panel A) y el modelo de xenoinjerto de H292 (panel B) y se examinaron los niveles de fosfo-EGFR, fosfo-IGFR, EGFR total e IGFR total. Se cargaron cantidades iguales de lisado de proteína total en cada calle de los geles y las manchas de transferencia también se sondaron con GAPDH para demostrar una carga igual en todas las calles.

Figura 34. Secuencia de agente de unión a anti-EGFR 679F09. Los restos del bucle que se variaron están subrayados.

Figura 35. Análisis de la Secuencia del bucle BC I. Frecuencia de aminoácidos en cada posición en el bucle BC a partir de secuencias de unión a EGFR. Imagen creada usando WebLogo (Crooks GE, Hon G, Chandonia JM, Brenner SE. WebLogo: A sequence logo generator. *Genome Research*, 14: 1188-1190, 2004).

Figura 36. Análisis de Secuencia del bucle DE I. Frecuencia de aminoácidos en cada posición en el bucle DE a partir de secuencias de unión a EGFR (263 secuencias de bucle DE únicas analizadas).

Figura 37. Análisis de la Secuencia del bucle FG (10 aminoácidos de longitud) I. Frecuencia de aminoácidos en cada posición en el bucle FG a partir de secuencias de unión a EGFR con bucles FG de 10 aminoácidos de longitud (228 bucles FG únicos de 10 aminoácidos de longitud analizados).

Figura 38. Análisis de Secuencia de bucle FG (15 aminoácidos de longitud) I. Frecuencia de aminoácidos en cada posición en el bucle FG a partir de secuencias de unión a EGFR con bucles FG de 15 aminoácidos de longitud (349 bucles FG únicos de 15 aminoácidos de longitud analizados).

Figura 39. Análisis de Secuencia del bucle BC II. Frecuencia de aminoácidos en cada posición en el bucle BC a partir de todas las secuencias "potentes" (85 secuencias de bucle BC únicas analizadas).

Figura 40. Análisis de Secuencia de bucle DE II.

Frecuencia de aminoácidos en cada posición en el bucle DE a partir de todas las secuencias "potentes" (60 secuencias de bucle DE únicas analizadas).

Figura 41. Análisis de Secuencia de bucle FG (10 aminoácidos de longitud) II. Frecuencia de aminoácidos en cada posición en el bucle FG a partir de todas las secuencias "potentes" con bucles FG de 10 aminoácidos de longitud (6 bucles FG únicos de 10 aminoácidos de longitud analizados).

Figura 42. Análisis de Secuencia de bucle FG (15 aminoácidos de longitud) II. Frecuencia de aminoácidos en cada posición en el bucle FG a partir de todas las secuencias "potentes" con bucles FG de 15 aminoácidos de longitud (65 bucles FG únicos de 15 aminoácidos de longitud analizados).

Figura 43. Tabla que resume diversas características de agentes de unión a E/I basados en ^{10}Fn3 como se describe en el Ejemplo 22.

Figura 44. Tabla que resume diversos parámetros farmacocinéticos de agentes de unión a E/I basados en ^{10}Fn3 como se describe en el Ejemplo 30.

Figura 45. Secuencias de aminoácidos de monómeros de E como se describe en el Ejemplo 32. Los bucles BC, DE y FG en cada secuencia están subrayados.

Figura 46. Alineamiento de secuencia de núcleo de tipo silvestre (aminoácidos 9-94 de la SEC ID N°: 1) con núcleo de I1 (SEC ID N°: 65), núcleo de E1 (SEC ID N°: 66),

núcleo de E2 (SEC ID N°: 67), núcleo de E3 (SEC ID N°: 68), núcleo de E4 (SEC ID N°: 108), núcleo de E5 (SEC ID N°: 114), núcleo de E85 (SEC ID N°: 141), núcleo de E90 (SEC ID N°: 156), núcleo de E96 (SEC ID N°: 171), núcleo de E105 (SEC ID N°: 186) y núcleo de E112 (SEC ID N°: 199). Los bucles BC, DE y FG en las secuencias de tipo silvestre se muestran en negrita y subrayados. Los restos aminoacídicos cambiados realmente en comparación con el tipo silvestre para los núcleos de I y E se muestran en negrita y subrayados.

Figura 47. Secuencias de ácidos nucleico de monómeros de E e I. A menos que se especifique otra cosa, las secuencias de nucleótidos codifican un monómero que tiene una extensión N-terminal N+10, una cola de Ser y un marcador his.

Figura 48. Secuencia de ácido nucleico de agentes de unión a E/I basados en ^{10}Fn3. Todas las secuencias de nucleótidos codifican un agente de unión a E/I basado en ^{10}Fn3 que tiene una extensión N-terminal N+10 en el primer monómero en la construcción y una cola de Cys y un marcador his en el segundo monómero en la construcción.

Descripción detallada de la invención

Definiciones

Como se usan en este documento, los siguientes términos y expresiones tendrán los significados expuestos a continuación. A menos que se definan de otro modo, todos los

términos técnicos y científicos usados en este documento tienen el mismo significado que el especialista habitual en la técnica comprende de forma común.

Las formas singulares "un", "una", "el" y "la" incluyen referencias plurales a menos que el contexto lo indique claramente de otro modo.

Los términos "comprender" y "que comprende" se usan en el sentido abierto, incluyente, significando que se pueden incluir elementos adicionales.

La expresión "incluyendo" se usa para querer decir "incluyendo pero sin limitación". "Incluyendo" e "incluyendo pero sin limitación" se usan de forma intercambiable.

La expresión "proteína similar a anticuerpo" se refiere a una proteína no inmunoglobulina que tiene un "pliegue similar a inmunoglobulina", es decir, comprende aproximadamente 80-150 restos aminoacídicos que se organizan estructuralmente en un conjunto de hélices beta o similares a beta, que forman láminas beta, donde las hélices beta o similares a beta están conectadas por porciones de bucle intermedias. Las láminas beta forman el núcleo estable de la proteína similar a anticuerpo, mientras que crean dos "caras" compuestas por los bucles que conectan las hélices beta o similares a beta. Como se describe en este documento, estos bucles se pueden variar para crear sitios de unión a ligando personalizados y tales variaciones se pueden generar sin

alterar la estabilidad global de la proteína. Un ejemplo de tal proteína similar a anticuerpo es una "proteína de armazón basada en fibronectina", con lo que se quiere decir un polipéptido basado en un dominio de fibronectina de tipo III (Fn3). En un aspecto, una proteína similar a anticuerpo se basa en un décimo dominio de fibronectina de tipo III (^{10}Fn3).

Con un "polipéptido" se quiere decir cualquier secuencia de dos o más aminoácidos, independientemente de la longitud, modificación post-traducción o función. "Polipéptido", "péptido" y "proteína" se usan de forma intercambiable en este documento.

"Porcentaje (%) de identidad de secuencia de aminoácidos" se define en este documento como el porcentaje de restos aminoacídicos en una secuencia candidata que son idénticos a los restos aminoacídicos en una secuencia seleccionada, después de alinear las secuencias e introducir huecos, si fuera necesario, para conseguir el máximo porcentaje de identidad de secuencia y no considerando ninguna sustitución conservativa como parte de la identidad de secuencia. El alineamiento con propósitos de la determinación del porcentaje de identidad de secuencia de aminoácidos se puede conseguir de diversos modos que están dentro de la especialidad de la técnica, por ejemplo, mediante el uso de software informático disponible públicamente tal como software BLAST, BLAST-2, ALIGN, ALIGN-2

o Megalign (DNASTAR). Los especialistas en la técnica pueden determinar parámetros apropiados para medir el alineamiento, que incluyen cualquier algoritmo necesario para conseguir el alineamiento máximo a lo largo de la longitud completa de las secuencias que se están comparando. Sin embargo, para los propósitos de este documento, los valores del % de identidad de secuencia de aminoácidos se obtienen como se describe más adelante mediante el uso del programa informático de comparación de secuencias ALIGN-2. El programa informático de comparación de secuencias ALIGN-2 se creó por Genentech, Inc., se ha presentado con documentación de usuario en U.S. Copyright Office, Washington D.C., 20559, donde está registrado con el N° de Registro de U.S. Copyright TXU510087 y está disponible públicamente en Genentech, Inc., South San Francisco, Calif. El programa ALIGN-2 se debe compilar para el uso en un sistema operativo UNIX, preferiblemente UNIX digital V4.0D. Todos los parámetros de comparación de secuencias se ajustan por el programa ALIGN-2 y no varían.

Para los propósitos de este documento, el % de identidad de secuencia de aminoácidos de una secuencia dada de aminoácidos A con respecto, con o frente a una secuencia de aminoácidos dada B (que se puede indicar alternativamente como una secuencia de aminoácidos dada A que tiene o comprende un determinado % de identidad de secuencia de aminoácidos con respecto, con o frente a una secuencia de

aminoácidos dada B) se calcula del siguiente modo: 100 veces la fracción X/Y donde X es el número de restos aminoacídicos puntuados como coincidencias idénticas por el programa de alineamiento de secuencias ALIGN-2 en ese alineamiento del programa de A y B y donde Y es el número total de restos aminoacídicos en B. Se entenderá que cuando la longitud de la secuencia de aminoácidos A no sea igual a la longitud de secuencia de aminoácidos B, el % de identidad de secuencia de aminoácidos de A con B no igualará al % de identidad de secuencia de aminoácidos de B con A.

La expresión "cantidad terapéuticamente eficaz" se refiere a una cantidad de un fármaco eficaz para tratar una enfermedad o un trastorno en un mamífero. En el caso de cáncer, la cantidad terapéuticamente eficaz del fármaco puede reducir el número de células cancerosas; reducir el tamaño del tumor; inhibir (es decir, ralentizar hasta cierto alcance y preferiblemente detener) la infiltración con células cancerosas en órganos periféricos; inhibir (es decir, ralentizar hasta cierto alcance y preferiblemente detener) la metástasis del tumor; inhibir, hasta cierto alcance, el crecimiento del tumor; y/o aliviar hasta cierto alcance uno o más de los síntomas asociados con el trastorno. En el sentido de que el fármaco puede prevenir el crecimiento y/o inactivar células cancerosas existentes, puede ser citostático y/o citotóxico. Para terapia de cáncer, la

eficacia *in vivo* se puede medir, por ejemplo, evaluando el tiempo hasta la progresión de la enfermedad (TTP) y/o determinando las tasas de respuesta (RR).

La semivida de una secuencia de aminoácidos o un compuesto se puede definir generalmente como el tiempo necesario para que la concentración en suero del polipéptido se reduzca el 50% *in vivo* por ejemplo, debido a degradación de la secuencia o el compuesto y/o aclaramiento o secuestro de la secuencia o el compuesto mediante mecanismos naturales. La semivida se puede determinar de cualquier manera conocida en la técnica, tal como por análisis farmacocinético. Véase, por ejemplo, M Gibaldi & D Perron "Pharmacokinetics", publicado por Marcel Dekker, 2ª edición rev. (1982).

La expresión "agente de unión a E/I" se refiere a una molécula biespecífica que comprende un dominio de unión a EGFR y un domino de unión a IGFIR distinto. Los dos dominios pueden estar unidos covalentemente o no covalentemente. Un agente de unión a E/I ejemplar es un dímero similar a anticuerpo que comprende un ^{10}Fn3 de unión a EGFR y un ^{10}Fn3 de unión a IGFIR, es decir, un agente de unión a E/I basado en ^{10}Fn3.

Visión de conjunto

El receptor del factor de crecimiento epidérmico (EGFR) y el receptor del factor de crecimiento similar a insulina (IFGR) desempeñan papeles clave en la tumorigénesis

de varios tipos de cáncer humano. La inhibición de cualquier receptor reduce de forma eficaz el crecimiento del tumor en modelos preclínicos así como clínicamente. El bloqueo de la ruta de EGFR induce el cambio a la ruta de IGFR para dirigir el crecimiento con modelos de tumor *in vitro*. Por lo tanto, el bloqueo de ambos receptores simultáneamente puede conseguir una eficacia superior a bloquear cada ruta en solitario superando el cambio de ruta. En ejemplos de modalidades, la actividad de un agente de unión a E/I es sinérgica en comparación con los componentes monoméricos del agente de unión a E/I.

La memoria descriptiva describe, entre otras, moléculas biespecíficas que se unen a EGFR e IGFIR, denominadas en este documento "agentes de unión a E/I". Los solicitantes han descubierto que tales moléculas biespecíficas inhiben la proliferación de una línea celular de modelo de cáncer con mayor potencia que los agentes de unión monoespecíficos correspondientes (véase, por ejemplo, el Ejemplo 9 y la Figura 8).

Los agentes de unión a E/I serán útiles en numerosas aplicaciones terapéuticas, especialmente en el tratamiento de cáncer. Además de las aplicaciones terapéuticas, los agentes de unión a E/I se pueden usar en cualquier circunstancia en la que sea deseable detectar EGFR y/o IGFIR.

Los agentes de unión a E/I tienen un dominio de unión a EGFR y un dominio de unión a IGFIR distinto. Los dominios de unión típicos incluyen anticuerpos; por lo tanto, se pueden generar anticuerpos biespecíficos para funcionar como agentes de unión a E/I. Los anticuerpos biespecíficos que comprenden pares complementarios de regiones V_H y V_L se conocen en la técnica. Estos anticuerpos biespecíficos comprenden dos pares de V_H y V_L, uniéndose cada par $V_{H/L}$ a un único antígeno (véase, por ejemplo, Hu y col., Cancer Res. 1996 56: 3055-306; Neri y col., J. Mol. Biol. 1995 246: 367-373; Atwell y col., Mol. Immunol. 1996 33: 1301-1312; y Carter y col., Protein Sci. 1997 6: 781-788). Un anticuerpo biespecífico ejemplar es un diacuerpo, es decir, un fragmento de anticuerpo pequeño con dos sitios de unión a antígeno, fragmentos que comprenden un dominio variable de cadena pesada conectado a un dominio variable de cadena ligera en la misma cadena polipeptídica (Hollinger y col., Proc. Natl. Acad. Sci. USA 1993 90: 6444-6448).

Los agentes de unión a E/I también incluyen dímeros de proteínas de armazón de unión a ligando. Las proteínas de armazón están bien descritas en la bibliografía e incluyen, por ejemplo, tendamistato, affibody, dominio de fibronectina de tipo III, anticalina, tetranectina y anquirina. Las proteínas de armazón adicionales que se pueden usar para generar agentes de unión a E/I se revisan en Binz y col.,

Nature Biotech 23: 1257-1268 (2005). Las proteínas de armazón están basadas en una estructura central rígida o 'flanqueante' que es importante para determinar y estabilizar la estructura tridimensional. Entre los restos fijos o conservados del armazón se sitúan regiones variables tales como bucles, superficies o cavidades que se pueden aleatorizar para alterar la unión a ligando. Se proporciona una gran variedad de aminoácidos en las regiones variables entre los restos de armazón fijos para proporcionar unión específica a una molécula diana.

Una proteína de armazón de unión a ligando ejemplar se basa en un dominio de fibronectina de tipo III (Fn3). La fibronectina es una proteína grande que desempeña papeles esenciales en la formación de matriz extracelular y en interacciones célula-célula; está constituida por muchas repeticiones de tres tipos (tipos I, II y III) de pequeños dominios.

La Fn3 es pequeña, monomérica, soluble y estable. Carece de enlaces disulfuro y, por lo tanto, es estable en condiciones reductoras. La estructura global de Fn3 se parece al pliegue de inmunoglobulina. Los dominios de Fn3 comprenden, en orden desde el N-terminal al C-terminal, una hélice beta o similar a beta, A; un bucle, AB; una hélice beta o similar a beta, B; un bucle, BC; una hélice beta o similar a beta, C; un bucle CD; una hélice beta o similar a

beta D; un bucle DE; una hélice beta o similar a beta, E; un bucle, EF; una hélice beta o similar a beta F; un bucle FG; y una hélice beta o similar a beta G. Las siete hélices β antiparalelas se disponen como dos láminas beta que forman un núcleo estable, mientras que crean dos "caras" compuestas por los bucles que conectan las hélices beta o similares a beta. Los bucles AB, CD y EF están localizados en una cara y los bucles BC, DE y FG están localizados en la cara opuesta. Cualquiera de o todos los bucles AB, BC, CD, DE, EF y FG pueden participar en la unión a ligando. Existen al menos 15 módulos diferentes de Fn3, y aunque la homología de secuencia entre las moléculas es baja, todas comparten una alta similitud en la estructura terciaria.

Las Adnectin™ (Adnexus, una Compañía R&D de Bristol-Myers Squibb) son proteínas de armazón de unión a ligando basadas en el décimo dominio de fibronectina de tipo III, es decir, el décimo módulo de Fn3, (^{10}Fn3). La secuencia de aminoácidos de un ^{10}Fn3 humano de origen natural se expone en la SEC ID N°: 1.

VSDVPRDLEVVAATPTSLLI**SWDAPAVTVR**YYRITYGETGGNSPVQEFTV**PGSKST**ATISG LKPGVDYTITVYAV**TGRGDSPASSKPIS**INYRT (SEC ID N°:1) (se resaltan los bucles BC, FG y DE).

En la SEC ID N°:1, el bucle AB se corresponde a los restos 15-16, el bucle BC se corresponde a los restos 21-30, el bucle CD se corresponde a los restos 39-45, el bucle DE se

corresponde a los restos 51-56, el bucle EF se corresponde a los restos 60-66 y el bucle FG se corresponde a los restos 76-87. (Xu y col., Chemistry & Biology 2002 9: 933-942). Los bucles BC, DE y FG se alinean a lo largo de una cara de la molécula y los bucles AB, CD y EF se alinean a lo largo de la cara opuesta de la molécula. En la SEC ID N°: 1, la cadena beta A se corresponde a los restos 9-14, la cadena beta B se corresponde a los restos 17-20, la cadena beta C se corresponde a los restos 31-38, la cadena beta D se corresponde a los restos 46-50, la cadena beta E se corresponde a los restos 57-59, la cadena beta F se corresponde a los restos 67-75 y la cadena beta G se corresponde a los restos 88-94. Las cadenas están conectadas entre sí mediante el correspondiente bucle, por ejemplo, las cadenas A y B están conectadas por el bucle AB en la formación cadena A, bucle AB, cadena B, etc. Los restos implicados en la formación del núcleo hidrófobo (los "restos aminoacídicos centrales") incluyen los aminoácidos correspondientes a los siguientes aminoácidos de la SEC ID N°: 1: L8, V10, A13, L18, I20, W22, Y32, I34, Y36, F48, V50, A57, I59, L62, Y68, I70, V72, A74, I88, I90 e Y92, donde los restos aminoacídicos centrales están representados por el código de aminoácidos de una única letra seguido de la posición en la que se localizan dentro de la SEC ID N°: 1. Véase, por ejemplo, Dickinson y col., J. Mol. Biol. 236:

1079-1092 (1994).

Como se ha descrito anteriormente, los restos aminoacídicos correspondientes a los restos 21-30, 51-56 y 76-87 de la SEC ID N°: 1 definen los bucles BC, DE y FG, respectivamente. Sin embargo, debe entenderse que no es necesario modificar todos los restos dentro de la región del bucle para conseguir un agente de unión a ^{10}Fn3 que tenga una fuerte afinidad por una diana deseada, tal como IGF-IR o EGFR. Por ejemplo, en muchos de los ejemplos descritos en el presente documento, sólo se modificaron los restos correspondientes a los aminoácidos 23-30, 52-55 y 77-86 de la SEC ID N°: 1 para producir agentes de unión a ^{10}Fn3 de alta afinidad (véase la Figura 46. Por consiguiente, en ciertas modalidades, el bucle BC puede definirse por aminoácidos que corresponden a los restos 23-30 de la SEC ID N°: 1, el bucle DE puede definirse por aminoácidos que corresponden a los restos 52-55 de la SEC ID N°: 1, y el bucle FG puede definirse por aminoácidos que corresponden a los restos 77-86 de la SEC ID N°: 1.

Los ^{10}Fn3 son estructural y funcionalmente análogos a anticuerpos, específicamente la región variable de un anticuerpo. Aunque los dominios de ^{10}Fn3 se pueden describir como "miméticos de anticuerpo" o "proteínas similares a anticuerpo", ofrecen varias ventajas con respecto a anticuerpos convencionales. En particular, muestran mejores

propiedades de plegamiento y termoestabilidad en comparación con anticuerpos y carecen de enlaces disulfuro, que se conoce que impiden o evitan el plegamiento apropiado en ciertas condiciones. Ejemplos de agentes de unión a E/I basados en ^{10}Fn3 son predominantemente monoméricos, alcanzando las Tm como promedio ~50°C.

Los bucles BC, DE y FG de ^{10}Fn3 son análogos a las regiones determinantes de complementariedad (CDR) de inmunoglobulinas. La alteración de la secuencia de aminoácidos en estas regiones de bucle cambia la especificidad de unión de ^{10}Fn3. Las secuencias de proteína fuera de los bucles similares a CDR son análogas a las regiones flanqueantes de inmunoglobulinas y desempeñan un papel en la conformación estructural del ^{10}Fn3. Las alteraciones en las regiones similares a regiones flanqueantes de ^{10}Fn3 se permiten hasta el punto en el que no se altera la conformación estructural en cuanto a interrupción de la unión a ligando. Se han descrito procedimientos para generar agentes de unión específicos de ligando de ^{10}Fn3 en las Publicaciones PCT N° WO 00/034787, WO 01/64942 y WO 02/032925, que describen agentes de unión de TNFα de alta afinidad, la Publicación PCT N° WO 2008/097497, que describe agentes de unión de VEGFR2 de alta afinidad y la Publicación PCT N° WO 2008/066752, que describe agentes de unión de IGFIR de alta afinidad. Las referencias adicionales

que analizan agentes de unión de ^{10}Fn3 y procedimientos para seleccionar agentes de unión incluyen las Publicaciones PCT N° WO 98/056915, WO 02/081497 y WO 2008/031098 y la Publicación de Estados Unidos N° 2003186385.

Las proteínas similares a anticuerpo basadas en el armazón de ^{10}Fn3 se pueden definir generalmente por la secuencia:

VSDVPRDLEVVAATPTSLLI$(X)_n$YYRITYGETGGNSPVQEFTV$(X)_o$ATISGLKPGVDYTI TVYAV$(X)_p$ISINYRT (SEC ID N°: 32), en la que n es un número entero de 1-20, o es un número entero de 1-20 y p es un número entero de 1-40. Los bucles BC, DE y FG están representados respectivamente por $(X)_n$, $(X)_o$ y $(X)_p$.

^{10}Fn3 generalmente empieza con el resto aminoacídico que corresponde al número 1 de la SEC ID N°: 1. Sin embargo, la invención también incluye dominios con deleciones de aminoácidos. En algunas modalidades, se delecionan restos aminoacídicos que corresponden a los ocho primeros aminoácidos de la SEC ID N°: 1. También pueden añadirse secuencias adicionales en el N-terminal o C. Por ejemplo, una secuencia MG adicional puede ponerse en el N-terminal de ^{10}Fn3. Normalmente se escindirá la M, dejando una G en el N-terminal. En algunas modalidades, pueden ponerse secuencias en el C-terminal del dominio ^{10}Fn3, por ejemplo, EIDKPSQ (SEC ID N°: 9), EIDKPCQ (SEC ID N°: 10), EGSGS (SEC ID N°: 96) o EGSGC (SEC ID N°: 97).

Las secuencias de ^{10}Fn3 que no se unen a ligando, es decir, el "armazón de ^{10}Fn3", pueden alterarse siempre que el ^{10}Fn3 retenga la función de unión al ligando y/o estabilidad estructural. En algunas modalidades, uno o más de Asp 7, Glu 9 y Asp 23 se reemplazan por otro aminoácido, tal como por ejemplo un resto aminoacídico no cargado negativamente (por ejemplo Asn, Lys, etc.). Se ha notificado que estas mutaciones tienen el efecto de promover una mayor estabilidad del ^{10}Fn3 mutante a pH neutro en comparación con la forma de tipo silvestre (Véase la Publicación PCT N° WO 02/04523). Se han descrito una diversidad de alteraciones adicionales en el armazón de ^{10}Fn3 que son beneficiosas o neutras. Véase, por ejemplo, Batori y col., Protein Eng. 2002 15(12): 1015-20; Koide y col., Biochemistry 2001 40(34): 10326-33.

El armazón de ^{10}Fn3 puede modificarse por una o más sustituciones conservativas. Hasta un 5%, 10%, 20% o incluso un 30% o más de los aminoácidos del armazón de ^{10}Fn3 pueden alterarse por una sustitución conservativa sin alterar sustancialmente la afinidad del ^{10}Fn3 por un ligando. Por ejemplo, la modificación del armazón preferiblemente reduce la afinidad de unión del agente de unión de ^{10}Fn3 por un ligando en menos 100 veces, 50 veces, 25 veces, 10 veces, 5 veces o 2 veces. Es posible que estos cambios alteren la inmunogenicidad del ^{10}Fn3 *in vivo*, y cuando se reduce la inmunogenicidad, estos cambios son deseables. Como se usa en

el presente documento, "sustituciones conservativas" son restos que son física o funcionalmente similares a los restos de referencia correspondientes. Es decir, una sustitución conservativa y su resto de referencia tienen un tamaño, forma, carga eléctrica y propiedades químicas similares incluyendo la capacidad de formar enlaces covalentes o enlaces de hidrógeno, o similares. Son sustituciones conservativas preferidas las que cumplen los criterios definidos para una mutación puntual aceptada en Dayhoff y col., Atlas of Protein Sequence and Structure 5: 345-352 (1978 & Supp.). Son ejemplos de sustituciones conservativas las sustituciones dentro de los siguientes grupos: (a) valina, glicina; (b) glicina, alanina; (c) valina, isoleucina, leucina; (d) ácido aspártico, ácido glutámico; (e) asparagina, glutamina; (f) serina, treonina; (g) lisina, arginina, metionina y (h) fenilalanina, tirosina.

Agentes de Unión a E

En un aspecto, la descripción proporciona proteínas de tipo anticuerpo que comprenden un dominio de unión a EGFR de ^{10}Fn3. En ciertas modalidades, un ^{10}Fn3 de unión a EGFR puede proporcionarse como parte de una proteína de fusión o multímero. Por ejemplo, un ^{10}Fn3 de unión a EGFR puede unirse de forma covalente o no covalente a al menos un segundo dominio de unión de ^{10}Fn3. El segundo dominio de unión de ^{10}Fn3 puede unirse a EGFR o a una diana diferente. En un

ejemplo de modalidad, un ^{10}Fn3 de unión a EGFR puede unirse de forma covalente o no covalente a un ^{10}Fn3 de unión a IGF-IR.

En ejemplos de modalidades, las proteínas ^{10}Fn3 de unión a EGFR descritas en este documento se unen a EGFR con un valor de K_D menor de 500 nM, 100 nM, 50 nM, 10 nM, 1 nM, 500 pM, 100 pM. 100 pM, 50 pM o 10 pM.

En ejemplos de modalidades, el bucle BC de las proteínas ^{10}Fn3 de unión a EGFR corresponde a los aminoácidos 23-30 de la SEC ID N°: 1, el bucle DE de las proteínas ^{10}Fn3 de unión a EGFR corresponde a los aminoácidos 52-55 de la SEC ID N°: 1, y el bucle FG de las proteínas ^{10}Fn3 corresponde a los aminoácidos 77-86 de la SEC ID N°: 1.

En una modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene YQ en las posiciones correspondientes a los aminoácidos 29 y 30 de la SEC ID N°: 1.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene YQ en las posiciones correspondientes a los aminoácidos 29 y 30 de la SEC ID N°: 1 y un bucle FG que tiene una longitud de 15 aminoácidos, por ejemplo, un bucle FG que se extiende en longitud en 5 aminoácidos debido a una inserción de 5 aminoácidos entre restos correspondientes a los aminoácidos 77-86 de la SEC ID N°: 1.

En otra modalidad, la invención proporciona un ^{10}Fn3

de unión a EGFR que comprende un bucle BC que tiene YQ en las posiciones correspondientes a los aminoácidos 29 y 30 de la SEC ID N°: 1 y un bucle DE que tiene un resto V, I, L, M o A en la posición correspondiente al aminoácido 54 de la SEC ID N°: 1.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene YQ en las posiciones correspondientes a los aminoácidos 29 y 30 de la SEC ID N°: 1, un bucle DE que tiene un resto V, I, L, M o A en la posición correspondiente al aminoácido 54 de la SEC ID N°: 1, y un bucle FG que tiene una longitud de quince aminoácidos, por ejemplo un bucle FG que se extiende en longitud en cinco aminoácidos debido a una inserción de cinco aminoácidos entre los restos correspondientes a los aminoácidos 77-86 de la SEC ID N°: 1.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene YQ en las posiciones correspondientes a los aminoácidos 29 y 30 de la SEC ID N°: 1 y un bucle FG que comprende D o N en la posición correspondiente al aminoácido 77 de la SEC ID N°: 1.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene YQ en las posiciones correspondientes a los aminoácidos 29 y 30 de la SEC ID N°: 1 y un bucle FG (i) que tiene quince aminoácidos de longitud, por ejemplo, un bucle FG que se extiende en

longitud en cinco aminoácidos debido a una inserción de cinco aminoácidos entre los restos correspondientes a los aminoácidos 77-86 de la SEC ID N°: 1 y (ii) comprende D o N en la posición correspondiente al aminoácido 77 de la SEC ID N°: 1.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle DE que comprende un resto V, I, L, M o A en la posición correspondiente al aminoácido 54 de la SEC ID N°: 1 y un bucle FG que comprende D o N en la posición correspondiente al aminoácido 77 de la SEC ID N°: 1.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle DE que comprende un resto V, I, L, M o A en la posición correspondiente al aminoácido 54 de la SEC ID N°: 1 y un bucle FG (i) que tiene quince aminoácidos de longitud, por ejemplo, un bucle FG que se extiende en longitud en cinco aminoácidos debido a una inserción de cinco aminoácidos entre los restos correspondientes a los aminoácidos 77-86 de la SEC ID N°: 1 y (ii) comprende D o N en la posición correspondiente al aminoácido 77 de la SEC ID N°: 1.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene YQ en las posiciones correspondientes a los aminoácidos 29 y 30 de la SEC ID N°: 1, un bucle DE que comprende un resto V, I, L, M o

A en la posición correspondiente al aminoácido 54 de la SEC ID N°: 1, y un bucle FG que comprende D o N en la posición correspondiente al aminoácido 77 de la SEC ID N°: 1.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene YQ en las posiciones correspondientes a los aminoácidos 29 y 30 de la SEC ID N°: 1, un bucle DE que comprende un resto V, I, L, M o A en la posición correspondiente al aminoácido 54 de la SEC ID N°: 1, y un bucle FG (i) que tiene quince aminoácidos de longitud, por ejemplo, un bucle FG que se extiende en longitud en cinco aminoácidos debido a una inserción de cinco aminoácidos entre los restos correspondientes a los aminoácidos 77-86 de la SEC ID N°: 1 y (ii) comprende D o N en la posición correspondiente al aminoácido 77 de la SEC ID N°: 1.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que comprende la secuencia de aminoácidos XXXXXXYQ, un bucle DE que comprende la secuencia de aminoácidos XX(V/I/L/M/A)X, y un bucle FG que comprende la secuencia de aminoácidos (D/N)X_n, donde X es cualquier aminoácido y n es 9-14 aminoácidos. En un ejemplo de modalidad, n es 14 aminoácidos.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que corresponde a los aminoácidos 23-30 de la SEC ID N°: 1 que comprende la

secuencia de aminoácidos XXXXXXYQ, un bucle DE que corresponde a los aminoácidos 52-55 de la SEC ID N°: 1 que comprende la secuencia de aminoácidos XX(V/I/L/M/A)X, y un bucle FG que corresponde a los aminoácidos 77-86 de la SEC ID N°: 1 que comprende la secuencia de aminoácidos $(D/N)X_n$, donde X es cualquier aminoácido y n es 9-14 aminoácidos. En un ejemplo de modalidad, n es 14 aminoácidos.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que comprende la secuencia de aminoácidos XXXXXXYQ, un bucle DE que comprende la secuencia de aminoácidos XX(V/I/L/M/A)X y un bucle FG que comprende una secuencia de aminoácidos seleccionada entre:

i.

(D/N)(Y/M)(Y/A/M)(Y/H/F)(K/Q/V)(E/P/R)(Y/T/K)X(E/Y/Q)(Y/G/H); y

ii.

D(Y/F/W)(Y/F/K)(N/D/P)(P/H/L)(A/T/V)(T/D/S)(H/Y/G)(E/P/V)(Y/H) (T/K/I)(Y/F)(H/N/Q)(T/Q/E)(T/S/I);

donde X es cualquier aminoácido.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que comprende la secuencia de aminoácidos XXXXXXYQ, un bucle DE que comprende la secuencia de aminoácidos (G/Y/H)(D/M/G)(V/L/I)X y un bucle

FG que comprende una secuencia de aminoácidos (D/N)(Y/M)(Y/A/M)(Y/H/F)(K/Q/V)(E/P/R)(Y/T/K)X(E/Y/Q)(Y/G/H), donde X es cualquier aminoácido.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que comprende la secuencia de aminoácidos XXXXXXYQ, un bucle DE que comprende la secuencia de aminoácidos (G/Y/H)(D/M/G)(V/L/I)X y un bucle FG que comprende una secuencia de aminoácidos D(Y/F/W)(Y/F/K)(N/D/P)(P/H/L)(A/T/V)(T/D/S)(H/Y/G)(E/P/V)(Y/H) (T/K/I)(Y/F)(H/N/Q)(T/Q/E)(T/S/I), donde X es cualquier aminoácido.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que comprende la secuencia de aminoácidos XXXXXXYQ, un bucle DE que comprende la secuencia de aminoácidos XX(V/I/L/M/A)X y un bucle FG que comprende una secuencia de aminoácidos seleccionada entre:

i. DY(A/Y)GKPYXEY (SEC ID N°: 473);

ii. DY(A/Y)Y(K/R/Q/T)PYXEY (SEC ID N°: 474);

iii. (D/N)Y(A/Y)(Y/F)(K/R/Q/T)EYXE(Y/H) (SEC ID N°: 475);

iv. DYY(H/Y)X(R/K)X(E/T)YX (SEC ID N°: 476);

v. DYY(H/Y)(K/H/Q)(R/K)T(E/T)Y(G/P) (SEC ID N°: 477);

vi. (D/N)MMHV(E/D)YXEY (SEC ID N°: 478);

vii. DYMHXXYXEY (SEC ID N°: 479); y

viii. D(M/Y)YHX(K/R)X(V/I/L/M)YG (SEC ID N°: 480);

donde X es cualquier aminoácido.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que comprende la secuencia de aminoácidos XXXXXXYQ, un bucle DE que comprende la secuencia de aminoácidos XX(V/I/L/M/A)X y un bucle FG que comprende una secuencia de aminoácidos seleccionada entre:

i. D(Y/F)(Y/F)NPXTHEYXYXXX (SEC ID N°: 481);

ii. D(Y/F)(Y/F)D(P/L)X(T/S)HXYXYXXX (SEC ID N°: 482); y

iii. D(Y/F)(K/R)PHXDGPH(T/I)YXE(S/Y) (SEC ID N°: 483);

donde X es cualquier aminoácido.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que comprende la secuencia de aminoácidos XXXXXXYQ, un bucle DE que comprende la secuencia de aminoácidos XX(V/I/L/M/A)X y un bucle FG que comprende la secuencia de aminoácidos (D/N)(M/Y)(M/A/W)(H/F/Y)(V/K)EY(A/Q/R/S/T)E(Y/H/D), donde X es cualquier aminoácido.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que comprende la secuencia de aminoácidos XXXXXXYQ, un bucle DE que comprende la secuencia de aminoácidos XX(V/I/L/M/A)X y un bucle FG que

comprende la secuencia de aminoácidos D(Y/F/W)(Y/F/K)(N/P/D)(P/H/L)X(T/D/S)(H/G/Y)(E/P/Y)(Y/H)XYXXX, donde X es cualquier aminoácido.

En diversas modalidades, el bucle DE de ^{10}Fn3 de unión a EGFR puede comprender la secuencia (G/Y/H)(D/M/G)(V/L/I)X.

En otra modalidad, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle FG que comprende una secuencia de aminoácidos seleccionada entre:

i. D(Y/F)(Y/F)NPXTHEYXYXXX (SEC ID N°: 481);

ii. D(Y/F)(Y/F)D(P/L)X(T/S)HXYXYXXX (SEC ID N°: 482); y

iii. D(Y/F)(K/R)PHXDGPH(T/I)YXE(S/Y) (SEC ID N°: 483);

donde X es cualquier aminoácido.

En ciertas modalidades, el ^{10}Fn3 de unión a EGFR comprende cualquiera de las secuencias consenso proporcionadas anteriormente, con la condición de que el ^{10}Fn3 de unión a EGFR no comprenda una o más de las siguientes secuencias:

i. VSDVPRDLEVVAATPTSLLISWQVPRPMYQRYYRITYGETGGNSPVQ EFTVPGGVRTATISGLKPGVDYTITVYAVTDYMHSEYRQYPISINYRT (SEC ID N°: 484), y

ii. VSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSP VQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYMHSEYRQYPISINYRT (SEC ID

N°: 485), y

iii. VSDVPRDLEVVAATPTSLLISWQVPRPMYQRYYRITYGETGGN SPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYMHSEYRQYPISINYRTEIDKPCQ (SEC ID N°: 486).

En ciertas modalidades, un ^{10}Fn3 de unión a EGFR que comprende una de las secuencias consenso proporcionadas anteriormente tiene al menos un 40%, 50%, 60%, 70%, 75% o 80% de identidad con la SEC ID N°: 1. En ciertas modalidades, la estructura global de un ^{10}Fn3 de unión a EGFR que comprende una de las secuencias consenso proporcionadas anteriormente se parece al plegamiento de las inmunoglobulinas. En cierta modalidad, un ^{10}Fn3 de unión a EGFR que comprende una de las secuencias consenso proporcionadas anteriormente comprende además los restos aminoacídicos centrales del armazón. En ciertas modalidades, un ^{10}Fn3 de unión a EGFR que comprende una de las secuencias consenso proporcionadas anteriormente tiene al menos un 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98% o 99% de identidad con una cualquiera de las SEC ID N°: 5-8, 52, 66-68, 106-108, 112-114, 140-142, 155-157, 170-172, 182, 185-187, 198-200 ó 219-327. En ciertas modalidades, un ^{10}Fn3 de unión a EGFR que comprende una de las secuencias consenso proporcionadas anteriormente tiene al menos un 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98% ó 99% de identidad con la secuencia de aminoácidos de restos aminoacídicos correspondientes a E9 de la SEC ID N°: 1 hasta T94 de la SEC ID N°: 1 de una

cualquiera de las SEC ID N°: 5-8, 52, 66-68, 106-108, 112-114, 140-142, 155-157, 170-172, 182, 185-187, 198-200 ó 219-327. En ciertas modalidades, el ^{10}Fn3 de unión a EGFR que comprende una de las secuencias consenso proporcionadas anteriormente comprende un armazón de ^{10}Fn3 que tiene de 0 a 20, de 0 a 15, de 0 a 10, de 0 a 8, de 0 a 6, de 0 a 5, de 0 a 4, de 0 a 3, de 0 a 2 o de 0 a 1 sustituciones, sustituciones conservativas, deleciones o adiciones con respecto a los restos aminoacídicos del armazón de la SEC ID N°: 1.

En ciertas modalidades, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 23-30, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 52-55 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 77-86 de una cualquiera de las SEC ID N°: 219-327. En ciertas modalidades, la invención proporciona un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-87 de una cualquiera de las SEC ID N°: 219-327. En ciertas modalidades, la invención proporciona un ^{10}Fn3 de unión a EGFR

que comprende una secuencia de aminoácidos idéntica en al menos un 60%, 75%, 80%, 85%, 90%, 95% o 98% a una cualquiera de las SEC ID N°: 219-327.

En una modalidad, se proporciona una proteína de tipo anticuerpo que comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une a EGFR con una K_D menor de 500 nM y comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 5, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 5, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-92 de la SEC ID N°: 5. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos X_gDSGRGSYQX_h (SEC ID N°: 40), un bucle DE que tiene la secuencia de aminoácidos X_iGPVHX_j (SEC ID N°: 42), y un bucle FG que tiene la secuencia de aminoácidos X_kDHKPHADGPHTYHEX_l (SEC ID N°: 44); donde X es cualquier aminoácido y g, h, i, j, k y l son números enteros seleccionados independientemente de 0 a 5. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos SWDSGRGSYQ (SEC ID N°: 39), un bucle DE que tiene la secuencia de aminoácidos PGPVHT (SEC ID N°: 41) y un bucle FG que tiene la secuencia de aminoácidos TDHKPHADGPHTYHESP (SEC ID N°: 43). En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una

secuencia de aminoácidos idéntica en al menos un 80, 90, 95 o 100% a las SEC ID N°: 5 ó 6.

En una modalidad, se proporciona una proteína de tipo anticuerpo que comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une a EGFR con una K_D menor de 500 nM y comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 7, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 7, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-87 de la SEC ID N°: 7. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos $X_mVAGAEDYQX_n$ (SEC ID N°: 34), un bucle DE que tiene la secuencia de aminoácidos X_oHDLVX_p (SEC ID N°: 36), y un bucle FG que tiene la secuencia de aminoácidos $X_qDMMHVEYTEHX_r$ (SEC ID N°: 38); donde X es cualquier aminoácido y m, n, o, p, q y r son números enteros seleccionados independientemente de 0 a 5. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos SWVAGAEDYQ (SEC ID N°: 33), un bucle DE que tiene la secuencia de aminoácidos PHDLVT (SEC ID N°: 35) y un bucle FG que tiene la secuencia de aminoácidos TDMMHVEYTEHP (SEC ID N°: 37). En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95 o

100% a las SEC ID N°: 7 u 8.

En una modalidad, se proporciona una proteína de tipo anticuerpo que comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une a EGFR con una K_D menor de 500 nM y comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 23-30 de la SEC ID N°: 82, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-55 de la SEC ID N°: 82, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-86 de la SEC ID N°: 82. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos $X_sLPGKLRYQX_t$ (SEC ID N°: 60), un bucle DE que tiene la secuencia de aminoácidos X_uHDLRX_w (SEC ID N°: 62) y un bucle FG que tiene la secuencia de aminoácidos $X_yNMMHVEYSEYX_z$ (SEC ID N°: 64); donde X es cualquier aminoácido y s, t, u, w, y y z son números enteros seleccionados independientemente de 0 a 5. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos LPGKLRYQ (SEC ID N°: 59), un bucle DE que tiene la secuencia de aminoácidos PHDLR (SEC ID N°: 61), y un bucle FG que tiene la secuencia de aminoácidos TNMMHVEYSEY (SEC ID N°: 63). En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95 o 100% a las SEC ID N°: 52 u 82.

En una modalidad, se proporciona una proteína de tipo anticuerpo que comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une EGFR con una K_D menor de 500 nM y comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 23-30 de la SEC ID N°: 106, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-55 de la SEC ID N°: 106 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-86 de la SEC ID N°: 106. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos X_gHERDGSRQX$_h$ (SEC ID N°: 134), un bucle DE que tiene la secuencia de aminoácidos X_iGGVRX$_j$ (SEC ID N°: 135), y un bucle FG que tiene la secuencia de aminoácidos X_kDYFNPTTHEYIYQTTX$_l$ (SEC ID N°: 136); donde X es cualquier aminoácido y g, h, i, j, k y l son números enteros seleccionados independientemente de 0 a 5. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos SWHERDGSRQ (SEC ID N°: 109), un bucle DE que tiene la secuencia de aminoácidos PGGVRT (SEC ID N°: 110), y un bucle FG que tiene la secuencia de aminoácidos TDYFNPTTHEYIYQTTP (SEC ID N°: 111). En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95 o 100% a una cualquiera de las SEC ID N°: 106-108.

En una modalidad, se proporciona una proteína de

tipo anticuerpo que comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une EGFR con una K_D menor de 500 nM y comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 23-30 de la SEC ID N°: 112, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-55 de la SEC ID N°: 112, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-86 de la SEC ID N°: 112. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos X_gWAPVDRYQX_h (SEC ID N°: 137), un bucle DE que tiene la secuencia de aminoácidos X_iRDVYX_j (SEC ID N°: 138) y un bucle FG que tiene la secuencia de aminoácidos X_kDYKPHADGPHTYHESX$_l$ (SEC ID N°: 139); donde X es cualquier aminoácido y g, h, i, j, k y l son números enteros seleccionados independientemente de 0 a 5. En algunas modalidades, el ^{10}Fn3 unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos SWWAPVDRYQ (SEC ID N°: 115), un bucle DE que tiene la secuencia de aminoácidos PRDVYT (SEC ID N°: 116) y un bucle FG que tiene la secuencia de aminoácidos TDYKPHADGPHTYHESP (SEC ID N°: 117). En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95 o 100% a una cualquiera de las SEC ID N°: 112-114.

En una modalidad, se proporciona una proteína de tipo anticuerpo que comprende un décimo dominio de

fibronectina de tipo III (^{10}Fn3) que se une EGFR con una K_D menor de 500 nM y comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 13-22 de la SEC ID N°: 141, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 43-48 de la SEC ID N°: 141, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 68-84 de la SEC ID N°: 141. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos X_gTQGSTHYQX_h (SEC ID N°: 146), un bucle DE que tiene la secuencia de aminoácidos X_iGMVYX$_j$ (SEC ID N°: 147) y un bucle FG que tiene la secuencia de aminoácidos X_kDYFDRSTHEYKYRTTX$_l$ (SEC ID N°: 148); donde X es cualquier aminoácido y g, h, i, j, k y l son números enteros seleccionados independientemente de 0 a 5. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos SWTQGSTHYQ (SEC ID N°: 143), un bucle DE que tiene la secuencia de aminoácidos PGMVYT (SEC ID N°: 144) y un bucle FG que tiene la secuencia de aminoácidos TDYFDRSTHEYKYRTTP (SEC ID N°: 145). En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95 o 100% a una cualquiera de las SEC ID N°: 140-142.

En una modalidad, se proporciona una proteína de tipo anticuerpo que comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une EGFR con una K_D

menor de 500 nM y comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 13-22 de la SEC ID N°: 156, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 43-48 de la SEC ID N°: 156, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 68-84 de la SEC ID N°: 156. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos X_gYWEGLPYQX_h (SEC ID N°: 161), un bucle DE que tiene la secuencia de aminoácidos X_iRDVNX_j (SEC ID N°: 162), y un bucle FG que tiene la secuencia de aminoácidos X_kDWYNPDTHEYIYHTIX_l (SEC ID N°: 163); donde X es cualquier aminoácido y g, h, i, j, k y l son números enteros seleccionados independientemente de 0 a 5. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos SWYWEGLPYQ (SEC ID N°: 158), un bucle DE que tiene la secuencia de aminoácidos PRDVNT (SEC ID N°: 159), y un bucle FG que tiene la secuencia de aminoácidos TDWYNPDTHEYIYHTIP (SEC ID N°: 160). En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95 o 100% a una cualquiera de las SEC ID N°: 155-157.

En una modalidad, se proporciona una proteína de tipo anticuerpo que comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une EGFR con una K_D menor de 500 nM y comprende un bucle BC que tiene la

secuencia de aminoácidos expuesta en los aminoácidos 13-22 de la SEC ID N°: 171, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 43-48 de la SEC ID N°: 171, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 68-84 de la SEC ID N°: 171. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos X_gASNRGTYQX_h (SEC ID N°: 176), un bucle DE que tiene la secuencia de aminoácidos X_iGGVSX_j (SEC ID N°: 177) y un bucle FG que tiene la secuencia de aminoácidos X_kDAFNPTTHEYNYFTTX$_l$ (SEC ID N°: 178); donde X es cualquier aminoácido y g, h, i, j, k y l son números enteros seleccionados independientemente de 0 a 5. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos SWASNRGTYQ (SEC ID N°: 173), un bucle DE que tiene la secuencia de aminoácidos PGGVST (SEC ID N°: 174) y un bucle FG que tiene la secuencia de aminoácidos TDAFNPTTHEYNYFTTP (SEC ID N°: 175). En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95 o 100% a una cualquiera de las SEC ID N°: 170-172.

En una modalidad, se proporciona una proteína de tipo anticuerpo que comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une EGFR con una K_D menor de 500 nM y comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 13-22 de

la SEC ID N°: 186, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 43-48 de la SEC ID N°: 186, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 68-84 de la SEC ID N°: 186. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos X_gDAPTSRYQX_h (SEC ID N°: 190), un bucle DE que tiene la secuencia de aminoácidos X_iGGLSX_j (SEC ID N°: 191) y un bucle FG que tiene la secuencia de aminoácidos X_kDYKPHADGPHTYHESX_l (SEC ID N°: 139); donde X es cualquier aminoácido y g, h, i, j, k y l son números enteros seleccionados independientemente de 0 a 5. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos SWDAPTSRYQ (SEC ID N°: 188), un bucle DE que tiene la secuencia de aminoácidos PGGLST (SEC ID N°: 189), y un bucle FG que tiene la secuencia de aminoácidos TDYKPHADGPHTYHESP (SEC ID N°: 117). En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95 o 100% a una cualquiera de las SEC ID N°: 185-187.

En una modalidad, se proporciona una proteína de tipo anticuerpo que comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une EGFR con una K_D menor de 500 nM y comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 13-22 de la SEC ID N°: 199, un bucle DE que tiene la secuencia de

aminoácidos expuesta en los aminoácidos 43-48 de la SEC ID N°: 199, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 68-84 de la SEC ID N°: 199. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos X_gDAGAVTYQX_h (SEC ID N°: 203), un bucle DE que tiene la secuencia de aminoácidos X_iGGVRX_j (SEC ID N°: 135) y un bucle FG que tiene la secuencia de aminoácidos X_kDYKPHADGPHTYHEYX_l (SEC ID N°: 204); donde X es cualquier aminoácido y g, h, i, j, k y l son números enteros seleccionados independientemente de 0 a 5. En algunas modalidades, el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos SWDAGAVTYQ (SEC ID N°: 201), un bucle DE que tiene la secuencia de aminoácidos PGGVRT (SEC ID N°: 110) y un bucle FG que tiene la secuencia de aminoácidos TDYKPHADGPHTYHEYP (SEC ID N°: 202). En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95 o 100% a una cualquiera de las SEC ID N°: 198-200.

En ciertas modalidades, un dominio ^{10}Fn3 de unión a EGFR está unido de forma covalente o no covalente a un dominio ^{10}Fn3 de unión a EGF-IR. En ejemplos de modalidades, el ^{10}Fn3 de unión a IGF-IR puede comprender un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID

N°: 3 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-83 de la SEC ID N°: 3. En algunas modalidades, el ^{10}Fn3 de unión a IGF-IR comprende un bucle BC que tiene la secuencia de aminoácidos $X_aSARLKVAX_b$ (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°: 48), y un bucle FG que tiene la secuencia de aminoácidos $X_eRFRDYQX_f$ (SEC ID N°: 50), donde X es cualquier aminoácido y a, b, c, d, e, f, g, h, i, j, k, y l son números enteros seleccionados independientemente de 0 a 5, o donde a es 2 y b-f son 1, o donde a-f son cero. En algunas modalidades, el ^{10}Fn3 de unión a IGF-IR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95, 98, 99 o 100% a la SEC ID N°: 3. En ciertas modalidades, el ^{10}Fn3 de unión a IGF-IR comprende un armazón de ^{10}Fn3 que tiene de 0 a 20, de 0 a 15, de 0 a 10, de 0 a 8, de 0 a 6, de 0 a 5, de 0 a 4, de 0 a 3, de 0 a 2, o de 0 a 1 sustituciones, sustituciones conservativas, deleciones o adiciones con respecto a los restos aminoacídicos del armazón de la SEC ID N°: 1. En ciertas modalidades, el ^{10}Fn3 de unión a IGF-IR tiene de 0 a 15, de 0 a 10, de 0 a 8, de 0 a 6, de 0 a 5, de 0 a 4, de 0 a 3, de 0 a 2, o de 0 a 1 sustituciones, sustituciones conservativas, deleciones o adiciones con respecto a las secuencias de bucle correspondientes de la SEC ID N°: 3.

Agentes de Unión a E/I de ^{10}Fn3

Un aspecto de la descripción proporciona agentes de

unión a E/I construidos a partir de multímeros de proteína similar a anticuerpo. En algunas modalidades, un multímero de proteína similar a anticuerpo comprende al menos un ^{10}Fn3 de unión a EGFR unido covalentemente o no covalentemente con al menos un ^{10}Fn3 de unión a IGFIR. En ciertas modalidades, los agentes de unión a E/I descritos en este documento se pueden construir como una cadena polipeptídica única en la que las subunidades de E y I pueden estar en cualquier orientación, por ejemplo, del N-terminal al C-terminal, en la orientación E-I o en la orientación I-E.

La descripción se refiere, en parte, al descubrimiento sorprendente de que múltiples ^{10}Fn3 unidos a través de un adaptador polipeptídico se pliegan correctamente de forma independiente entre sí, conservan alta afinidad de unión y que cada uno de los dominios conserva sus propiedades funcionales (véase, por ejemplo, los Ejemplos 5-10). Adicionalmente, estos agentes de unión a E/I basados en ^{10}Fn3 demuestran propiedades biofísicas deseables tales como baja agregación y alta temperatura de fusión (T_m) (véase, por ejemplo, el Ejemplo 4). Los Ejemplos caracterizan una diversidad de agentes de unión a E/I basados en ^{10}Fn3. Un ^{10}Fn3 de unión a IGFIR ejemplar se expone en la SEC ID N°: 4. Se expone un ^{10}Fn3 de unión a EGFR ejemplar en las SEC ID N°: 8, 52, 107, 113, 140, 155, 170, 185 y 198.

En algunas modalidades, un agente de unión a E/I

comprende un ^{10}Fn3 de unión a EGFR y un ^{10}Fn3 de unión a IGFIR, que tienen independientemente una secuencia de aminoácidos idéntica al menos en el 40, 50, 60, 70 o el 80% al dominio de ^{10}Fn3 humano, mostrado en la SEC ID N°:1. Gran parte de la variabilidad tendrá lugar generalmente en uno o más de los bucles.

En algunas modalidades, un agente de unión a E/I comprende un ^{10}Fn3 de unión a EGFR y un ^{10}Fn3 de unión a IGFIR, que tienen independientemente una secuencia de aminoácidos idéntica al menos en el 70, 80, 85, 90, 95, 98 o el 100% a la SEC ID N°: 32, en la que n es un número entero de 1-20, o es un número entero de 1-20 y p es un número entero de 1-40. En algunas modalidades, n es un número entero de 8-12, o es un número entero de 4-8 y p es un número entero de 4-28. En algunas modalidades, n es 10, o es 6 y p es 12.

En algunas modalidades, la descripción proporciona multímeros de ^{10}Fn3 que tienen al menos un bucle seccionado del bucle BC, DE y FG con una secuencia de aminoácidos alterada con respecto a la secuencia del bucle correspondiente del ^{10}Fn3 humano. Con "alterado" se quiere decir una o más alteraciones de secuencia de aminoácidos con respecto a una secuencia de molde (correspondiente al dominio de fibronectina humana) e incluye adiciones, deleciones y sustituciones de aminoácidos. La alteración de una secuencia

de aminoácidos se puede conseguir mediante variación de secuencia deliberada, ciega o espontánea, generalmente de una secuencia codificante de ácido nucleico y puede tener lugar mediante cualquier técnica, por ejemplo, PCR, PCR con tendencia a error o síntesis química de ADN. En algunas modalidades, una secuencia de aminoácidos está alterada por sustitución con o adición de aminoácidos de origen natural.

En algunas modalidades, uno o más bucles seleccionados de BC, DE y FG se pueden prolongar o acortar en la longitud con respecto al bucle de fibronectina humana correspondiente. En particular, el bucle FG del ^{10}Fn3 humano tiene 12 restos de longitud, mientras que el bucle correspondiente en las cadenas pesadas de anticuerpos varía entre 14-28 restos. Para optimizar la unión a antígeno, por lo tanto, la longitud del bucle FG de ^{10}Fn3 puede estar alterada en la longitud así como en la secuencia para obtener la mayor flexibilidad y afinidad posibles en la unión a antígeno.

En algunas modalidades de las moléculas de ^{10}Fn3, el bucle BC alterado tiene hasta 10 sustituciones de aminoácidos, hasta 9 deleciones de aminoácidos, hasta 10 inserciones de aminoácidos o una combinación de sustituciones y deleciones o inserciones. En algunas modalidades, el bucle DE alterado tiene hasta 6 sustituciones de aminoácidos, hasta 5 deleciones de aminoácidos, hasta 14 inserciones de

aminoácidos o una combinación de sustituciones y deleciones o inserciones. En algunas modalidades, el bucle FG tiene hasta 12 sustituciones de aminoácidos, hasta 11 deleciones de aminoácidos, hasta 28 inserciones de aminoácidos o una combinación de sustituciones y deleciones o inserciones.

El ^{10}Fn3 de origen natural comprende un motivo de unión a integrina "arginina-glicina-ácido aspártico" (RGD) en el bucle FG. Los multímeros preferidos de ^{10}Fn3 carecen de un motivo de unión a integrina RGD.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína similar a anticuerpo que comprende a) un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 5, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 5 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-92 de la SEC ID N°: 5; unido covalentemente o no covalentemente con b) un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 3 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-83 de la SEC ID N°: 3. En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de

aminoácidos que es idéntica al menos en el 80, 90, 95, 98, 99 o el 100% a la SEC ID N°: 5. En algunas modalidades, el ^{10}Fn3 de unión a IGFIR tiene una secuencia de aminoácidos que es idéntica al menos en el 80, 90, 95, 98, 99 o el 100% a la SEC ID N° 3. En algunas modalidades, el agente de unión a E/I comprende una secuencia de aminoácidos que idéntica al menos en el 80, 85, 90, 95, 98, 99 o el 100% a la SEC ID N°: 20, 21, 23, 24, 90, 92, 101 ó 103.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína similar a anticuerpo que comprende a) un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 7, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 7 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-87 de la SEC ID N°: 7; unido covalentemente o no covalentemente con b) un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 3 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-83 de la SEC ID N°: 3. En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos que es idéntica al menos en el 80, 90, 95, 98 o

el 100% a la SEC ID N°: 7. En algunas modalidades, el ^{10}Fn3 de unión a IGFIR tiene una secuencia de aminoácidos idéntica al menos en el 80, 90, 95, 98 o el 100% a la SEC ID N° 3. En algunas modalidades, el agente de unión a E/I comprende una secuencia de aminoácidos que es idéntica al menos en el 80, 85, 90, 95, 98 o el 100% a la SEC ID N°: 26, 27, 29, 30, 89, 91, 100 ó 102.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína similar a anticuerpo que comprende a) un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 82, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 82 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-87 de la SEC ID N°: 82; unido covalentemente o no covalentemente con b) un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 3 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-83 de la SEC ID N°: 3. En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica al menos en el 80, 90, 95, 98 o el 100% a la SEC ID N°: 82. En algunas modalidades, el ^{10}Fn3 de unión

a IGFIR tiene una secuencia de aminoácidos idéntica al menos en el 80, 90, 95, 98 o el 100% a la SEC ID N°: 3. En algunas modalidades, el agente de unión a E/I comprende una secuencia de aminoácidos idéntica al menos en el 80, 85, 90, 95, 98 o el 100% a la SEC ID N°: 53, 54, 87, 88, 98, 99, 104 ó 105.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína similar a anticuerpo que comprende a) un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 106, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 106 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-92 de la SEC ID N°: 106; unido covalentemente o no covalentemente con b) un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 3 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-83 de la SEC ID N°: 3. En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica al menos en el 80, 90, 95, 98 o el 100% a la SEC ID N°: 106. En algunas modalidades, el ^{10}Fn3 de unión a IGFIR tiene una secuencia de aminoácidos idéntica al menos en el 80, 90, 95, 98 o el 100% a la SEC ID N°: 3. En

algunas modalidades, el agente de unión a E/I comprende una secuencia de aminoácidos idéntica al menos en el 80, 85, 90, 95, 98 o el 100% a las SEC ID N°: 118-125.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína similar a anticuerpo que comprende a) un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 112, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 112 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-92 de la SEC ID N°: 112; unido covalentemente o no covalentemente con b) un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 3 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-83 de la SEC ID N°: 3. En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica al menos en el 80, 90, 95, 98 o el 100% a la SEC ID N°: 112. En algunas modalidades, el ^{10}Fn3 de unión a IGFIR tiene una secuencia de aminoácidos idéntica al menos en el 80, 90, 95, 98 o el 100% a la SEC ID N°: 3. En algunas modalidades, el agente de unión a E/I comprende una secuencia de aminoácidos idéntica al menos en el 80, 85, 90,

95, 98 o el 100% a las SEC ID N°: 126-133.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende a) un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 13-22 de la SEC ID N°: 141, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 43-48 de la SEC ID N°: 141 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 68-84 de la SEC ID N°: 141; unido de forma covalente o no covalente a b) un ^{10}Fn3 de unión a IGF-IR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 3 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-83 de la SEC ID N°: 3. En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95, 98 o 100% a las SEC ID N°: 140, 141, 142 ó 300. En algunas modalidades, el ^{10}Fn3 de unión a IGFIR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95, 98 o 100% a la SEC ID N°: 3. En algunas modalidades, el agente de unión a E/I comprende una secuencia de aminoácidos al menos un 80, 85, 90, 95, 98 o 100% idéntica a las SEC ID N°: 149-154.

En algunas modalidades, un agente de unión a E/I es

un dímero de proteína de tipo anticuerpo que comprende a) un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 13-22 de la SEC ID N°: 156, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 43-48 de la SEC ID N°: 156 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 68-84 de la SEC ID N°: 156; unido de forma covalente o no covalente a b) un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 3 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-83 de la SEC ID N°: 3. En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95, 98 o 100% a las SEC ID N°: 155, 156, 157 ó 305. En algunas modalidades, el ^{10}Fn3 de unión a IGFIR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95, 98 o 100% a la SEC ID N°: 3. En algunas modalidades, el agente de unión a E/I comprende una secuencia de aminoácidos al menos un 80, 85, 90, 95, 98 o 100% idéntica a las SEC ID N°: 158-166.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende a) un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la

secuencia de aminoácidos expuesta en los aminoácidos 13-22 de la SEC ID N°: 171, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 43-48 de la SEC ID N°: 171 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 68-84 de la SEC ID N°: 171; unido de forma covalente o no covalente a b) un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 3, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-83 de la SEC ID N°: 3. En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95, 98 o 100% a las SEC ID N°: 170, 171, 172 ó 311. En algunas modalidades, el ^{10}Fn3 de unión a IGFIR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95, 98 ó 100% a las SEC ID N°: 3. En algunas modalidades, el agente de unión a E/I comprende una secuencia de aminoácidos al menos un 80, 85, 90, 95, 98 o 100% idéntica a las SEC ID N°: 179-184.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende a) un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 13-22 de la SEC ID N°: 186, un bucle DE que tiene la secuencia de

aminoácidos expuesta en los aminoácidos 43-48 de la SEC ID N°: 186, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 68-84 de la SEC ID N°: 186; unido de forma covalente o no covalente a b) un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 3, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-83 de la SEC ID N°: 3. En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95, 98 o 100% a las SEC ID N°: 185, 186, 187 ó 320. En algunas modalidades, el ^{10}Fn3 de unión a IGFIR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95, 98 o 100% a la SEC ID N°: 3. En algunas modalidades, el agente de unión a E/I comprende una secuencia de aminoácidos al menos un 80, 85, 90, 95, 98 o 100% idéntica a las SEC ID N°: 192-197.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende a) un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 13-22 de la SEC ID N°: 199, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 43-48 de la SEC ID N°: 199, y un bucle FG que tiene la secuencia de aminoácidos

expuesta en los aminoácidos 68-84 de la SEC ID N°: 199; unido de forma covalente o no covalente a b) un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 3, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-83 de la SEC ID N°: 3. En algunas modalidades, el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95, 98 o 100% a las SEC ID N°: 198, 199, 200 ó 327. En algunas modalidades, el ^{10}Fn3 de unión a IGFIR tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95, 98 o 100% a las SEC ID N°: 3. En algunas modalidades, el agente de unión a E/I comprende una secuencia de aminoácidos al menos un 80, 85, 90, 95, 98 o 100% idéntica a las SEC ID N°: 205-210.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína similar a anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos X_aSARLKVAX_b (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°: 48) y un bucle FG que tiene la secuencia de aminoácidos X_eRFRDYQX_f (SEC ID N°: 50); unida covalentemente o no covalentemente con un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos X_gDSGRGSYQX_h

(SEC ID N°: 40), un bucle DE que tiene la secuencia de aminoácidos X_iGPVHX_j (SEC ID N°: 42) y un bucle FG que tiene la secuencia de aminoácidos $X_kDHKPHADGPHTYHEX_l$ (SEC ID N°: 44); donde X es cualquier aminoácido y a, b, c, d, e, f, g, h, i, j, k y l son números enteros seleccionados independientemente de 0 a 5. En algunas modalidades, a, g y l son 2; b-f e i-k son 1; y h es cero. En algunas modalidades, a-l son cero.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína similar a anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47) y un bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°: 49); unido covalentemente o no covalentemente con un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos SWDSGRGSYQ (SEC ID N°: 39), un bucle DE que tiene la secuencia de aminoácidos PGPVHT (SEC ID N°: 41) y un bucle FG que tiene la secuencia de aminoácidos TDHKPHADGPHTYHESP (SEC ID N°: 43).

En algunas modalidades, un agente de unión a E/I es un dímero de proteína similar a anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos $X_aSARLKVAX_b$ (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°:

48) y un bucle FG que tiene la secuencia de aminoácidos $X_eRFRDYQX_f$ (SEC ID N°: 50); unido covalentemente o no covalentemente con un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos $X_mVAGAEDYQX_n$ (SEC ID N°: 34), un bucle DE que tiene la secuencia de aminoácidos X_oHDLVX_p (SEC ID N°: 36) y un bucle FG que tiene la secuencia de aminoácidos $X_qDMMHVEYTEHX_r$ (SEC ID N°: 38); donde X es cualquier aminoácido y a, b, c, d, e, f, m, n, o, p, q y r son números enteros de 0 a 5, independientemente. En algunas modalidades, a y m son 2; b-f y o-r son 1; y n es cero. En algunas modalidades, a-f y m-r son cero.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína similar a anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47) y un bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°: 49); unido covalentemente o no covalentemente con un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos SWVAGAEDYQ (SEC ID N°: 33), un bucle DE que tiene la secuencia de aminoácidos PHDLVT (SEC ID N°: 35) y un bucle FG que tiene la secuencia de aminoácidos TDMMHVEYTEHP (SEC ID N°: 37).

En algunas modalidades, un agente de unión a E/I es un dímero de proteína similar a anticuerpo que comprende un

^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos $X_aSARLKVAX_b$ (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°: 48) y un bucle FG que tiene la secuencia de aminoácidos $X_eRFRDYQX_f$ (SEC ID N°: 50); unida covalentemente o no covalentemente con un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos $X_sLPGKLRYQX_t$ (SEC ID N°: 60), un bucle DE que tiene la secuencia de aminoácidos X_uHDLRX_w (SEC ID N°: 62) y un bucle FG que tiene la secuencia de aminoácidos $X_yNMMHVEYSEYX_z$ (SEC ID N°: 64); donde X es cualquier aminoácido y a, b, c, d, e, f, s, t, u, w, y y z son números enteros de 0 a 5, independientemente. En algunas modalidades, a y s son 2; b-f, u, w, y z son 1; y t es cero. En algunas modalidades, a-f, s-u, w, y y z son cero.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína similar a anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47) y un bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°: 49); unida covalentemente o no covalentemente con un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos SWLPGKLRYQ (SEC ID N°: 59), un bucle DE que tiene la secuencia de

aminoácidos PHDLRT (SEC ID N°: 61) y un bucle FG que tiene la secuencia de aminoácidos TNMMHVEYSEYP (SEC ID N°: 63).

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos X_aSARLKVAX_b (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°: 48), y un bucle FG que tiene la secuencia de aminoácidos X_eRFRDYQX_f (SEC ID N°: 50); unido de forma covalente o no covalente a un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos X_gHERDGSRQX_h (SEC ID N°: 134), un bucle DE que tiene la secuencia de aminoácidos X_iGGVRX_j (SEC ID N°: 135), y un bucle FG que tiene la secuencia de aminoácidos X_kDYFNPTTHEYIYQTTX_l (SEC ID N°: 136); donde X es cualquier aminoácido y a, b, c, d, e, f, g, h, i, j, k y l son números enteros de 0 a 5, independientemente. En algunas modalidades, a y g son 2; b-f e i-l son 1; y h es cero. En algunas modalidades, a-l son cero.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína similar a anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47) y un bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°: 49); unida covalentemente o no

covalentemente con un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos SWHERDGSRQ (SEC ID N°: 109), un bucle DE que tiene la secuencia de aminoácidos PGGVRT (SEC ID N°: 110) y un bucle FG que tiene la secuencia de aminoácidos TDYFNPTTHEYIYQTTP (SEC ID N°: 111).

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos X_aSARLKVAX_b (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°: 48), y un bucle FG que tiene la secuencia de aminoácidos X_eRFRDYQX_f (SEC ID N°: 50); unido de forma covalente o no covalente a un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos X_gWAPVDRYQX_h (SEC ID N°: 137), un bucle DE que tiene la secuencia de aminoácidos X_iRDVYX_j (SEC ID N°: 138), y un bucle FG que tiene la secuencia de aminoácidos X_kDYKPHADGPHTYHESX_l (SEC ID N°: 139); donde X es cualquier aminoácido y a, b, c, d, e, f, g, h, i, j, k y l son números enteros de 0 a 5, independientemente. En algunas modalidades, a y g son 2; b-f e i-l son 1; y h es cero. En algunas modalidades, a-l son cero.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína similar a anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la

secuencia de aminoácidos SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47) y un bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°: 49); unida covalentemente o no covalentemente con un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos SWWAPVDRYQ (SEC ID N°: 115), un bucle DE que tiene la secuencia de aminoácidos PRDVYT (SEC ID N°: 116) y un bucle FG que tiene la secuencia de aminoácidos TDYKPHADGPHTYHESP (SEC ID N°: 117).

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos X_aSARLKVAX_b (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°: 48), y un bucle FG que tiene la secuencia de aminoácidos X_eRFRDYQX_f (SEC ID N°: 50); unido de forma covalente o no covalente a un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos X_gTQGSTHYQX_h (SEC ID N°: 146), un bucle DE que tiene la secuencia de aminoácidos X_iGMVYX_j (SEC ID N°: 147), y un bucle FG que tiene la secuencia de aminoácidos X_kDYFDRSTHEYKYRTTX_l (SEC ID N°: 148); donde X es cualquier aminoácido y a, b, c, d, e, f, g, h, i, j, k y l son números enteros de 0 a 5, independientemente. En algunas modalidades, a y g son 2; b-f e i-l son 1; y h es

cero. En algunas modalidades, a-l son cero.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47), y un bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°: 49); unido de forma covalente o no covalente a un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos SWTQGSTHYQ (SEC ID N°: 143), un bucle DE que tiene la secuencia de aminoácidos PGMVYT (SEC ID N°: 144), y un bucle FG que tiene la secuencia de aminoácidos TDYFDRSTHEYKYRTTP (SEC ID N°: 145).

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos X_aSARLKVAX_b (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°: 48), y un bucle FG que tiene la secuencia de aminoácidos X_eRFRDYQX_f (SEC ID N°: 50); unido de forma covalente o no covalente a un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos X_gYWEGLPYQX_h (SEC ID N°: 161), un bucle DE que tiene la secuencia de aminoácidos X_iRDVNX_j (SEC ID N°: 162), y un bucle FG que tiene la secuencia de aminoácidos X_kDWYNPDTHEYIYHTIX_l (SEC ID N°: 163);

donde X es cualquier aminoácido y a, b, c, d, e, f, g, h, i, j, k y l son números enteros de 0 a 5, independientemente. En algunas modalidades, a y g son 2; b-f e i-l son 1; y h es cero. En algunas modalidades, a-l son cero.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47), y un bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°: 49); unido de forma covalente o no covalente a un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos SWYWEGLPYQ (SEC ID N°: 158), un bucle DE que tiene la secuencia de aminoácidos PRDVNT (SEC ID N°: 159), y un bucle FG que tiene la secuencia de aminoácidos TDWYNPDTHEYIYHTIP (SEC ID N°: 160).

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos X_aSARLKVAX_b (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°: 48), y un bucle FG que tiene la secuencia de aminoácidos X_eRFRDYQX_f (SEC ID N°: 50); unido de forma covalente o no covalente a un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos X_gASNRGTYQX_h (SEC ID N°:

176), un bucle DE que tiene la secuencia de aminoácidos X_iGGVSX_j (SEC ID N°: 177), y un bucle FG que tiene la secuencia de aminoácidos $X_kDAFNPTTHEYNYFTTX_l$ (SEC ID N°: 178); donde X es cualquier aminoácido y a, b, c, d, e, f, g, h, i, j, k y l son números enteros de 0 a 5, independientemente. En algunas modalidades, a y g son 2; b-f e i-l son 1; y h es cero. En algunas modalidades, a-l son cero.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47), y un bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°: 49); unido de forma covalente o no covalente a un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos SWASNRGTYQ (SEC ID N°: 173), un bucle DE que tiene la secuencia de aminoácidos PGGVST (SEC ID N°: 174), y un bucle FG que tiene la secuencia de aminoácidos TDAFNPTTHEYNYFTTP (SEC ID N°: 175).

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos $X_aSARLKVAX_b$ (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°: 48), y un bucle FG que tiene la secuencia de aminoácidos

$X_eRFRDYQX_f$ (SEC ID N°: 50); unido de forma covalente o no covalente a un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos $X_gDAPTSRYQX_h$ (SEC ID N°: 190), un bucle DE que tiene la secuencia de aminoácidos X_iGGLSX_j (SEC ID N°: 191), y un bucle FG que tiene la secuencia de aminoácidos $X_kDYKPHADGPHTYHESX_l$ (SEC ID N°: 139); donde X es cualquier aminoácido y a, b, c, d, e, f, g, h, i, j, k y l son números enteros de 0 a 5, independientemente. En algunas modalidades, a y g son 2; b-f e i-l son 1; y h es cero. En algunas modalidades, a-l son cero.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47), y un bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°: 49); unido de forma covalente o no covalente a un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos SWDAPTSRYQ (SEC ID N°: 188), un bucle DE que tiene la secuencia de aminoácidos PGGLST (SEC ID N°: 189), y un bucle FG que tiene la secuencia de aminoácidos TDYKPHADGPHTYHESP (SEC ID N°: 117).

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la

secuencia de aminoácidos $X_aSARLKVAX_b$ (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°: 48), y un bucle FG que tiene la secuencia de aminoácidos $X_eRFRDYQX_f$ (SEC ID N°: 50); unido de forma covalente o no covalente a un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos $X_gDAGAVTYQX_h$ (SEC ID N°: 203), un bucle DE que tiene la secuencia de aminoácidos X_iGGVRX_j (SEC ID N°: 135), y un bucle FG que tiene la secuencia de aminoácidos $X_kDYKPHADGPHTYHEYX_l$ (SEC ID N°: 204); donde X es cualquier aminoácido y a, b, c, d, e, f, g, h, i, j, k y l son números enteros de 0 a 5, independientemente. En algunas modalidades, a y g son 2; b-f e i-l son 1; y h es cero. En algunas modalidades, a-l son cero.

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47), y un bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°: 49); unido de forma covalente o no covalente a un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos SWDAGAVTYQ (SEC ID N°: 201), un bucle DE que tiene la secuencia de aminoácidos PGGVRT (SEC ID N°: 110), y un bucle FG que tiene la secuencia de aminoácidos TDYKPHADGPHTYHEYP (SEC ID N°: 202).

En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende a) un ^{10}Fn3 de unión a IGFIR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 23-29 de la SEC ID N°: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 52-55 de la SEC ID N°: 3, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 77-82 de la SEC ID N°: 3; unido de forma covalente o no covalente a b) un ^{10}Fn3 de unión a EGFR que comprende los bucles BC, DE y FG como se expone en una cualquiera de las SEC ID N°: 219-327 (véase, por ejemplo, la Figura 45 en la que las secuencias de bucles BC, DE y FG para cada ^{10}Fn3 de unión a EGFR están subrayados). En algunas modalidades, un agente de unión a E/I es un dímero de proteína de tipo anticuerpo que comprende a) un ^{10}Fn3 de unión a IGFR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 23-29 de la SEC ID N°: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 52-55 de la SEC ID N°: 3, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 77-82 de la SEC ID N°: 3; unido de forma covalente o no covalente a b) un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos correspondientes a los restos aminoacídicos 23-30 de la SEC ID N°: 1 de una cualquiera de

las SEC ID N°: 5-8, 52, 66-68, 106-108, 112-114, 140-142, 155-157, 170-172, 182, 185-187, 198-200 ó 219-327, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos correspondientes a los restos aminoacídicos 52-55 de la SEC ID N°: 1 de una cualquiera de las SEC ID N°: 5-8, 52, 66-68, 106-108, 112-114, 140-142, 155-157, 170-172, 182, 185-187, 198-200 ó 219-327, y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos correspondiente a los restos aminoacídicos 77-86 de la SEC ID N°: 15-8, 52, 66-68, 106-108, 112-114, 140-142, 155-157, 170-172, 182, 185-187, 198-200 o 219-327. En algunas modalidades, el ^{10}Fn3 de unión a EGFR de un dímero de proteína de tipo anticuerpo comprende una secuencia de aminoácidos idéntica en al menos un 80, 90, 95 o 100% a la secuencia de aminoácidos de restos aminoacídicos correspondientes a E9 de la SEC ID N°: 1 hasta T94 de la SEC ID N°: 1 de una cualquiera de las SEC ID N°: 5-8, 52, 66-68, 106-108, 112-114, 140-142, 155-157, 170-172, 182, 185-187, 198-200, o 219-327. En algunas modalidades, el ^{10}Fn3 de unión a IGFIR de un dímero de proteína de tipo anticuerpo tiene una secuencia de aminoácidos idéntica en al menos un 80, 90, 95, 98, 99 o 100% a la secuencia de aminoácidos de restos aminoacídicos correspondientes a E9 de la SEC ID N°: 1 hasta T94 de la SEC ID N°: 1 de la SEC ID N°: 3. En algunas modalidades, el agente de unión a E/I comprende una secuencia de aminoácidos

idéntica en al menos un 80, 85, 90, 95, 98, 99 o 100% a una cualquiera de las SEC ID N°: 20-31, 53-58, 87-92, 98-105, 118-133, 149-154, 164-169, 179-184, 192-197, 205-210 y 211-216.

Preferiblemente, X como se define en este documento es un aminoácido de origen natural.

En ciertas modalidades, los agentes de unión a E, o los monómeros de E y/o I de los agentes de unión a E/I descritos en el presente documento pueden contener una sustitución del aminoácido Ser por Cys en una posición correspondiente a la serina 62 o la serina 91 de la SEC ID N°: 1.

En ciertos aspectos, la descripción proporciona secuencias peptídicas cortas que median en la unión a EGFR. Los ejemplos de tales secuencias incluyen los restos aminoacídicos que se corresponden a los bucles BC, DE y FG de las SEC ID N°: 5, 7, 82, 106, 112, 141, 156, 171, 186 y 199. Otros ejemplos de dichas secuencias incluyen los restos aminoacídicos que corresponden a los bucles BC, DE y FG de las SEC ID N°: 219-327. En algunas modalidades, los péptidos se unen a su respectivo ligando con una constante de disociación (K_D) menor de 500 nM, 100 nM, 50 nM, 5 nM o menos. Tales secuencias pueden mediar en la unión a ligando en una forma aislada o cuando se insertan en una estructura proteica particular, tal como un dominio de inmunoglobulina o

similar a inmunoglobulina.

En una modalidad, un dímero de proteína similar a anticuerpo comprende un polipéptido que tiene la estructura A-B-C, donde A es un polipéptido que comprende, está constituido esencialmente por, o que está constituido por un dominio de ^{10}Fn3 que se une a EGFR, B es un adaptador polipeptídico y C es un polipéptido que comprende, que está constituido esencialmente por o que está constituido por un dominio de ^{10}Fn3 que se une a IGF-IR. En otra modalidad, un dímero de proteína similar a anticuerpo comprende un polipéptido que tiene la estructura A-B-C, donde A es un polipéptido que comprende, que está constituido esencialmente por, o que está constituido por un dominio de ^{10}Fn3 que se une a IGF-IR, B es un adaptador polipeptídico y C es un polipéptido que comprende, está constituido esencialmente por o que está constituido por un dominio de ^{10}Fn3 que se une a EGFR. Los ejemplos específicos de dímeros de proteína similar a anticuerpo que tienen la estructura A-B-C son polipéptidos que comprenden (i) un polipéptido que tiene una secuencia de aminoácidos expuesta en una cualquiera de las SEC ID N°: 20-31, 53-58, 87-92, 98-105, 118-133, 149-154, 164-169, 179-184, 192-197, 205-210 y 211-216, o (ii) un polipéptido que comprende una secuencia de aminoácidos que es idéntica al menos en el 85%, 90%, 95%, 97%, 98% o 99% a una cualquiera de las secuencias de aminoácidos expuestas en las

SEC ID N°: 20-31, 53-58, 87-92, 98-105, 118-133, 149-154, 164-169, 179-184, 192-197, 205-210 y 211-216.

En ciertas modalidades, la región A o C es un polipéptido que comprende un dominio de ^{10}Fn3 que se une a EGFR; donde el dominio de ^{10}Fn3 tiene la estructura del N-terminal al C-terminal: cadena beta A, bucle AB, cadena beta B, bucle BC, cadena beta C, bucle CD, cadena beta D, bucle DE, cadena beta E, bucle EF, cadena beta F, bucle FG, cadena beta G; donde: (i) el bucle BC tiene la secuencia de aminoácidos de la SEC ID N°: 33 ó 34, el bucle DE tiene la secuencia de aminoácidos de la SEC ID N°: 35 ó 36 y el bucle FG tiene la secuencia de aminoácidos de la SEC ID N°: 37 ó 38, (ii) el bucle BC tiene la secuencia de aminoácidos de la SEC ID N°: 39 ó 40, el bucle DE tiene la secuencia de aminoácidos de la SEC ID N°: 41 ó 42 y el bucle FG tiene la secuencia de aminoácidos de la SEC ID N°: 43 ó 44 o (iii) el bucle BC tiene la secuencia de aminoácidos de la SEC ID N°: 59 ó 60, el bucle DE tiene la secuencia de aminoácidos de la SEC ID N°: 61 ó 62 y el bucle FG tiene la secuencia de aminoácidos de la SEC ID N°: 63 ó 64; (iv) el bucle BC tiene la secuencia de aminoácidos de la SEC ID N°: 109 ó 134, el bucle DE tiene la secuencia de aminoácidos de la SEC ID N°: 110 ó 135, y el bucle FG tiene la secuencia de aminoácidos de la SEC ID N°: 111 ó 136, (v) el bucle BC tiene la secuencia de aminoácidos de la SEC ID N°: 115 ó 137, el bucle DE tiene

la secuencia de aminoácidos de la SEC ID N°: 116 ó 138, y el bucle FG tiene la secuencia de aminoácidos de la SEC ID N°: 117 ó 139, (vi) el bucle BC tiene la secuencia de aminoácidos de la SEC ID N°: 143 ó 146, el bucle DE tiene la secuencia de aminoácidos de la SEC ID N°: 144 ó 147, y el bucle FG tiene la secuencia de aminoácidos de la SEC ID N°: 145 ó 148, (vii) el bucle BC tiene la secuencia de aminoácidos de la SEC ID N°: 158 ó 161, el bucle DE tiene la secuencia de aminoácidos de la SEC ID N°: 159 ó 162, y el bucle FG tiene la secuencia de aminoácidos de la SEC ID N°: 160 ó 163, (viii) el bucle BC tiene la secuencia de aminoácidos de la SEC ID N°: 173 ó 176, el bucle DE tiene la secuencia de aminoácidos de la SEC ID N°: 174 ó 177, y el bucle FG tiene la secuencia de aminoácidos de la SEC ID N°: 175 ó 178, (ix) el bucle BC tiene la secuencia de aminoácidos de la SEC ID N°: 188 ó 190, el bucle DE tiene la secuencia de aminoácidos de la SEC ID N°: 189 ó 191, y el bucle FG tiene la secuencia de aminoácidos de la SEC ID N°: 117 ó 139, (x) el bucle BC tiene la secuencia de aminoácidos de la SEC ID N°: 201 ó 203, el bucle DE tiene la secuencia de aminoácidos de la SEC ID N°: 110 ó 135, y el bucle FG tiene la secuencia de aminoácidos de la SEC ID N°: 202 ó 204, o (xi) los bucles BC, DE y FG tiene las secuencias de aminoácidos expuestas en una cualquiera de las SEC ID N°: 219-327 (véase, por ejemplo, la Figura 45 en la que los bucles BC, DE y FG para cada una de las SEC ID N°:

219-327 están subrayados); donde el dominio de ^{10}Fn3 se pliega en una estructura similar a región variable de cadena pesada de anticuerpo; y donde el polipéptido se une a EGFR con una K_D menor de 100 nM. El dominio de ^{10}Fn3 que se une a EGFR se pliega preferiblemente en una estructura en la que las 7 cadenas beta están distribuidas entre dos láminas beta que se compactan entre sí formando un núcleo estable y donde las cadenas beta están conectadas por los seis bucles que están expuestos a disolvente. En modalidades ilustrativas, el dominio de ^{10}Fn3 tiene una longitud de 80-150 aminoácidos.

En modalidades a modo de ejemplo,, la región A o C es un dominio de ^{10}Fn3 que se une a EGFR con una K_D menor de 100 nM que tiene una secuencia seleccionada entre el grupo constituido por la SEC ID N°: 83-85 y 466-472 como se expone a continuación:

EVVAATX$_{n1}$SLLIX$_{a1}$**SWVAGAEDYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PHDLVT**X$_{a4}$ATIX$_{n3}$DYT ITVYAVX$_{a5}$**TDMMHVEYTEHP**X$_{a6}$ISINYRT (SEC ID N°: 83);

EVVAATX$_{n1}$SLLIX$_{a1}$**SWDSGRGSYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PGPVHT**X$_{a4}$ATIX$_{n3}$DYT ITVYAVX$_{a5}$**TDHKPHADGPHTYHESP**X$_{a6}$ISINYRT (SEC ID N°: 84); o

EVVAATX$_{n1}$SLLIX$_{a1}$**SWLPGKLRYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PHDLRT**X$_{a4}$ATIX$_{n3}$DYT ITVYAVX$_{a5}$**TNMMHVEYSEYP**X$_{a6}$ISINYRT (SEC ID N°: 85).

EVVAATX$_{n1}$SLLIX$_{a1}$**SWHERDGSRQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PGGVRT**X$_{a4}$ATIX$_{n3}$DYT

ITVYAVX$_{a5}$**TDYFNPTTHEYIYQTTP**X$_{a6}$ISINYRT (SEC ID N°: 466).

EVVAATX$_{n1}$SLLIX$_{a1}$**SWWAPVDRYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PRDVYT**X$_{a4}$ATIX$_{n3}$DYT ITVYAVX$_{a5}$**TDYKPHADGPHTYHESP**X$_{a6}$ISINYRT (SEC ID N°: 467).

EVVAATX$_{n1}$SLLIX$_{a1}$**SWTQGSTHYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PGMVYT**X$_{a4}$ATIX$_{n3}$DYT ITVYAVX$_{a5}$**TDYFDRSTHEYKYRTTP**X$_{a6}$ISINYRT (SEC ID N°: 468).

EVVAATX$_{n1}$SLLIX$_{a1}$**SWYWEGLPYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PRDVNT**X$_{a4}$ATIX$_{n3}$DYT ITVYAVX$_{a5}$**TDWYNPDTHEYIYHTIP**X$_{a6}$ISINYRT (SEC ID N°: 469).

EVVAATX$_{n1}$SLLIX$_{a1}$**SWASNRGTYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PGGVST**X$_{a4}$ATIX$_{n3}$DYT ITVYAVX$_{a5}$**TDAFNPTTHEYNYFTTP**X$_{a6}$ISINYRT (SEC ID N°: 470).

EVVAATX$_{n1}$SLLIX$_{a1}$**SWDAPTSRYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PGGLST**X$_{a4}$ATIX$_{n3}$DYT ITVYAVX$_{a5}$**TDYKPHADGPHTYHESP**X$_{a6}$ISINYRT (SEC ID N°: 471).

EVVAATX$_{n1}$SLLIX$_{a1}$**SWDAGAVTYQ**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PGGVRT**X$_{a4}$ATIX$_{n3}$DYT ITVYAVX$_{a5}$**TDYKPHADGPHTYHEYP**X$_{a6}$ISINYRT (SEC ID N°: 472).

En las SEC ID N°: 83-85 y 466-472, los bucles BC, DE y FG tienen una secuencia fija como se muestra en negrita, o una secuencia idéntica en al menos el 75%, 80%, 85%, 90%, 95%, 97%, 98% o 99% a las secuencias mostradas en negrita, el bucle AB se representa por X$_{n1}$, el CD se representa por X$_{n2}$ y

el bucle EF se representa por X_{n3} y las cadenas beta A-G están subrayadas. X representa cualquier aminoácido y el subíndice después de la X representa un número entero del número de aminoácidos. En particular, n1 puede ser cualquiera de 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3 ó 1-2 aminoácidos; n2 y n3 pueden ser cada uno independientemente cualquiera entre 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 ó 6-7 aminoácidos; y a1-a6 pueden comprender cada uno independientemente 0-10, 0-5, 1-10, 1-5 ó 2-5 aminoácidos. En modalidades preferidas, n1 es 2 aminoácidos, n2 es 7 aminoácidos, n3 es 7 aminoácidos y a1-a6 es 0 aminoácidos. Las secuencias de las cadenas beta pueden tener cualquiera de 0 a 10, de 0 a 8, de 0 a 6, de 0 a 5, de 0 a 4, de 0 a 3, de 0 a 2 o de 0 a 1 sustituciones, deleciones o adiciones a lo largo de las 7 regiones de armazón con respecto a los correspondientes aminoácidos mostrados en la SEC ID N°: 1. En una modalidad ilustrativa, las secuencias de la cadena beta pueden tener cualquiera de 0 a 10, de 0 a 8, de 0 a 6, de 0 a 5, de 0 a 4, de 0 a 3, de 0 a 2 o de 0 a 1 sustituciones conservativas a lo largo de las 7 regiones de armazón con respecto a los aminoácidos correspondientes mostrados en la SEC ID N°: 1. En ciertas modalidades, los restos aminoacídicos centrales se fijan y cualquier sustitución, sustitución conservativa, deleción o adición tiene lugar en restos diferentes a los restos

aminoacídicos centrales. En ciertas modalidades, el agente de unión a EGFR se representa por una de las siguientes secuencias de aminoácidos:

EVVAATPTSLLI**SWVAGAEDYQ**YYRITYGETGGNSPVQEFTV**PHDLVT**ATISGLKPGVDYT ITVYAV**TDMMHVEYTEHP**ISINYRT (SEC ID N°: 66);

EVVAATPTSLLI**SWDSGRGSYQ**YYRITYGETGGNSPVQEFTV**PGPVHT**ATISGLKPGVDYT ITVYAV**TDHKPHADGPHTYHESP**ISINYRT (SEC ID N°: 67); o

EVVAATPTSLLISW**LPGKLRYQ**YYRITYGETGGNSPVQEFTV**PHDLR**TATISGLKPGVDYT ITVYAV**TNMMHVEYSEY**PISINYRT (SEC ID N°: 68);

EVVAATPTSLLISW**HERDGSRQ**YYRITYGETGGNSPVQEFTV**PGGVR**TATISGLKPGVDYT ITVYAV**TDYFNPTTHEYIYQTT**PISINYRT (SEC ID N°: 108); o

EVVAATPTSLLISW**WAPVDRYQ**YYRITYGETGGNSPVQEFTV**PRDVY**TATISGLKPGVDYT ITVYAV**TDYKPHADGPHTYHES**PISINYRT (SEC ID N°: 114).

EVVAATPTSLLISW**TQGSTHYQ**YYRITYGETGGNSPVQEFTVP**GMVY**TATISGLKPGVDYT ITVYAVT**DYFDRSTHEYKYRTT**PISINYRT (SEC ID N°: 141)

EVVAATPTSLLISW**YWEGLPYQ**YYRITYGETGGNSPVQEFTVP**RDVN**TATISGLKPGVDYT ITVYAVT**DWYNPDTHEYIYHTI**PISINYRT (SEC ID N°: 156)

EVVAATPTSLLISW**ASNRGTYQ**YYRITYGETGGNSPVQEFTVP**GGVS**TATISGLKPGVDYT

ITVYAVT**DAFNPTTHEYNYFTT**PISINYRT (SEC ID N°: 171)

EVVAATPTSLLISW**DAPTSRYQ**YYRITYGETGGNSPVQEFTVP**GGLS**TATISGLKPGVDYT ITVYAVT**DYKPHADGPHTYHES**PISINYRT (SEC ID N°: 186)

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EVVAATPTSLLISW**DAGAVTYQ**YYRITYGETGGNSPVQEFTVP**GGVR**TATISGLKPGVDYT ITVYAVT**DYKPHADGPHTYHEY**PISINYRT (SEC ID N°: 199)

En las SEC ID N°: 66-68, 108, 114, 141, 156, 171, 186 y 199, la secuencia de los bucles BC, DE y FG tiene una secuencia fija como se muestra en negrita, o una secuencia idéntica en al menos un 75%, 80%, 85%, 90%, 95%, 97%, 98% o 99% a las secuencias mostradas en negrita, y la secuencia remanente que está subrayada (por ejemplo, la secuencia de las 7 cadenas beta y los bucles AB, CD y EF) tiene cualquiera de 0 a 20, de 0 a 15, de 0 a 10, de 0 a 8, de 0 a 6, de 0 a 5, de 0 a 4, de 0 a 3, de 0 a 2 o de 0 a 1 sustituciones, sustituciones conservativas, deleciones o adiciones con respecto a los correspondientes aminoácidos mostrados en las SEC ID N°: 66-68, 108, 114, 141, 156, 171, 186 y 199. En ciertas modalidades, los restos aminoacídicos centrales se fijan y cualquier sustitución, sustitución conservativa, deleción o adición tiene lugar en restos diferentes a los restos aminoacídicos centrales. El dominio de ^{10}Fn3 que se une a EGFR puede comprender opcionalmente una extensión N-

terminal de 1-20, 1-15, 1-10, 1-8, 1-5, 1-4, 1-3, 1-2 ó 1 aminoácido de longitud. Las extensiones N-terminales ilustrativas incluyen (representadas por el código de aminoácidos de una única letra) M, MG, G, MGVSDVPRDL (SEC ID N°: 69), GVSDVPRDL (SEC ID N°: 70) y VSDVPRDL (SEC ID N°: 71) o truncamientos N-terminales de una cualquiera de las SEC ID N°: 69, 70 ó 71. Otras extensiones N-terminales adecuadas incluyen, por ejemplo, X_nSDVPRDL (SEC ID N°: 72), X_nDVPRDL (SEC ID N°: 73), X_nVPRDL (SEC ID N°: 74), X_nPRDL (SEC ID N°: 75), X_nRDL (SEC ID N°: 76), X_nDL (SEC ID N°: 77) o X_nL, donde n = 0, 1 ó 2 aminoácidos, donde cuando n = 1, X es Met o Gly y cuando n = 2, X es Met-Gly. El dominio de ^{10}Fn3 que se une a EGFR puede comprender opcionalmente una cola C-terminal. Ejemplos de colas C-terminales incluyen polipéptidos que tienen 1-20, 1-15, 1-10, 1-8, 1-5, 1-4, 1-3, 1-2 ó 1 aminoácido de longitud. Los ejemplos específicos de colas C-terminales incluyen EIDKPSQ (SEC ID N°: 9), EIDKPCQ (SEC ID N°: 10) y EIDK (SEC ID N°: 78). En otras modalidades, las colas C-terminales adecuadas pueden ser un fragmento truncado en el C-terminal de la SEC ID N°: 9, 10 ó 78, incluyendo, por ejemplo, una de las siguientes secuencias de aminoácidos (representadas por el código de aminoácidos de una única letra): E, EI, EID, EIDKP (SEC ID N°: 79), EIDKPS (SEC ID N°: 80) o EIDKPC (SEC ID N°: 81). Otras colas C-terminales adecuadas incluyen, por ejemplo, ES, EC, EGS, EGC, EGSGS (SEC

ID N°: 96) o EGSGC (SEC ID N°: 97) o EIEK (SEC ID N°: 217). En ciertas modalidades, el dominio de ^{10}Fn3 que se une a EGFR comprende tanto una extensión N-terminal como una cola C-terminal. En modalidades a modo de ejemplo, la región A comprende una extensión N-terminal que comienza con Gly o Met-Gly y una extensión C-terminal que no contiene ningún resto de cisteína y la región B comprende una extensión N-terminal que no comienza con una Met y una extensión C-terminal que comprende un resto de cisteína. Los ejemplos específicos de dominios de ^{10}Fn3 que se unen a EGFR son polipéptidos que comprenden (i) un polipéptido que tiene una secuencia de aminoácidos expuesta en una cualquiera de las SEC ID N°: 5-8, 52, 66-68, 82-85, 106-108, 112-114, 140-142, 155-157, 170-172, 185-187, 198-200 y 219-327, o (ii) un polipéptido que comprende una secuencia de aminoácidos que es idéntica al menos en el 85%, 90%, 95%, 97%, 98% o 99% a la secuencia de aminoácidos expuesta en una cualquiera de las SEC ID N°: 5-8, 52, 66-68, 82-85, 106-108, 112-114, 140-142, 155-157, 170-172, 185-187, 198-200 y 219-327.

En ciertas modalidades, la región A o C es un polipéptido que comprende un dominio de ^{10}Fn3 que se une a IGF-IR, donde el dominio de ^{10}Fn3 tiene la estructura del N-terminal al C-terminal: cadena beta A, bucle AB, cadena beta B, bucle BC, cadena beta C, bucle CD, cadena beta D, bucle DE, cadena beta E, bucle EF, cadena beta F, bucle FG, cadena

beta G, donde el bucle BC tiene la secuencia de aminoácidos de la SEC ID N°: 45 ó 46, el bucle DE tiene la secuencia de aminoácidos de la SEC ID N°: 47 ó 48 y el bucle FG tiene la secuencia de aminoácidos de la SEC ID N°: 49 ó 50, donde el dominio de ^{10}Fn3 se pliega en una estructura similar a región variable de cadena pesada de anticuerpo y donde el polipéptido se une a IGF-IR con una K_D menor de 100 nM. El dominio de ^{10}Fn3 que se une a IGF-IR se pliega preferiblemente en una estructura en la que las 7 cadenas beta están distribuidas entre dos láminas beta que se compactan entre sí formando un núcleo estable y en la que las cadenas beta están conectadas por los seis bucles que están expuestos a disolvente. En modalidades a modo de ejemplo, el dominio de ^{10}Fn3 tiene 80-150 aminoácidos de longitud.

En modalidades a modo de ejemplo, la región A o C es un dominio de ^{10}Fn3 que se une a IGF-IR con una K_D menor de 100 nM que tiene la secuencia expuesta a continuación:

EVVAATX$_{n1}$SLLIX$_{a1}$**SWSARLKVAR**X$_{a2}$YYRITYGEX$_{n2}$QEFTVX$_{a3}$**PKNVYT**X$_{a4}$ATIX$_{n3}$DYT ITVYAVX$_{a5}$**TRFRDYQP**X$_{a6}$ISINYRT (SEC ID N°: 86).

En la SEC ID N°: 86, los bucles BC, DE y FG tienen una secuencia fija como se muestra en negrita, o una secuencia idéntica al menos en el 75%, 80%, 85%, 90%, 95%, 97%, 98% o 99% a las secuencias mostradas en negrita, el bucle AB se representa por X_{n1}, el bucle CD se representa por X_{n2} y el bucle EF se representa por X_{n3} y las cadenas beta A-G

están subrayadas. X representa cualquier aminoácido y el subíndice después de la X representa un número entero del número de aminoácidos. En particular, n1 puede ser cualquiera de 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3 ó 1-2 aminoácidos; n2 y n3 pueden ser cada uno independientemente cualquiera de 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 ó 6-7 aminoácidos; y a1-a6 pueden comprender independientemente cada uno 0-10, 0-5, 1-10, 1-5 ó 2-5 aminoácidos. En modalidades preferidas, n1 es 2 aminoácidos, n2 es 7 aminoácidos, n3 es 7 aminoácidos y a1-a6 es 0 aminoácidos. Las secuencias de las cadenas beta pueden tener cualquiera de 0 a 10, de 0 a 8, de 0 a 6, de 0 a 5, de 0 a 4, de 0 a 3, de 0 a 2 o de 0 a 1 sustituciones, deleciones o adiciones a lo largo de las 7 regiones de armazón con respecto a los correspondientes aminoácidos mostrados en la SEC ID N°: 1. En una modalidad ilustrativa, las secuencias de las cadena beta pueden tener cualquiera de 0 a 10, de 0 a 8, de 0 a 6, de 0 a 5, de 0 a 4, de 0 a 3, de 0 a 2 o de 0 a 1 sustituciones conservativas a lo largo de las 7 regiones de armazón con respecto a los aminoácidos correspondientes mostrados en la SEC ID N°: 1. En ciertas modalidades, los restos aminoacídicos centrales se fijan y cualquier sustitución, sustitución conservativa, deleción o adición tiene lugar en restos diferentes a los restos aminoacídicos

centrales. En ciertas modalidades, el agente de unión a IGF-IR se representa por la siguiente secuencia de aminoácidos: EVVAATPTSLLI**SWSARLKVAR**YYRITYGETGGNSPVQEFTV**PKNVYT**ATISGLKPGVDYT ITVYAV**TRFRDYQP**ISINYRT (SEC ID N°: 65).

En la SEC ID N°: 65, la secuencia de los bucles BC, DE y FG tiene una secuencia fija como se muestra en negrita, o una secuencia idéntica al menos en el 75%, 80%, 85%, 90%, 95%, 97%, 98% o 99% a las secuencias mostradas en negrita, y la secuencia remanente que está subrayada (por ejemplo, la secuencia de las 7 cadenas beta y los bucles AB, CD y EF) tiene cualquiera de 0 a 20, de 0 a 15, de 0 a 10, de 0 a 8, de 0 a 6, de 0 a 5, de 0 a 4, de 0 a 3, de 0 a 2 o de 0 a 1 sustituciones, sustituciones conservativas, deleciones o adiciones con respecto a los correspondientes aminoácidos mostrados en la SEC ID N°: 65. En ciertas modalidades, los restos aminoacídicos centrales están fijados y cualquier sustitución, sustitución conservativa, deleción o adición tiene lugar en restos diferentes a los restos aminoacídicos centrales. El dominio de ^{10}Fn3 que se une a IGF-IR puede comprender opcionalmente una extensión N-terminal de 1-20, 1-15, 1-10, 1-8, 1-5, 1-4, 1-3, 1-2 ó 1 aminoácido de longitud. Las extensiones N-terminales ilustrativas incluyen (representadas por el código de aminoácidos de una única letra) M, MG, G, MGVSDVPRDL (SEC ID N°: 69), GVSDVPRDL (SEC ID N°: 70) y VSDVPRDL (SEC ID N°: 71) o truncamientos N-

terminales de una cualquiera de la SEC ID N°: 69, 70 ó 71. Otras extensiones N-terminales adecuadas incluyen, por ejemplo, X_nSDVPRDL (SEC ID N°: 72), X_nDVPRDL (SEC ID N°: 73), X_nVPRDL (SEC ID N°: 74), X_nPRDL (SEC ID N°: 75), X_nRDL (SEC ID N°: 76), X_nDL (SEC ID N°: 77) o X_nL, donde n = 0, 1 ó 2 aminoácidos, donde cuando n = 1, X es Met o Gly y cuando n = 2, X es Met-Gly. El dominio de ^{10}Fn3 que se une a IGF-IR puede comprender opcionalmente una cola C-terminal. Las colas C-terminales ejemplares incluyen polipéptidos que tienen 1-20, 1-15, 1-10, 1-8, 1-5, 1-4, 1-3, 1-2 ó 1 aminoácido de longitud. Los ejemplos específicos de colas C-terminales incluyen EIDKPSQ (SEC ID N°: 9), EIDKPCQ (SEC ID N°: 10) y EIDK (SEC ID N°: 78). En otras modalidades, las colas C-terminales adecuadas pueden ser un fragmento truncado en el C-terminal de la SEC ID N°: 9, 10 ó 78, que incluyen, por ejemplo, una de las siguientes secuencias de aminoácidos (representadas por el código de aminoácidos de una única letra): E, EI, EID, EIDKP (SEC ID N°: 79), EIDKPS (SEC ID N°: 80) o EIDKPC (SEC ID N°: 81). Otras colas C-terminales adecuadas incluyen, por ejemplo, ES, EC, EGS, EGC, EGSGS (SEC ID N°: 96) o EGSGC (SEC ID N°: 97) o EIEK (SEC ID N°: 217). En ciertas modalidades, el dominio de ^{10}Fn3 que se une a IGF-IR comprende tanto una extensión N-terminal como una cola C-terminal. En modalidades a modo de ejemplo, la región A comprende una extensión N-terminal que comienza con Gly o

Met-Gly y una extensión C-terminal que no contiene ningún resto de cisteína y la región B comprende una extensión N-terminal que no comienza con una Met y una extensión C-terminal que comprende un resto de cisteína. Los ejemplos específicos de dominios de ^{10}Fn3 que se unen a IGF-IR son polipéptidos que comprenden (i) un polipéptido que tiene una secuencia de aminoácidos expuesta en una cualquiera de las SEC ID N°: 3, 4, 65 u 86 o (ii) un polipéptido que comprende una secuencia de aminoácidos que es idéntica al menos en el 85%, 90%, 95%, 97%, 98% o 99% a la secuencia de aminoácidos expuesta en una cualquiera de las SEC ID N°: 3, 4, 65 u 86.

La región B es un adaptador como se describe adicionalmente en este documento. En modalidades a modo de ejemplo, la región B es un adaptador polipeptídico. Los adaptadores polipeptídicos ejemplares incluyen polipéptidos que tienen 1-20, 1-15, 1-10, 1-8, 1-5, 1-4, 1-3, ó 1-2 aminoácidos. Los ejemplos específicos de adaptadores polipeptídicos adecuados se describen más adelante en este documento e incluyen, por ejemplo, adaptadores que tienen una secuencia seleccionada entre el grupo constituido por las SEC ID N°: 11-19, 51, 93-95 y 218. En ciertas modalidades, el adaptador puede ser un polipéptido de cola C-terminal como se describe en este documento, un polipéptido de extensión N-terminal como se describe en este documento o una combinación de los mismos.

En una modalidad, un dímero de proteína similar a anticuerpo comprende un polipéptido que tiene la estructura X_1-A-X_2-B-X_3-C-X_4, en la que X_1 es una extensión N-terminal opcional, A es un dominio de ^{10}Fn3 que se une a EGFR, X_2 es una cola C-terminal opcional, B es un adaptador polipeptídico, X_3 es una extensión N-terminal opcional, C es un dominio de ^{10}Fn3 que se une a IGF-IR y X_4 es una cola C-terminal opcional. En otra modalidad, un dímero de proteína similar a anticuerpo comprende un polipéptido que tiene la estructura X_1-A-X_2-B-X_3-C-X_4, en la que X_1 es una extensión N-terminal opcional, A es un dominio de ^{10}Fn3 que se une a IGF-IR2, X_2 es una cola C-terminal opcional, B es un adaptador polipeptídico, X_3 es una extensión N-terminal opcional, C es un dominio de ^{10}Fn3 que se une a EGFR y X_4 es una cola C-terminal opcional. Los ejemplos específicos de extensiones N-terminales adecuadas y colas C-terminales se han descrito anteriormente. En ciertas modalidades, uno o más de X_1, X_2, B, X_3 o X_4 pueden comprender un resto aminoacídico adecuado para pegilación, tal como un resto de cisteína o lisina. En modalidades a modo de ejemplo, X_4 comprende al menos un aminoácido adecuado para pegilación, tal como un resto de cisteína o lisina. Los ejemplos específicos de adaptadores polipeptídicos adecuados se describen con más detalle más adelante. Los ejemplos específicos de dímeros de proteína similar a anticuerpo que tienen la estructura X_1-A-X_2-B-X_3-C-

X_4 son polipéptidos que comprenden (i) un polipéptido que tiene la secuencia de aminoácidos expuesta en una cualquiera de las SEC ID N°: 20-31, 53-58, 87-92, 98-105, 118-133, 149-154, 164-169, 179-184, 192-197, 205-210 y 211-216, o (ii) un polipéptido que comprende una secuencia de aminoácidos que es idéntica al menos en el 85%, 90%, 95%, 97%, 98% o 99% a la secuencia de aminoácidos expuesta en una cualquiera de las SEC ID N°: 20-31, 53-58, 87-92, 98-105, 118-133, 149-154, 164-169, 179-184, 192-197, 205-210 y 211-216.

En ciertas modalidades, puede ser deseable ajustar la potencia de un dominio de unión de ^{10}Fn3 con respecto al otro dominio de unión de ^{10}Fn3 en los dímeros de proteína similar a anticuerpo descritos en este documento. Por ejemplo, si la afinidad de unión del primer dominio de ^{10}Fn3 es significativamente superior a la afinidad de unión del segundo dominio de ^{10}Fn3, el efecto biológico del primer dominio de ^{10}Fn3 podría rebasar los efectos del segundo dominio de ^{10}Fn3. En consecuencia, en ciertas modalidades, puede ser deseable que las afinidades de unión del primer y segundo dominio de ^{10}Fn3 de un dímero de proteína similar a anticuerpo sean similares entre sí, por ejemplo, afinidades de unión en el intervalo de 100 veces, 30 veces, 10 veces, 3 veces, 1 vez, 0.3 veces o 0.1 veces, entre sí, o afinidades de unión en el intervalo de 0.1 veces a 10 veces, de 0.3 veces a 10 veces, de 0.1 veces a 3 veces, de 0.3 veces a 3

veces, de 0.1 veces a 1 vez, de 0.3 veces a 1 vez, de 1 vez a 10 veces, de 3 veces a 10 veces, de 3 veces a 30 veces o de 1 vez a 3 veces entre sí.

Conjugación

Los multímeros de proteínas similares a anticuerpo pueden estar unidas covalentemente o no covalentemente. En algunas modalidades, un ^{10}Fn3 de unión a EGFR se puede unir directamente o indirectamente a un ^{10}Fn3 de unión a IGFIR a través de un adaptador polipeptídico. Los adaptadores adecuados para conectar Fn3 son los que permiten que los dominios separados se plieguen independientemente entre sí formando una estructura tridimensional que permite la unión de alta afinidad a una molécula diana.

La descripción proporciona varios adaptadores adecuados que cumplen estos requisitos, que incluyen adaptadores basados en glicina-serina, adaptadores basados en glicina-prolina, así como el adaptador que tiene la secuencia de aminoácidos PSTSTST (SEC ID N°: 12). Los Ejemplos descritos en este documento demuestran que los dominios de Fn3 conectados por adaptadores polipeptídicos conservan su función de unión a diana. En algunas modalidades, el adaptador es un adaptador basado en glicina-serina. Estos adaptadores comprenden restos de glicina y serina y pueden tener entre 8 y 50, 10 y 30 y 10 y 20 aminoácidos de longitud. Los Ejemplos incluyen adaptadores que tienen una

secuencia de aminoácidos GSGSGSGSGSGSGSGSGSGS (SEC ID N°: 11), GSGSGSGSGS (SEC ID N°: 13), GGGGS GGGGS GGGGS (SEC ID N°: 14), GGGGS GGGGS GGGGS GGGGS (SEC ID N°: 15), GGGGS GGGGS GGGGS GGGGS GGGGS (SEC ID N°: 16) o GGGGSGGGGSGGGSG (SEC ID N°: 17). En algunas modalidades, el adaptador es un adaptador basado en glicina-prolina. Estos adaptadores comprenden restos de glicina y prolina y pueden tener entre 3 y 30, 10 y 30 y 3 y 20 aminoácidos de longitud. Los ejemplos incluyen adaptadores que tienen una secuencia de aminoácidos GPGPGPG (SEC ID N°: 18), GPGPGPGPGPG (SEC ID N°: 19) y GPG (SEC ID N°: 51). En algunas modalidades, el adaptador es un adaptador basado en prolina-alanina. Estos adaptadores comprenden restos de prolina y alanina y pueden tener entre 3 y 30, 10 y 30, 3 y 20 y 6 y 18 aminoácidos de longitud. Los ejemplos de tales adaptadores incluyen las SEC ID N°: 93, 94 y 95. Se considera que la longitud y composición de aminoácidos óptimas del adaptador se pueden determinar por experimentación rutinaria mediante procedimientos bien conocidos en la técnica.

En algunas modalidades, los multímeros de proteínas similares a anticuerpo se unen a través de un adaptador polipeptídico que tiene un sitio de proteasa que se puede escindir por una proteasa en la sangre o el tejido diana. Tales modalidades se pueden usar para liberar dos o más proteínas terapéuticas para suministro o propiedades

terapéuticas mejores o una producción más eficaz en comparación con la producción por separado de tales proteínas.

Se pueden introducir adaptadores o espaciadores adicionales, por ejemplo, las SEC ID N°: 9 y 10, en el C-terminal de un dominio de Fn3 entre el dominio de Fn3 y el adaptador polipeptídico. Se pueden introducir adaptadores o espaciadores adicionales en el N-terminal de un dominio de Fn3 entre el dominio de Fn3 y el adaptador polipeptídico.

En algunas modalidades, los multímeros de proteínas similares a anticuerpo se pueden unir directamente o indirectamente a través de un adaptador polimérico. Los adaptadores poliméricos se pueden usar para variar de forma óptima la distancia entre cada resto de proteína para crear una proteína con una o más de las siguientes características: 1) impedimento estérico reducido o aumentado de la unión de uno o más dominios de proteína cuando se une a una proteína de interés, 2) estabilidad o solubilidad de proteína aumentada, 3) agregación de proteína disminuida y 4) avidez o afinidad global de la proteína aumentada.

En algunas modalidades, los multímeros de proteínas similares a anticuerpo se unen por un polímero biocompatible tal como un azúcar polimérico. El azúcar polimérico puede incluir un sitio de escisión enzimática que se puede escindir por una enzima en la sangre o el tejido diana. Tales

modalidades se pueden usar para liberar dos o más proteínas terapéuticas para suministro o propiedades terapéuticas mejores o una producción más eficaz en comparación con la producción por separado de tales proteínas.

En algunas modalidades, los multímeros de proteínas similares a anticuerpo se unen por un polioxialquileno, en particular, un resto de polietilenglicol (PEG). Las proteínas similares a anticuerpo pueden comprenden un adaptador que contiene cisteína, tal como el adaptador expuesto en la SEC ID N°: 10, 81, 97 ó 218. Se puede conjugar PEG con el resto de cisteína en la secuencia engarzadora y puede unir de forma operativa los dos dominios.

Restos farmacocinéticos

En un aspecto, la descripción proporciona agentes de unión a E y agentes de unión a E/I que comprenden además un resto farmacocinético (PK). En algunas modalidades, el agente de unión a E/I es un multímero de proteínas similares a anticuerpo, en particular, un dímero de un ^{10}Fn3 de unión a EGFR y un ^{10}Fn3 de unión a IGFIR. Se pueden evaluar farmacocinéticas mejoradas de acuerdo con la necesidad terapéutica percibida. Con frecuencia es deseable aumentar la biodisponibilidad y/o aumentar el tiempo entre dosis, posiblemente aumentando el tiempo que una proteína permanece disponible en el suero después de la dosificación. En algunos casos, es deseable mejorar la continuidad de la

concentración sérica de la proteína a lo largo del tiempo (por ejemplo, disminuir la diferencia en la concentración sérica de la proteína poco después de la administración y poco antes de la siguiente administración). Los agentes de unión a I y agentes de unión a E/I se pueden unir a un resto que reduzca la velocidad de aclaramiento del polipéptido en un mamífero (por ejemplo, ratón, rata o ser humano) más de tres veces con respecto al polipéptido no modificado. Otras medidas de farmacocinética mejorada pueden incluir semivida sérica, que se divide con frecuencia en una fase alfa y una fase beta. Cualquiera o las dos fases se pueden mejorar significativamente por adición de un resto apropiado.

Los restos que tienden a ralentizar el aclaramiento de una proteína de la sangre incluyen restos de polioxialquileno (por ejemplo, polietilenglicol); azúcares (por ejemplo, ácido siálico); y restos de proteína bien tolerados (por ejemplo, Fc, fragmentos de Fc, transferrina o albúmina sérica).

En algunas modalidades, el resto PK es una proteína de unión a albúmina sérica tal como las descritas en las Publicaciones de Estados Unidos N° 2007/0178082 y 2007/0269422.

En algunas modalidades, el resto PK es una proteína de unión a inmunoglobulina sérica tal como la descrita en la Publicación de Estados Unidos N° 2007/0178082.

En algunas modalidades, el resto PK es polietilenglicol (PEG).

La velocidad de aclaramiento sérico de un multímero de proteína similar a anticuerpo modificado por PK se puede disminuir aproximadamente el 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% o incluso el 90% con respecto a la velocidad de aclaramiento de los agentes de unión a E/I no modificados. El multímero modificado por PK puede tener una semivida ($t_{1/2}$) que está mejorada con respecto a la semivida del multímero no modificado. La semivida del polipéptido de unión a PK se puede mejorar al menos el 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 250%, 300%, 400% o el 500% o incluso el 1000% con respecto a la semivida del multímero no modificado. En algunas modalidades, la semivida del multímero se determina *in vitro*, tal como en una solución salina amortiguada o en suero. En otras modalidades, la semivida del multímero es una semivida *in vivo*, tal como la semivida del multímero en el suero u otro fluido corporal de un animal.

En algunas modalidades, un resto PK está unido a un multímero de proteína similar a anticuerpo por al menos un enlace disulfuro, un enlace peptídico, un polipéptido, un azúcar polimérico o un resto de polietilenglicol. Los adaptadores polipeptídicos ejemplares incluyen adaptadores PSTSTST (SEC ID N°: 12), EIDKPSQ (SEC ID N°: 9) y GS, tales

como GSGSGSGSGS (SEC ID N°: 13) y multímeros de los mismos.

Unión/Selección

La descripción proporciona agentes de unión a E y agentes de unión a E/I, en particular, multímeros de proteína similar a anticuerpo tales como un dímero de un ^{10}Fn3 de unión a EGFR y un ^{10}Fn3 de unión a IGFIR. La unión a EGFR o IGFIR se puede evaluar en términos de constantes de equilibrio (por ejemplo, disociación, K_D) y en términos de constantes cinéticas (por ejemplo, constante de velocidad de asociación, k_{on} y constante de velocidad de disociación, k_{off}). En algunas modalidades, un monómero o multímero de proteína similar a anticuerpo se unirá a EGFR con una K_D menor de 500 nM, 100 nM, 50 nM, 5 nM o menos. En algunas modalidades, un multímero de proteína similar a anticuerpo se unirá a IGFIR con una K_D menor de 500 nM, 100 nM, 50 nM, 5 nM o menos. Se pueden tolerar mayores valores de K_D cuando la k_{off} es suficientemente baja o la k_{on} es suficientemente alta.

Los agentes de unión a E y los agentes de unión a E/I se pueden unir a cualquier parte de EGFR, incluyendo el dominio extracelular de un EGFR, en particular, el dominio de unión a ligando de EGFR. La unión de los agentes de unión a E y agentes de unión a E/I a EGFR puede alterar la interacción de EGFR con uno o más ligandos, incluyendo TGF-alfa y EGF, y/o alterar la dimerización del receptor. En algunas modalidades, los agentes de unión a E y agentes de

unión a E/I compiten con un anticuerpo anti-EGFR por la unión a EGFR. El anticuerpo anti-EGFR se puede seleccionar de cualquier anticuerpo anti-EGFR incluyendo panitumumab (Amgen), nimotuzumab (YM Biosciences), zalutumumab (Genmab), EMD72000 (Merck KGaA) y cetuximab (ImClone Systems).

En algunas modalidades, los agentes de unión a E y agentes de unión a E/I inhiben la señalización cadena debajo de EGFR. La unión a ligando de EGFR conduce a la dimerización de receptor homo- o heterodimérica con EGFR u otro miembro de la familia de HER. La dimerización promueve la autofosforilación de receptor, lo que, a su vez, conduce a la activación de varias rutas de señalización.

Los agentes de unión a E/I pueden unirse a cualquier parte de IGFIR, incluyendo el dominio extracelular de un IGFIR, en particular, el domino de unión a ligando de IGFIR. La unión de agentes de unión a E/I a IGFIR puede alterar la interacción de IGFIR con uno o más ligandos, por ejemplo, IGF-I e IGF-II; y/o alterar el ensamblaje de heterotetrámeros de receptor. En algunas modalidades, los agentes de unión a E/I compiten con un anticuerpo anti-IGFIR por la unión a IGFIR. El anticuerpo anti-IGFIR se puede seleccionar entre cualquier anticuerpo anti-IGFIR conocido.

En algunas modalidades, los agentes de unión a E/I inhiben la señalización cadena abajo de IGFIR. El receptor de IGF-I está compuesto por dos tipos de subunidades: una

subunidad alfa (una proteína de 130-135 kDa que es completamente extracelular y funciona en la unión a ligando) y una subunidad beta (una proteína transmembrana de 95 kDa, con dominios transmembrana y citoplásmicos). La IGFIR inicialmente se sintetiza como un polipéptido prorreceptor de cadena única que se procesa por glucosilación, escisión proteolítica y unión covalente para ensamblarse en un heterotetrámero de 460 kDa maduro que comprende dos subunidades alfa y dos subunidades beta. La subunidad o las subunidades beta poseen actividad tirosina cinasa activada por ligando.

La señalización de receptor EGFR e IGFIR activa independientemente la ruta de MAPK, incluyendo la fosforilación de MEK. Otra ruta activada es la ruta de fosfatidilinositol 3-cinasa (PI3K), incluyendo la fosforilación de AKT. La señalización de receptor se transduce al núcleo, dando como resultado la activación de diversos factores de transcripción.

Se pueden diseñar ensayos de selección para identificar y caracterizar agentes de unión a E y agentes de unión a E/I. Los ensayos de unión, tales como resonancia de plasmón superficial y ELISA y ensayos que detectan rutas de señalización activadas, se conocen bien en la técnica, véase, por ejemplo, el Ejemplo 5. Se han producido diversos anticuerpos, incluyendo muchos que están disponibles en el

mercado, que se unen específicamente a isoformas fosforiladas, activadas de EGFR e IGFIR, véase, por ejemplo, los Ejemplos 6 y 7. Los acontecimientos de señalización cadena abajo también se pueden usar como un indicador de la inhibición de receptor, tal como midiendo los niveles de fosforilación de AKT, véase, por ejemplo, el Ejemplo 8. Los ensayos de proliferación celular también son un procedimiento útil para caracterizar la capacidad de agentes de unión a E/I candidatos para unirse e inhibir la señalización de EGFR e IGFIR, véase, por ejemplo, el Ejemplo 9.

Conjugación con polímero

La conjugación con un polímero biocompatible se puede usar para unir multímeros de proteína similar a anticuerpo y/o para mejorar la farmacocinética de las proteínas. La identidad, tamaño y estructura del polímero se seleccionan a fin de mejorar la semivida en circulación del multímero o disminuir la antigenicidad del multímero sin una disminución inaceptable de la actividad.

Los ejemplos de polímeros útiles en la invención incluyen, pero sin limitación, poli(alquilenglicoles) tales como polietilenglicol (PEG). El polímero no está limitado a ninguna estructura particular y puede ser lineal (por ejemplo, PEG alcoxi o PEG bifuncional) o no lineal tal como ramificado, ahorquillado, multibrazo (por ejemplo, PEG unidos a un núcleo de poliol) y dendrítico.

Típicamente, el PEG y otros polímeros solubles en agua (es decir, reactivos poliméricos) se activan con un grupo de activación adecuado apropiado para el acoplamiento a un sitio deseado sobre el polipéptido. Por tanto, un reactivo polimérico poseerá un grupo reactivo para la reacción con el polipéptido. Los reactivos poliméricos y procedimientos representativos para conjugar estos polímeros con un resto activo se conocen bien en la técnica y se describen adicionalmente en Zalipsky, S., y col., "Use of Functionalized Poly(Ethylene Glycols) for Modification of Polypeptides" en Polyethylene Glycol Chemistry: Biotechnical and Biomedical Applications, J. M. Harris, Plenus Press, New York (1992) y en Zalipsky (1995) Advanced Drug Reviews 16: 157-182.

Típicamente, el peso molecular promedio en peso del polímero es de aproximadamente 100 Dalton a aproximadamente 150.000 Dalton. Los pesos moleculares promedio en peso ejemplares para el polímero biocompatible incluyen aproximadamente 20.000 Dalton, aproximadamente 40.000 Dalton, aproximadamente 60.000 Dalton y aproximadamente 80.000 Dalton. También se pueden usar versiones ramificadas del polímero biocompatible que tienen un peso molecular total de cualquiera de los anteriores.

En algunas modalidades, el polímero es PEG. El PEG es un polímero soluble en agua bien conocido, que está

disponible en el mercado o que se puede preparar por polimerización de apertura de anillo de etilenglicol de acuerdo con procedimientos bien conocidos en la técnica (Sandler y Karo, Polymer Synthesis, Academic Press, New York, Vol. 3, páginas 138-161). El término "PEG" se usa de forma amplia para incluir cualquier molécula de polietilenglicol, sin tener en cuenta el tamaño o modificación en un extremo del PEG, y se puede representar por la fórmula: $X-O(CH_2CH_2O)_{n-1}CH_2CH_2OH$, donde n es de 20 a 2300 y X es H o una modificación terminal, por ejemplo, un alquilo C_{1-4}. El PEG puede contener además grupos químicos que son necesarios para reacciones de unión, que se producen por la síntesis química de la molécula; o que actúan como un espaciador para la distancia óptima de partes de la molécula. Además, tal PEG puede estar constituido por una o más cadenas laterales de PEG que están unidas entre sí. Los PEG con mas de una cadena de PEG se denominan PEG multibrazo o ramificados. Los PEG ramificados se describen, por ejemplo, en la Solicitud Publicada Europea N° 473084A y la Patente de Estados Unidos N° 5.932.462.

Para efectuar la unión covalente de la molécula o las moléculas poliméricas a un polipéptido, los grupos terminales hidroxilo de la molécula polimérica se tienen que proporcionar en forma activada, es decir, con grupos funcionales reactivos. Las moléculas poliméricas activadas de forma adecuada están disponibles en el mercado, por

ejemplo, en Nektar Therapeutics, Inc., Huntsville, Ala., EE.UU; PolyMASC Pharmaceuticals plc, RU; or SunBio Corporation, Anyang City, Corea del Sur. Como alternativa, se pueden activar las moléculas de polímero por procedimientos convencionales conocidos en la técnica, por ejemplo, como se describe en el documento WO 90/13540. Los ejemplos específicos de polímeros de PEG activados incluyen los siguientes PEG lineales: NHS-PEG, SPA-PEG, SSPA-PEG, SBA-PEG, SS-PEG, SSA-PEG, SC-PEG, SG-PEG, SCM-PEG, NOR-PEG, BTC-PEG, EPOX-PEG, NCO-PEG, NPC-PEG, CDI-PEG, ALD-PEG, TRES-PEG, VS-PEG, OPSS-PEG, IODO-PEG y MAL-PEG, y PEG ramificados, tales como PEG2-NHS, PEG2-MAL y los descritos en la Patente de Estados Unidos N° 5.932.462 y la Patente de Estados Unidos N° 5.643.575, que se incorporan ambas como referencia en este documento.

En algunas modalidades en las que las moléculas de PEG están conjugadas con restos de cisteína en un multímero de proteína similar a anticuerpo, los restos de cisteína son nativos de la proteína, mientras que en otras modalidades, uno o más restos de cisteína se introducen por modificación en la proteína. Las mutaciones se pueden introducir en una secuencia codificante de proteína para generar restos de cisteína. Esto se puede conseguir, por ejemplo, mutando uno o más restos aminoacídicos a cisteína. Los aminoácidos preferidos para mutar a un resto de cisteína incluyen serina,

treonina, alanina y otros restos hidrófilos. Preferiblemente, el resto a mutar a cisteína es un resto expuesto en la superficie. Los algoritmos se conocen bien en la técnica para predecir accesibilidad de superficie de restos basándose en la secuencia primaria o una proteína. Alternativamente, los restos de superficie se pueden predecir comparando las secuencias de aminoácidos de polipéptidos de unión, dado que la estructura cristalina del armazón sobre cuya base se diseñan y desarrollan los polipéptidos de unión se ha resuelto (véase Himanen y col., Nature. (2001) 20-27; 414(6866): 933-8) y, por tanto, se identifican los restos expuestos en la superficie. En algunas modalidades se introducen restos de cisteína en multímeros de proteína similar a anticuerpo en o cerca del N-terminal y/o C o dentro de regiones de bucle. Se puede realizar la pegilación de restos de cisteína usando, por ejemplo, PEG-maleimida, PEG-vinilsulfona, PEG-yodoacetamida o PEG-ortopiridil disulfuro.

En algunas modalidades, el multímero de proteína similar a anticuerpo pegilado comprende una molécula de PEG unida covalentemente con el grupo amino alfa del aminoácido N-terminal. Se describe la aminación reductora N-terminal específica de sitio en Pepinsky y col., (2001) JPET, 297,1059 y la Patente de Estados Unidos N° 5.824.784. El uso de un PEG-aldehído para la aminación reductora de una proteína utilizando otros grupos aminos nucleófilos disponibles se

describe en la patente de Estados Unidos N° 4.002.531, en Wieder y col., (1979) J. Biol. Chem. 254, 12579 y en Chamow y col., (1994) Bioconjugate Chem. 5, 133.

En otra modalidad, el multímero de proteína similar a anticuerpo pegilado comprende una o más moléculas de PEG unidas covalentemente con un adaptador, que, a su vez, se une al grupo amino alfa del resto aminoacídico en el N-terminal del polipéptido de unión. Tal estrategia se describe en la publicación de Estados Unidos N° 2002/0044921 y la Publicación PCT N° WO 94/01451.

En algunas modalidades, un multímero de proteína similar a anticuerpo está pegilado en el C-terminal. Una proteína puede estar pegilada en el C-terminal mediante la introducción de azido-metionina C-terminal y la conjugación posterior de un compuesto metil-PEG-triarilfosfina por la reacción de Staudinger. Este procedimiento de conjugación C-terminal se describe en Cazalis y col., C-Terminal Site-Specific PEGylation of a Truncated Thrombomodulin Mutant with Retention of Full Bioactivity, *Bioconjug Chem.* 2004; 15(5): 1005-1009.

Se pueden usar técnicas de separación y purificación convencionales conocidas en la técnica para purificar multímeros de proteína similar a anticuerpo PEGilados, tales como cromatografía de exclusión por tamaño (por ejemplo, filtración en gel) y de intercambio iónico.

Los productos también se pueden separar usando SDS-PAGE. Los productos que se pueden separar incluyen polipéptido de unión mono-, di-, tri-, poli- y no pegilado, así como PEG libre. El porcentaje de conjugados de mono-PEG se puede controlar combinando fracciones más amplias alrededor del pico de elución para aumentar el porcentaje de mono-PEG en la composición. Aproximadamente el noventa por ciento de conjugados de mono-PEG representa un buen equilibrio de rendimiento y actividad.

En algunas modalidades, los multímeros de proteína similar a anticuerpo pegilados conservarán preferiblemente al menos aproximadamente el 25%, 50%, 60%, 70%, 80%, 85%, 90%, 95% o el 100% de la actividad biológica asociada con la proteína no modificada. En algunas modalidades, la actividad biológica se refiere a su capacidad de unirse a EGFR e IGFIR, como se evalúa por K_D, k_{on} o k_{off}. En algunas modalidades, el multímero de proteína similar a anticuerpo pegilado muestra un aumento en la unión a EGFR y/o IGFIR con respecto a la proteína no pegilada.

Desinmunización de polipéptidos de unión

Las secuencias de aminoácidos de agentes de unión a E y agentes de unión a E/I, en particular, multímeros de proteína similar a anticuerpo, tales como un dímero de un ^{10}Fn3 de unión a EGFR y un ^{10}Fn3 de unión a IGFIR, pueden estar alteradas para eliminar uno o más epítopos de células B

o T. Una proteína, o un multímero de proteínas, se puede desinmunizar para convertir la misma en no inmunógena, o menos inmunógena, para una especie dada. La desinmunización se puede conseguir mediante alteraciones estructurares en la proteína. Se puede emplear cualquier técnica de desinmunización conocida por los especialistas en la técnica, véase, por ejemplo, el documento WO 00/34317, cuya descripción se incorpora en este documento en su totalidad.

En una modalidad, las secuencias de los agentes de unión a E y agentes de unión a E/I pueden analizarse para determinar la presencia de motivos de unión a MHC de clase II. Por ejemplo, puede realizarse una comparación con bases de datos de motivos de unión a MHC tal como, por ejemplo, por búsqueda en la base de datos de "motivos" en la red global mundial en sitewehil.wehi.edu.au. Como alternativa, pueden identificarse péptidos de unión a MHC de clase II usando procedimientos de enhebrado computacional tales como los ideados por Altuvia y col. (J. Mol. Biol. 249 244-250 (1995)) por los que se ensayan péptidos solapantes consecutivos del polipéptido para determinar sus energías de unión a proteínas de MHC de clase II. Los algoritmos de predicción de unión computacional incluyen iTope™, Tepitope, SYFPEITHI, EpiMatrix (EpiVax) y MHCpred. Para contribuir a la identificación de péptidos de unión a MHC de clase II, pueden buscarse características de secuencia asociadas que

estén relacionadas con péptidos presentados con éxito, tales como motivos de anfipaticidad y Rothbard y sitios de escisión para catepsina B y otras enzimas de procesamiento.

Habiéndose identificado epítopos potenciales de células T (por ejemplo, humanos), estos epítopos se eliminan entonces por alteración de uno más aminoácidos, según sea necesario para eliminar el epítopo de célula T. Habitualmente, esto implicará la alteración de uno o más aminoácidos dentro del propio epítopo de célula T. Esto podría implicar alterar un aminoácido adyacente al epítopo en términos de la estructura primaria de la proteína o uno que no sea adyacente en la estructura primaria pero sea adyacente en la estructura secundaria de la molécula. La alteración habitual que se contempla será sustitución de aminoácidos, pero es posible que en determinadas circunstancias sea apropiada la adición o deleción de aminoácidos. Todas las alteraciones pueden realizarse mediante tecnología de ADN recombinante, de modo que la molécula final puede prepararse por expresión a partir de un huésped recombinante, por ejemplo, mediante procedimientos bien establecidos, pero también puede usarse el uso de química de proteínas o cualquier otro medio de alteración molecular.

Una vez identificados, los epítopos de células T se eliminan, la secuencia desinmunizada puede analizarse de nuevo para asegurarse de que no se han generado nuevos

epítopos de células T, y si se han generado, el epítopo o epítopos pueden delecionarse.

No todos los epítopos de células T identificados informáticamente deben eliminarse. Un especialista en la técnica apreciará la significación de la "potencia" o más bien la inmunogenicidad potencial de epítopos particulares. Los diversos procedimientos computacionales generan puntuaciones para epítopos potenciales. Un especialista en la técnica reconocerá que solamente puede ser necesario eliminar los epítopos de alta puntuación. Un especialista también reconocerá que existe un equilibrio entre eliminar epítopos potenciales y mantener la afinidad de unión de la proteína. Por lo tanto, una estrategia es introducir secuencialmente sustituciones en la proteína y después ensayar para determinar la unión a antígeno y la inmunogenicidad.

En un aspecto, la proteína desinmunizada es menos inmunogénica (o más bien, provoca una respuesta HAMA reducida) que la proteína original en un sujeto humano. Están bien dentro del conocimiento del especialista ensayos para determinar la inmunogenicidad. Pueden realizarse procedimientos reconocidos en la técnica para determinar la respuesta inmune para controlar una respuesta HAMA en un sujeto particular o durante ensayos clínicos. A los sujetos a los que se les administra proteína desinmunizada se les

puede proporcionar una evaluación de inmunogenicidad al comienzo y durante toda la administración de dicha terapia. La respuesta HAMA se mide, por ejemplo, detectando anticuerpos contra la el proteína desinmunizada en muestras de suero del sujeto usando un procedimiento conocido para un especialista en la técnica, incluyendo tecnología de resonancia de plasmón superficial (BIACORE) y/o análisis de ELISA en fase sólida. Como alternativa, los ensayos *in vitro* diseñados para medir un acontecimiento de activación de células T también son indicativos de inmunogenicidad.

Modificaciones Adicionales

En ciertas modalidades, los agentes de unión a E y agentes de unión a E/I, en particular, multímeros de proteína similar a anticuerpo tales como un dímero de un ^{10}Fn3 de unión a EGFR y un ^{10}Fn3 de unión a IGFIR, pueden comprender además modificaciones post-traducción. La modificación de proteína post-traducción ejemplar incluye fosforilación, acetilación, metilación, ADP-ribosilación, ubiquitinación, glucosilación, carbonilación, sumoilación, biotinilación o adición de una cadena lateral de polipéptido o de un grupo hidrófobo. Como resultado, los agentes de unión a E y agentes de unión a E/I modificados pueden contener elementos no aminoacídicos, tales como lípidos, poli- o mono-sacáridos y fosfatos. Una forma preferida de glucosilación es la sialilación, que conjuga uno o más restos de ácido siálico al polipéptido. Los restos de

ácido siálico mejoran la solubilidad y la semivida sérica mientras que también reducen la posible inmunogenicidad de la proteína. Véase, por ejemplo, Raju y col. Biochemistry. 31 de jul de 2001; 40(30): 8868-76. Los efectos de tales elementos no aminoacídicos sobre la funcionalidad de un agente de unión a E o agente de unión a E/I se pueden ensayar para su papel de antagonización en la función de señalización de EGFR e IGFIR.

En algunas modalidades, los agentes de unión a E y agentes de unión a E/I se modifican para potenciar la citotoxicidad mediada por células dependiente de antígeno (ADCC) y/o la citotoxicidad dependiente del complemento (CDC). En algunas modalidades, el agente de unión a E/I es un dímero de un ^{10}Fn3 de unión a EGFR y un ^{10}Fn3 de unión a IGFIR que comprende además una región Fc. En algunas modalidades, la región Fc es una variante que potencia ADCC o CDC. La variante de región Fc puede comprender una secuencia de región Fc humana (por ejemplo, una región Fc de IgG1, IgG2, IgG3 o IgG4 humana) que comprende una modificación aminoacídica (por ejemplo, una sustitución) en una o más posiciones de aminoácidos, incluyendo las posiciones 256, 290, 298, 312, 326, 330, 333, 334, 360, 378 ó 430, en las que la numeración de los restos en la región Fc es la del índice EU como en Kabat.

Modalidades de Vectores y Polinucleótidos

También se incluyen en la presente descripción secuencias de ácido nucleico que codifican cualquiera de las proteínas descritas en este documento. Como se entenderá por los especialistas en la técnica, debido a la degeneración de tercera base, prácticamente cualquier aminoácido se puede representar por más de un codón de triplete en una secuencia de nucleótidos codificante. Además, cambios de pares de bases menores pueden dar como resultado una sustitución conservativa en la secuencia de aminoácidos codificada pero no se espera que alteren sustancialmente la actividad biológica del producto génico. Por lo tanto, una secuencia de ácido nucleico que codifica una proteína descrita en este documento se puede modificar ligeramente en la secuencia y todavía codificar su producto génico respectivo.

Los ejemplos de ácidos nucleicos que codifican los agentes de unión a E/I descritos en este documento incluyen ácidos nucleicos que tienen las SEC ID N°: 442-465 o ácidos nucleicos que tienen una secuencia idéntica en al menos un 80%, 85%, 90%, 95%, 97%, 98%, 99% o 100% a una cualquiera de las SEC ID N°: 442-465. También están dentro del alcance de la invención ácidos nucleicos aislados que difieren de los ácidos nucleicos indicados en la SEC ID N°: 442-465 debido a la degeneración del código genético. También se proporcionan agentes de unión a E/I que comprenden un monómero I

codificado por una secuencia de nucleótidos idéntica en al menos un 80%, 85%, 90%, 95%, 97%, 98%, 99% o 100% a la SEC ID N°: 328 y/o agentes de unión a E/I que comprenden un monómero E codificado por una secuencia de nucleótidos idéntica en un 80%, 85%, 90%, 95%, 97%, 98%, 99% o 100% a una cualquiera de las SEC ID N°: 329-441 ó 495. También se proporcionan agentes de unión a E codificados por una secuencia de nucleótidos idéntica en un 80%, 85%, 90%, 95%, 97%, 98%, 99% o 100% a una cualquiera de las SEC ID N°: 329-441 ó 495. En ciertas modalidades, las secuencias de nucleótidos que codifican los agentes de unión a E/I, un monómero de E o un monómero de I no contienen una secuencia que codifica un marcador de 6XHis.

Pueden sintetizarse químicamente ácidos nucleicos que codifican cualquiera de las diversas proteínas o polipéptidos descritos en este documento. Puede seleccionarse el uso de codones a fin de mejorar la expresión en una célula. Dicho uso de codones dependerá del tipo celular seleccionado. Se han desarrollado patrones de uso de codones especializados para *E. coli* y otras bacterias, así como células de mamífero, células vegetales, células de levadura y células de insecto. Véase, por ejemplo: Mayfield y col., Proc Natl Acad Sci U S A. 2003; 100 (2): 438-42; Sinclair y col. Protein Expr Purif. 2002 (1): 96-105; Connell ND. Curr Opin Biotechnol. 2001 (5): 446-9; Makrides

y col. Microbiol Rev. 1996 60 (3): 512-38; y Sharp y col. Yeast. 1991 7 (7): 657-78.

Las técnicas generales para manipulación de ácidos nucleicos pertenecen al ámbito del especialista en la técnica y también se describen, por ejemplo, en Sambrook y col., Molecular Cloning: A Laboratory Manual, Vols. 1-3, Cold Spring Harbor Laboratory Press, 2ª ed., 1989, o F. Ausubel y col., Current Protocols in Molecular Biology (Green Publishing and Wiley-Interscience: Nueva York, 1987) y actualizaciones periódicas, incorporados en este documento como referencia. El ADN que codifica una proteína está unido operativamente a elementos reguladores de la transcripción o de la traducción adecuados procedentes de genes de mamífero, virus o insecto. Tales elementos reguladores incluyen un promotor de la transcripción, una secuencia operadora opcional para controlar la transcripción, una secuencia que codifica sitios de unión al ribosoma del ARNm adecuados y secuencias que controlan la terminación de la transcripción y de la traducción. La capacidad para replicarse en un huésped, habitualmente conferida por un origen de replicación, y un gen de selección para facilitar el reconocimiento de transformantes, se incorporan adicionalmente. En la técnica se conocen bien los elementos reguladores adecuados.

Las proteínas descritas en este documento pueden

producirse como una proteína de fusión con un polipéptido heterólogo, que preferiblemente es una secuencia señal u otro polipéptido que tiene un sitio de escisión específico en el N-terminal de la proteína o polipéptido maduro. La secuencia señal heteróloga seleccionada preferiblemente es una que es reconocida y procesada (es decir, escindida por un peptidasa de señal) por la célula huésped. Para células huésped procariotas que no reconocen y procesan una secuencia señal nativa, la secuencia señal se sustituye por una secuencia señal procariota seleccionada, por ejemplo, del grupo de los líderes de fosfatasa alcalina, penicilinasa, lpp, o enterotoxina termoestable II. Para la secreción en levaduras, la secuencia señal nativa puede sustituirse, por ejemplo, por el líder de la invertasa de levaduras, un líder de factor (incluyendo líderes de factor alfa de *Saccharomyces* y *Kluyveromyces*), o el líder de la fosfatasa ácida, el líder de la glucoamilasa de *C. albicans* o la señal descrita en la Publicación PCT N° WO 90/13646. En la expresión en células de mamífero, están disponibles secuencias señal de mamíferos, así como líderes secretores virales, por ejemplo, la señal gD del herpes simple. El ADN para tales regiones precursoras puede ligarse en la fase de lectura con el ADN que codifica la proteína.

Los vectores de expresión usados en células huésped eucariotas (por ejemplo, células de levaduras, hongos,

insectos, plantas, animales, seres humanos o nucleadas de otros organismos multicelulares) también contendrán secuencias necesarias para la terminación de la transcripción y para estabilizar el ARNm. Tales secuencias están comúnmente disponibles de las regiones no traducidas 5' y, ocasionalmente 3', de ADN o ADNc eucariotas o virales. Estas regiones contienen segmentos de nucleótidos transcritos como fragmentos poliadenilados en la porción no traducida del ARNm que codifica el anticuerpo multivalente. Un componente de terminación de la transcripción útil es la región de poliadenilación de la hormona de crecimiento bovina. Véase la publicación PCT N° WO 94/11026 y el vector de expresión descrito en el mismo.

El ADN recombinante también puede incluir cualquier tipo de secuencia marcadora de proteína que puede ser útil para purificar la proteína. Los ejemplos de marcadores de proteínas incluyen, pero sin limitación, un marcador histidina, un marcador FLAG, un marcador myc, un marcador HA o un marcador GST. Pueden encontrar vectores de clonación y expresión apropiados para usar con huéspedes celulares bacterianos, fúngicos, de levaduras y mamífero en Cloning Vectors: A Laboratory Manual,. (Elsevier, Nueva York, 1985), cuya descripción pertinente se incorpora en este documento como referencia.

La construcción de expresión se introduce en la

célula huésped usando un procedimiento apropiado para la célula huésped, como será evidente para un especialista en la técnica. Se conoce en la técnica una diversidad de procedimientos para introducir ácidos nucleicos en células huésped, incluyendo, pero sin limitación, electroporación; transfección empleando cloruro de calcio, cloruro de rubidio, fosfato de calcio, DEAE-dextrano u otras sustancias; bombardeo con microproyectiles; lipofección; e infección (en la que el vector es un agente infeccioso).

Las células huésped adecuadas incluyen células procariotas, de levaduras, células de mamífero o células bacterianas. Las bacterias adecuadas incluyen organismos gram negativos o gram positivos, por ejemplo *E. coli* o *Bacillus spp.* También pueden usarse levaduras, preferiblemente de la especie *Saccharomyces*, tales como *S. cerevisiae,* para la producción de polipéptidos. También pueden emplearse diversos sistemas de cultivo de células de mamífero o insecto para expresar proteínas recombinantes. Se revisan sistemas de baculovirus para la producción de proteínas heterólogas en células de insecto por Luckow y Summers (Bio/Technology, 6: 47, 1988). En algún caso se deseará producir proteínas en células de vertebrados, tal como para glucosilación, y la propagación de células de vertebrados en cultivo (cultivo tisular) se ha convertido en un procedimiento rutinario. Los ejemplos de líneas celulares

huésped de mamífero adecuadas incluyen células endoteliales, células de riñón de mono COS-7, CV-1, células L, C127, 3T3, células de ovario de hámster chino (CHO), células de riñón embrionario humano, líneas celulares HeLA, 293, 293T y BHK. Para muchas aplicaciones, el pequeño tamaño de los multímeros de proteína descritos en este documento hará que *E. coli* sea el procedimiento preferido para la expresión.

Producción de proteína

Las células huésped se transforman con los vectores de expresión o clonación descritos en este documento para producción de proteína y se cultivan en medios de nutrientes convencionales modificados según sea apropiado para inducir promotores, seleccionar transformantes o amplificar los genes que codifican las secuencias deseadas.

Las células huésped usadas para producir las proteínas de esta invención pueden cultivarse en una diversidad de medios. Los medios disponibles en el mercado tales como F10 de Ham (Sigma), Medio Mínimo Esencial ((MEM), Sigma), RPMI-1640 (Sigma) y Medio de Eagle Modificado por Dulbecco ((DMEM), (Sigma)) son adecuados para cultivar las células huésped. Además, cualquiera de los medios descritos en Ham y col., Meth. Enz. 58: 44 (1979), Barnes y col., Anal. Biochem. 102: 255 (1980), Patentes de Estados Unidos N° 4.767.704; 4.657.866; 4.927.762; 4.560.655 ó 5.122.469; documentos WO 90/03430; WO 87/00195; o la Patente de Estados

Unidos N° Re. 30.985 pueden usarse como medios de cultivo para las células huésped. Cualquiera de estos medios puede complementarse según sea necesario con hormonas y/o otros factores de crecimiento (tales como insulina, transferrina o factor de crecimiento epidérmico), sales (tales como cloruro de sodio, calcio, magnesio y fosfato), amortiguadores (tales como HEPES), nucleótidos (tales como adenosina y timidina), antibióticos (tales como fármaco GENTAMYCIN™), oligoelementos (definidos como compuestos inorgánicos habitualmente presentes a concentraciones finales en el intervalo micromolar) y glucosa o una fuente de energía equivalente. También puede incluirse cualquier otro complemento necesario a concentraciones apropiadas que conocerán los especialistas en la técnica. Las condiciones de cultivo, tales como temperatura, pH y similares, son las previamente usadas con la célula huésped seleccionada para la expresión y serán evidentes para el especialista habitual.

Las proteínas descritas en este documento también pueden producirse usando sistemas de traducción celulares. Para tales fines, los ácidos nucleicos que codifican las proteínas deben modificarse para permitir la transcripción *in vitro* para producir ARNm y para permitir la traducción sin células del ARNm en el sistema sin células particular que se esté utilizando. Los sistemas de traducción sin células eucariotas ejemplares incluyen, por ejemplo, sistemas de

traducción sin células de mamífero o levadura y los sistemas de traducción sin células procariotas ejemplares incluyen, por ejemplo, sistemas de traducción sin células bacterianos.

Las proteínas descritas en este documento también pueden producirse mediante síntesis química (por ejemplo, mediante los procedimientos descritos en Solid Phase Peptide Synthesis, 2ª ed., 1984, The Pierce Chemical Co., Rockford, IL). También pueden producirse modificaciones en la proteína mediante síntesis química.

Las proteínas descritas en este documento pueden purificarse mediante procedimientos de aislamiento/purificación para proteínas conocidos en general en el campo de la química de proteínas. Los ejemplos no limitantes incluyen extracción, recristalización, precipitación salina (por ejemplo, con sulfato de amonio o sulfato de sodio), centrifugación, diálisis, ultrafiltración, cromatografía de adsorción, cromatografía de intercambio iónico, cromatografía hidrófoba, cromatografía en fase normal, cromatografía en fase inversa, filtración en gel, cromatografía de permeación en gel, cromatografía de afinidad, electroforesis, distribución contracorriente o cualquier combinación de las mismas. Después de la purificación, las proteínas pueden cambiarse a diferentes amortiguadores y/o concentrarse por cualquiera de una diversidad de procedimientos conocidos en la técnica,

incluyendo, pero sin limitación, filtración y diálisis.

Las proteínas purificadas tiene preferiblemente una pureza de al menos el 85%, más preferiblemente una pureza de al menos el 95% y más preferiblemente una pureza de al menos el 98%. Independientemente del valor numérico exacto de la pureza, las proteínas son suficientemente puras para el uso como un producto farmacéutico.

Formación de Imágenes, Diagnóstico y Otras Aplicaciones

Los agentes de unión a E descritos en este documento se pueden marcar de forma detectable y usar para ponerse en contacto con células que expresan EGFR para aplicaciones de formación de imágenes o de diagnóstico. Los agentes de unión a E/I descritos en este documento se pueden marcar de forma detectable y usar para ponerse en contacto con células que expresan EGFR y/o IGFIR para aplicaciones de formación de imágenes o de diagnóstico. Cualquier procedimiento conocido en la técnica para conjugar una proteína con el resto detectable puede emplearse, incluyendo los procedimientos descritos por Hunter, y col., Nature 144: 945 (1962); David, y col., Biochemistry 13: 1014 (1974); Pain, y col., J. Immunol. Meth. 40: 219 (1981); y Nygren, J. Histochem. and Cytochem. 30: 407 (1982).

En ciertas modalidades, los agentes de unión a E y agentes de unión a E/I descritos en este documento se unen

adicionalmente a un marcador que es capaz de ser detectado (por ejemplo, el marcador puede ser un radioisótopo, compuesto fluorescente, enzima o co-factor enzimático). El marcador puede ser un agente radiactivo, tal como: metales pesado radiactivos tales como quelatos de hierro, quelatos radiactivos de gadolinio o manganeso, emisores de positrones de oxígeno, nitrógeno, hierro, carbono o galio, ^{43}K, ^{52}Fe, ^{57}Co, ^{67}Cu, ^{67}Ga, ^{68}Ga, ^{123}I, ^{125}I, ^{131}I, ^{132}I o ^{99}Tc. Un agente de unión a E y agente de unión a E/I fijado a tal resto se puede usar como un agente de formación de imágenes y se administra en una cantidad eficaz para uso de diagnóstico en un mamífero tal como un ser humano y después se detectan la localización y la acumulación del agente de formación de imágenes. La localización y acumulación del agente formador de imágenes se puede detectar por radioscintigrafía, formación de imágenes por resonancia magnética nuclear, tomografía computarizada o tomografía de emisión de positones. Como será evidente para el especialista, la cantidad de radioisótopo a administrar depende del radioisótopo. Los especialistas habituales en la técnica pueden formular de forma sencilla la cantidad del agente de formación de imágenes a administrar basándose en la actividad específica y energía de un radionúclido dado usado como el resto activo.

Los agentes de unión a E y agentes de unión a E/I también son útiles como agentes de purificación por afinidad.

En este procedimiento, las proteínas se inmovilizan sobre un soporte adecuado, tal como una resina Sephadex o papel de filtro, usando procedimientos bien conocidos en la técnica. Las proteínas se pueden emplear en cualquier procedimiento de ensayo conocido, tal como ensayos de unión de competencia, ensayos sándwich directo e indirecto y ensayos de inmunoprecipitación (Zola, Monoclonal Antibodies: A Manual of Techniques, págs. 147-158 (CRC Press, Inc., 1987)).

Los agentes de unión a E son útiles en métodos para detectar EGFR en una muestra. Los agentes de unión a E/I también son útiles en procedimientos para detectar EGFR y/o IGFIR en una muestra. La muestra será con frecuencia una muestra biológica, tal como una biopsia y, particularmente, una biopsia de un tumor, un tumor que se sospecha. La muestra puede ser de un ser humano u otro mamífero. El agente de unión a E o agente de unión a E/I se puede marcar con un resto marcador, tal como un resto radiactivo, un resto fluorescente, un resto cromogénico, un resto quimioluminiscente o un resto hapteno; y se puede inmovilizar sobre un soporte sólido. La detección se puede llevar a cabo usando cualquier técnica conocida en la técnica, tal como, por ejemplo, radiografía, ensayo inmunológico, detección por fluorescencia, espectrometría de masas o resonancia de plasmón superficial.

Usos terapéutico/*in vivo*

Los agentes de unión a E descritos en este documento también son útiles en procedimientos para tratar afecciones que responden a una inhibición de actividad biológica de EGFR. Los agentes de unión a E/I descritos en este documento también son útiles en procedimientos para tratar afecciones que responden a una inhibición de actividad biológica de EGFR y/o IGFIR. El EGFR e IGFIR están implicados directamente o indirectamente en las rutas de transducción de señal de diversas actividades celulares, que incluyen proliferación, adhesión y migración, así como diferenciación.

En un aspecto, la solicitud proporciona procédimientos para tratar un sujeto afectado con un trastorno hiperproliferativo con una cantidad terapéuticamente eficaz de un agente de unión a E o un agente de unión a E/I. En particular, los agentes de unión a E y agentes de unión a E/I son útiles para el tratamiento y/o la profilaxis de tumores y/o metástasis tumorales. En modalidades a modo de ejemplo, el agente de unión a E/I es un multímero de proteína similar a anticuerpo tal como un dímero de un ^{10}Fn3 de unión a EGFR y un ^{10}Fn3 de unión a IGFIR.

En algunas modalidades se administran composiciones farmacéuticas que comprenden agentes de unión a E o agentes de unión a E/I a un sujeto afectado con un tumor, incluyendo,

pero sin limitación, un tumor cerebral, tumor del tracto urogenital, tumor del sistema linfático, tumor de estomago, tumor laríngeo, leucemia monocítica, adenocarcinoma de pulmón, carcinoma pulmonar microcítico, cáncer pancreático, glioblastoma y carcinoma de mama; o una enfermedad cancerosa, incluyendo, pero sin limitación, carcinoma de células escamosas, cáncer de vejiga, cáncer de estomago, cáncer de hígado, cáncer de riñón, cáncer colorrectal, cáncer de mama, cáncer de cabeza, cáncer de cuello, cáncer esofágico, cáncer ginecológico, cáncer tiroideo, linfoma, leucemia crónica y leucemia aguda.

Se puede administrar un agente de unión a E o un agente de unión a E/I solo o en combinación con una o más terapias adicionales tales como quimioterapia, radioterapia, inmunoterapia, intervención quirúrgica o una combinación de las mismas. La terapia a largo plazo igualmente es posible como una terapia adyuvante en el contexto de otras estrategias de tratamiento, como se ha descrito en el presente documento. Las técnicas y dosificaciones para administración variarán dependiendo del tipo de polipéptido específico y la afección específica que se está tratando, pero se pueden determinar fácilmente por el especialista.

Agentes Adicionales Que Se Pueden Usar Con Agentes de Unión a E/I

Un aspecto de la solicitud proporciona

combinaciones de agentes de unión a E o agentes de unión a E/I y un agente terapéutico adicional, tal como un agente citotóxico. En algunas modalidades, un agente de unión a E o agente de unión a E/I está unido a un agente citotóxico. Tales modalidades se pueden preparar por procedimientos *in vitro* o *in vivo* cuando sea apropiado. Los procedimientos *in vitro* incluyen química de conjugación bien conocida en la técnica, tal como conjugación con restos de cisteína y lisina. Para unir un agente citotóxico a un polipéptido, se usa un grupo de unión o grupo reactivo. Los grupos de unión adecuados se conocen bien en la técnica e incluyen grupos disulfuro, grupos tioéter, grupos inestables a ácidos, grupos fotolábiles, grupos inestables a peptidasa y grupos inestables a esterasa. Los agentes citotóxicos también se pueden unir a agentes de unión a E o agentes de unión a E/I mediante una molécula transportadora intermediara tal como albúmina sérica.

Los agentes citotóxicos ilustrativos que se pueden unir a agentes de unión a E o agentes de unión a E/I incluyen maitansinoides, taxanos, análogos de CC-1065, toxina bacteriana, toxina vegetal, ricina, abrina, una ribonucleasa (RNasa), DNasa I, una proteasa, enterotoxina Estafilocócica A, proteína antiviral de fitolaca americana, gelonina, toxina diftérica, exotoxinas de *Pseudomonas*, endotoxina de *Pseudomonas*, Ranpimasa (Rap), Rap (N69Q), metotrexato,

daunorrubicina, doxorrubicina, vincristina, vinblastina, melfalano, mitomicina C, clorambucilo y calicheamicina.

En otros tratamientos o composiciones terapéuticas, los agentes de unión a E o agentes de unión a E/I se co-administran, o administran de forma secuencial, con uno o más agentes terapéuticos adicionales. Los agentes terapéuticos adecuados incluyen, pero sin limitación, agentes citotóxicos o citostáticos, tales como agentes terapéuticos del cáncer.

Los agentes terapéuticos del cáncer son los agentes que intentan destruir o limitar el crecimiento de células cancerosas mientras que tienen efectos mínimos sobre el paciente. Por tanto, tales agentes pueden aprovecharse de cualquier diferencia en las propiedades de células cancerosas (por ejemplo, metabolismo, vascularización o presentación de antígeno sobre la superficie celular) con respecto a células huésped. Los agentes terapéuticos que se pueden combinar con agentes de unión a E/I para eficacia anti-cancerosa mejorada incluyen diversos agentes usados en práctica oncológica (Referencia: Cancer, Principles & Practice of Oncology, DeVita, V. T., Hellman, S., Rosenberg, S. A., 6a edición, Lippincott-Raven, Philadelphia, 2001), tales como doxorrubicina, epirrubicina, ciclofosfamida, trastuzumab, capecitabina, tamoxifeno, toremifeno, letrozol, anastrozol, fulvestrant, exemestano, goserelina, oxaliplatino, carboplatino, cisplatino, dexametasona, antida, bevacizumab,

5-fluorouracilo, leucovorina, levamisol, irinotecano, etopósido, topotecano, gemcitabina, vinorelbina, estramustina, mitoxantrona, abarelix, zoledronato, estreptozocina, rituximab, idarubicina, busulfan, clorambucilo, fludarabina, imatinib, citarabina, ibritumomab, tositumomab, interferón alfa-2b, melfalam, bortezomib, altretamina, asparaginasa, gefitinib, erlonitib, anticuerpo anti-receptor de EGF (por ejemplo, cetuximab o panitumab), ixabepilona, epotilonas o derivados de las mismas, agentes de platino (tales como carboplatino, oxliplatino, cisplatino), taxanos (tales como paclitaxel, docetaxel) y camptotecina.

Formulaciones Terapéuticas y Modos de Administración

La presente solicitud proporciona procedimientos para tratar afecciones que responden a una inhibición de actividad biológica de EGFR y/o de IGFIR. Las técnicas y dosificaciones para administración varían dependiendo del tipo de polipéptido específico y la afección específica que se está tratando, pero se pueden determinar fácilmente por el especialista. En general, las agencias reguladoras requieren que un reactivo de proteína a usar como un terapéutico se formule a fin de tener niveles aceptablemente bajos de pirógenos. Por consiguiente, las formulaciones terapéuticas generalmente se distinguirán de otras formulaciones en el hecho de que están sustancialmente libres de pirógenos o al

menos contienen no más que niveles aceptables de pirógeno como se determina por la agencia reguladora apropiada (por ejemplo, FDA).

En algunas modalidades, los agentes de unión a E y agentes de unión a E/I son farmacéuticamente aceptables para un mamífero, en particular, un ser humano. Un polipéptido "farmacéuticamente aceptable" se refiere a un polipéptido que se administra a un animal sin consecuencias médicas adversas significativas. Los ejemplos de agentes de unión a E y agentes de unión a E/I farmacéuticamente aceptables incluyen dominios de ^{10}Fn3 que carecen del domino de unión a integrina (RGD) y dominios de ^{10}Fn3 que están esencialmente libres de endotoxinas o tienen niveles de endotoxinas muy bajos.

Las composiciones terapéuticas se pueden administrar con un diluyente, vehículo o excipiente farmacéuticamente aceptable en una forma farmacéutica unitaria. La administración puede ser parenteral (por ejemplo, intravenosa, subcutánea), oral o tópica, como ejemplos no limitantes. Además, se puede emplear cualquier técnica de terapia génica que use ácidos nucleicos que codifiquen agentes de unión a E o agentes de unión a E/I, tales como suministro de ADN desnudo, genes y vectores recombinantes, suministro basado en células, incluyendo manipulación *ex vivo* de células del paciente y similares.

La composición puede estar en forma de una píldora,

comprimido, cápsula, líquido o comprimido de liberación sostenida para administración oral; un líquido para administración intravenosa, subcutánea o parenteral; o un gel, loción, pomada, crema o un polímero u otro vehículo de liberación sostenida para administración local.

Los procedimientos bien conocidos en la técnica para preparar formulaciones se encuentran, por ejemplo, en "Remington: The Science and Practice of Pharmacy" (20a ed., ed. A. R. Gennaro AR., 2000, Lippincott Williams & Wilkins, Philadelphia, PA). Las formulaciones para administración parenteral pueden contener, por ejemplo, excipientes, agua estéril, solución salina, polialquilenglicoles tales como polietilenglicol, aceites de origen vegetal o naftalenos hidrogenados. Se pueden usar polímero de lactida biodegradable, biocompatible, copolímero de lactida/glicolida o copolímeros de polioxietileno-polioxipropileno para controlar la liberación de los compuestos. Se pueden usar formulaciones en forma de nanopartículas (por ejemplo, nanopartículas biodegradables, nanopartículas de lípidos sólidos, liposomas) para controlar la biodistribución de los compuestos. Otros sistemas de suministro parenteral potencialmente útiles incluyen partículas de copolímero de etileno-acetato de vinilo, bombas osmóticas, sistemas de infusión implantables y liposomas. La concentración del compuesto en la formulación varía

dependiendo de varios factores, que incluyen la dosificación del fármaco a administrar y la vía de administración.

El polipéptido se puede administrar opcionalmente como una sal farmacéuticamente aceptable, tal como sales de adición de ácidos no tóxicas o complejos metálicos que se usan comúnmente en la industria farmacéutica. Los ejemplos de sales de adición de ácidos incluyen ácidos orgánicos tales como ácido acético, láctico, pamoico, maleico, cítrico, málico, ascórbico, succínico, benzoico, palmítico, subérico, salicílico, tartárico, metanoslfónico, toluenosulfónico o trifluoroacético o similares; ácidos poliméricos tales como ácido tánico, carboximetilcelulosa o similares; y ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido fosfórico o similares. Los complejos metálicos incluyen cinc, hierro y similares. En un ejemplo, el polipéptido se formula en presencia de acetato sódico para aumentar la estabilidad térmica.

Las formulaciones para uso oral incluyen comprimidos que contienen el ingrediente o los ingredientes activos en una mezcla con excipientes farmacéuticamente aceptables no tóxicos. Estos

excipientes pueden ser, por ejemplo, diluyentes o cargas inertes (por ejemplo, sacarosa y sorbitol), agentes lubricantes, emolientes y anti-adhesivos (por ejemplo, estearato de magnesio, estearato de cinc, ácido esteárico, sílices, aceites vegetales hidrogenados o talco).

También se pueden proporcionar formulaciones para uso oral como comprimidos masticables o como cápsulas de gelatina dura en las que el ingrediente activo se mezcla con un diluyente sólido inerte o como cápsulas de gelatina blanda en las que el ingrediente activo se mezcla con agua o un medio oleoso.

Una dosis terapéuticamente eficaz se refiere a una dosis que produce los efectos terapéuticos para los que se administra. La dosis exacta dependerá del trastorno a tratar y se puede evaluar por el especialista en la técnica usando técnicas conocidas. En general, el agente de unión a E o agente de unión a E/I se administra con de aproximadamente 0.01 µg/kg a aproximadamente 50 mg/kg pro día, preferiblemente de 0.01 mg/kg a aproximadamente 30 mg/kg por día, más preferiblemente de 0.1 mg/kg a aproximadamente 20 mg/kg por día. El polipéptido se puede administrar diariamente (por ejemplo, una vez, dos veces, tres

veces o cuatro veces al día) o menos frecuentemente (por ejemplo, una vez cada dos días, una o dos veces por semana o mensualmente). Además, como se conoce en la técnica, pueden ser necesarios ajustes para la edad así como el peso corporal, estado general, sexo, alimentación, momento de la administración, interacción con fármaco y la gravedad de la enfermedad y se podrán evaluar con experimentación rutinaria por los especialistas en la técnica.

EJEMPLIFICACIÓN

La invención que se está describiendo ahora de forma general se comprenderá más fácilmente con referencia a los siguientes ejemplos que se incluyen únicamente con propósitos de ilustración de ciertos aspectos y modalidades de la presente invención y no tienen por objeto limitar la invención de ningún modo.

Resumen de Secuencias

Muchas de las secuencias a las que se hace referencia en esta solicitud se resumen en la siguiente tabla. A menos que se especifique de otro modo, la extensiones N-terminales se indican con un subrayado sencillo, las colas C-terminales se indican con un subrayado doble, y las secuencias enlazadoras se indican en negrita.

SEC ID N°:	Descripción	Secuencia
1	Dominio ^{10}Fn3 humano de tipo silvestre	VSDVPRDLEVVAATPTSLLISWDAPAVTV RYYRITYGETGGNSPVQEFTVPGSKSTAT ISGLKPGVDYTITVYAVTGRGDSPASSKP ISINYRT
2	^{10}Fn3 humano variante con el motivo de unión a integrina eliminado (RGD cambiado a SGE; los cambios de la SEC ID N°: 1 están subrayados)	VSDVPRDLEVVAATPTSLLISWDAPAVTV RYYRITYGETGGNSPVQEFTVPGSKSTAT ISGLKPGVDYTITVYAVTGSGESPASSKP ISINYRT
3	Monómero de I1 IGF-IR con extensión N-terminal (N+8) y sin cola	VSDVPRDLEVVAATPTSLLISWSARLKVA RYYRITYGETGGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRFRDYQPISIN YRT
4	Monómero de I1 IGF-IR con extensión N-terminal (N+10) y cola de Ser con marcador de His	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDKPSQHHHHHH

SEC ID N°:	Descripción	Secuencia
5	Monómero de EGFR E2 con extensión N terminal (N+8) y sin cola	VSDVPRDLEVVAATPTSLLISWDSGRGSY QYYRITYGETGGNSPVQEFTVPGPVHTAT ISGLKPGVDYTITVYAVTDHKPHADGPHT YHESPISINYRT
6	Monómero de EGFR E2 con extensión N terminal (N+10) y cola de Ser con marcador de His	MGVSDVPRDLEVVAATPTSLLISWDSGRG SYQYYRITYGETGGNSPVQEFTVPGPVHT ATISGLKPGVDYTITVYAVTDHKPHADGP HTYHESPISINYRTEIDKPSQHHHHHH
7	monómero de EGFR E1 con extensión N-terminal (N+8) y sin cola	VSDVPRDLEVVAATPTSLLISWVAGAEDY QYYRITYGETGGNSPVQEFTVPHDLVTAT ISGLKPGVDYTITVYAVTDMMHVEYTEHP ISINYRT
8	monómero de EGFR E1 con extensión N-terminal (N+10) y cola de Ser con marcador de His	MGVSDVPRDLEVVAATPTSLLISWVAGAE DYQYYRITYGETGGNSPVQEFTVPHDLVT ATISGLKPGVDYTITVYAVTDMMHVEYTE HPISINYRTEIDKPSQHHHHHH
9	Cola de Ser	EIDKPSQ
10	Cola de Cys	EIDKPCQ
11	Adaptador $(GS)_{10}$	GSGSGSGSGSGSGSGSGSGS

SEC ID Nº:	Descripción	Secuencia
12	Adaptador basado en Fn	PSTSTST
13	Adaptador $(GS)_5$	GSGSGSGSGS
14	Adaptador $(GGGGS)_3$	GGGGS GGGGS GGGGS
15	Adaptador $(GGGGS)_4$	GGGGS GGGGS GGGGS GGGGS
16	Adaptador $(GGGGS)_5$	GGGGS GGGGS GGGGS GGGGS GGGGS
17	Adaptador $G_4SG_4SG_3SG$	GGGGS GGGGS GGGSG
18	Adaptador	GPGPGPG
19	Adaptador	GPGPGPGPGPG
20	I1-GS10-E2: Tándem de I/E que tiene I1 (con extensión N-terminal (N+8) y cola corta) fusionado a través del adaptador GS_{10} a E2 (con extensión N-terminal (N+8) y sin cola)	VSDVPRDLEVVAATPTSLLISWSARLKVA RYYRITYGETGGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRPRDYQPISIN YRTEIDK**GSGSGSGSGSGSGSGSGSGS**VS DVPRDLEVVAATPTSLLISWDSGRGSYQY YRITYGETGGNSPVQEFTVPGPVHTATIS GLKPGVDYTITVYAVTDHKPHADGPHTYH ESPISINYRT
21	I1-GS10-E2: Tándem de I/E que tiene I1	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT

SEC ID N°:	Descripción	Secuencia
	(con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS_{10} a E2 (con extensión N-terminal (N+8) y cola de Ser)	ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWDSGRGSY QYYRITYGETGGNSPVQEFTVPGPVHTAT ISGLKPGVDYTITVYAVTDHKPHADGPHT YHESPISINYRTEIDKPSQ
22	I1-GS10-E2: Tándem de I/E I1 (con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS_{10} a E2 (con extensión N-terminal (N+8) y cola de Ser con marcador de His)	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWDSGRGSY QYYRITYGETGGNSPVQEFTVPGPVHTAT ISGLKPGVDYTITVYAVTDHKPHADGPHT YHESPISINYRTEIDKPSQHHHHHH
23	E2-GS10-I1: Tándem de E/I que tiene E2 (con extensión N-terminal (N+8) y	VSDVPRDLEVVAATPTSLLISWDSGRGSY QYYRITYGETGGNSPVQEFTVPGPVHTAT ISGLKPGVDYTITVYAVTDHKPHADGPHT YHESPISINYRTEIDK**GSGSGSGSGSGSG**

SEC ID N°:	Descripción	Secuencia
	cola corta) fusionado a través de adaptador GS_{10} a I1 (con extensión N-terminal (N+8) y cola de Ser)	**SGSGSGS**VSDVPRDLEVVAATPTSLLISW SARLKVARYYRITYGETGGNSPVQEFTVP KNVYTATISGLKPGVDYTITVYAVTRFRD YQPISINYRTEIDKPSQ
24	E2-GS10-I1: Tándem de E/I que tiene E2 (con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS_{10} a I1 (con extensión N-terminal (N+8) y cola de Ser)	MGVSDVPRDLEVVAATPTSLLISWDSGRG SYQYYRITYGETGGNSPVQEFTVPGPVHT ATISGLKPGVDYTITVYAVTDHKPHADGP HTYHESPISINYRTEIDK**GSGSGSGSGSG** **SGSGSGSGS**VSDVPRDLEVVAATPTSLLI SWSARLKVARYYRITYGETGGNSPVQEFT VPKNVYTATISGLKPGVDYTITVYAVTRF RDYQPISINYRTEIDKPSQ
25	E2-GS10-I1:Tándem de E/I que tiene E2 (con extensión N-terminal (N+10) y cola corta) fusionado a través	MGVSDVPRDLEVVAATPTSLLISWDSGRG SYQYYRITYGETGGNSPVQEFTVPGPVHT ATISGLKPGVDYTITVYAVTDHKPHADGP HTYHESPISINYRTEIDK**GSGSGSGSGSG** **SGSGSGSGS**VSDVPRDLEVVAATPTSLLI SWSARLKVARYYRITYGETGGNSPVQEFT

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	del adaptador GS_{10} a I1 (con extensión N-terminal (N+8) y cola de Ser con marcador de His)	VPKNVYTATISGLKPGVDYTITVYAVTRF RDYQPISINYRTEIDKPSQHHHHHH
26	I1-GS10-E1: Tándem de I/E que tiene I1 (con extensión N-terminal (N+8) y cola corta) fusionado a través del adaptador GS_{10} a E1 (con extensión N-terminal (N+8) y sin cola)	VSDVPRDLEVVAATPTSLLISWSARLKVA RYYRITYGETGGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRFRDYQPISIN YRTEIDK**GSGSGSGSGSGSGSGSGSGS**VS DVPRDLEVVAATPTSLLISWVAGAEDYQY YRITYGETGGNSPVQEFTVPHDLVTATIS GLKPGVDYTITVYAVTDMMHVEYTEHPIS INYRT
27	I1-GS10-E1: Tándem de I/E que tiene I1 (con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS_{10} a	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWVAGAEDY QYYRITYGETGGNSPVQEFTVPHDLVTAT ISGLKPGVDYTITVYAVTDMMHVEYTEHP

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	E1 (con extensión N-terminal (N+8) y cola de Ser)	ISINYRTEIDKPSQ
28	I1-GS10-E1: Tándem de I/E que tiene I1 (con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS_{10} a E1 (con extensión N-terminal (N+8) y cola de Ser con marcador de His)	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWVAGAEDY QYYRITYGETGGNSPVQEFTVPHDLVTAT ISGLKPGVDYTITVYAVTDMMHVEYTEHP ISINYRTEIDKPSQHHHHHH
29	E1-GS10-I1: Tándem de E/I que tiene E1 (con extensión N-terminal (N+8) y cola corta) fusionado a través del adaptador GS_{10} a I1 (con extensión N-	VSDVPRDLEVVAATPTSLLISWVAGAEDY QYYRITYGETGGNSPVQEFTVPHDLVTAT ISGLKPGVDYTITVYAVTDMMHVEYTEHP ISINYRTEIDK**GSGSGSGSGSGSGSGSGS** **GS**VSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRT

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	terminal (N+8) y sin cola)	
30	E1-GS10-I1: Tándem de E/I que tiene E1 (con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS_{10} a I1 (con extensión N-terminal (N+8) y cola de Ser)	MGVSDVPRDLEVVAATPTSLLISWVAGAE DYQYYRITYGETGGNSPVQEFTVPHDLVT ATISGLKPGVDYTITVYAVTDMMHVEYTE HPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWSAR LKVARYYRITYGETGGNSPVQEFTVPKNV YTATISGLKPGVDYTITVYAVTRFRDYQP ISINYRTEIDKPSQ
31	E1-GS10-I1: Tándem de E/I que tiene E1 (con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS_{10} a I1 (con extensión N-terminal (N+8) y cola de Ser con	MGVSDVPRDLEVVAATPTSLLISWVAGAE DYQYYRITYGETGGNSPVQEFTVPHDLVT ATISGLKPGVDYTITVYAVTDMMHVEYTE HPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWSAR LKVARYYRITYGETGGNSPVQEFTVPKNV YTATISGLKPGVDYTITVYAVTRFRDYQP ISINYRTEIDKPSQHHHHHH

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	marcador de His)	
32	Armazón de ^{10}Fn3, donde los bucles BC, DE y FG se representan por $(X)_n$, $(X)_o$, y $(X)_p$, respectivamente, y n es un número entero de 1-20, o es un número entero de 1-20, y p es un número entero de 1-40	VSDVPRDLEVVAATPTSLLI $(X)_n$YYRITYGETGGNSPVQEFTV$(X)_o$AT ISGLKPGVDYTITVYAV$(X)_p$ISINYRT
33	Secuencia de bucle BC de agente de unión a EGFR E1	SWVAGAEDYQ
34	Secuencia de bucle BC de agente de unión a EGFR E1, donde X es cualquier aminoácido y m y n se seleccionan	X_mVAGAEDYQX_n

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	independientemente de 0 a 5 aminoácidos	
35	Secuencia de bucle DE de agente de unión a EGFR E1	PHDLVT
36	Secuencia de bucle DE de agente de unión a EGFR E1, donde X es cualquier aminoácido y o y p se seleccionan independientemente de 0 a 5 aminoácidos	X_oHDLVX_p
37	Secuencia de bucle FG de agente de unión a EGFR E1	TDMMHVEYTEHP
38	Secuencia de bucle FG de agente de unión a EGFR E1, donde X es cualquier aminoácido y q y r	$X_qDMMHVEYTEHX_r$

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	se seleccionan independientemente de 0 a 5 aminoácidos	
39	Secuencia de bucle BC de agente de unión a EGFR E2	SWDSGRGSYQ
40	Secuencia de bucle BC de agente de unión a EGFR E2, donde X es cualquier amincácido y g y h se seleccionan independientemente de 0 a 5 aminoácidos	$X_gDSGRGSYQX_h$
41	Secuencia de bucle DE de agente de unión a EGFR E2	PGPVHT
42	Secuencia de bucle DE de agente de unión a EGFR E2, dcnde X es cualquier	X_iGPVHX_j

SEC ID N°:	Descripción	Secuencia
	aminoácido y i y j se seleccionan independientemente de 0 a 5 aminoácidos	
43	Secuencia de bucle FG de agente de unión a EGFR E2	TDHKPHADGPHTYHESP
44	Secuencia de bucle FG de agente de unión a EGFR E2, donde X es cualquier aminoácido y k y l se seleccionan independientemente de 0 a 5 aminoácidos	X_kDHKPHADGPHTYHEX_l
45	Secuencia de bucle BC de agente de unión a IGF-IR I1	SWSARLKVAR
46	Secuencia de bucle BC de agente de unión a IGF-IR I1,	X_aSARLKVAX_b

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	donde X es cualquier aminoácido y a y b se seleccionan independientemente de 0 a 5 aminoácidos	
47	Secuencia de bucle DE de agente de unión a IGF-IR I1	PKNVYT
48	Secuencia de bucle DE de agente de unión a IGF-IR I1, donde X es cualquier aminoácido y c y d se seleccionan independientemente de 0 a 5 aminoácidos	X_cKNVYX_d
49	Secuencia de bucle FG de agente de unión a IGF-IR I1	IRFRDYQP
50	Secuencia de bucle FG de agente de	$X_eRFRDYQX_f$

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	unión a IGF-IR I1, donde X es cualquier aminoácido y e y f se seleccionan independientemente de 0 a 5 amincácidos	
51	Adaptador	GPG
52	monómero de EGFR E3 con extensión N-terminal (N+10), cola de Ser y marcador de his	MGVSDVPRDLEVVAATPTSLLISWLPGKL RYQYYRITYGETGGNSPVQEFTVPHDLRT ATISGLKPGVDYTITVYAVTNMMHVEYSE YPISINYRTEIDKPSQHHHHHH
53	E3-GS10-I1: Tándem de E/I que tiene E3 (con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS_{10} a I1 (con extensión N-terminal (N+8) y	MGVSDVPRDLEVVAATPTSLLISWLPGKL RYQYYRITYGETGGNSPVQEFTVPHDLRT ATISGLKPGVDYTITVYAVTNMMHVEYSE YPISINYRTEIDK**GSGSGSGSGSGSGSGS GSGS**VSDVPRDLEVVAATPTSLLISWSAR LKVARYYRITYGETGGNSPVQEFTVPKNV YTATISGLKPGVDYTITVYAVTRFRDYQP ISINYRTEIDKPCQHHHHHH

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	cola de Cys con marcador de his;	
54	I1-GS10-E3: Tándem de I/E que tiene I1 con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS_{10} a E3 (con extensión N-terminal (N+8) y cola de Cys con marcador de his;	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWIPGKLRY QYYRITYGETGGNSPVQEFTVPHDLRTAT ISGLKPGVDYTITVYAVTNMMHVEYSEYP ISINYRTEIDKPCQHHHHHH
55	E1-GS10-I1: Tándem de E/I que tiene E1 (con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS_{10} a I1 (con extensión N-terminal (N+8) y	MGVSDVPRDLEVVAATPTSLLISWVAGAE DYQYYRITYGETGGNSPVQEFTVPHDLVT ATISGLKPGVDYTITVYAVTDMMHVEYTE HPISINYRTEIDK**GSGSGSGSGSGSGSGS** **GSGS**VSDVPRDLEVVAATPTSLLISWSAR LKVARYYRITYGETGGNSPVQEFTVPKNV YTATISGLKPGVDYTITVYAVTRFRDYQP ISINYRTEIDKPCQHHHHHH

SEC ID N°:	Descripción	Secuencia
	cola de Cys con marcador de his)	
56	E2-GS10-I1: Tándem de E/I que tiene E2 (con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS_{10} a I1 (con extensión N-terminal (N+8) y cola de Cys con marcador de his)	MGVSDVPRDLEVVAATPTSLLISWDSGRG SYQYYRITYGETGGNSPVQEFTVPGPVHT ATISGLKPGVDYTITVYAVTDHKPHADGP HTYHESPISINYRTEIDK**GSGSGSGSGSG SGSGSGSGS**VSDVPRDLEVVAATPTSLLI SWSARLKVARYYRITYGETGGNSPVQEFT VPKNVYTATISGLKPGVDYTITVYAVTRF RDYQPISINYRTEIDKPCQHHHHHH
57	I1-GS10-E1: Tándem de I/E que tiene I1 (con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS_{10} a E1 (con extensión N-terminal (N+8) y	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWVAGAEDY QYYRITYGETGGNSPVQEFTVPKDLVTAT ISGLKPGVDYTITVYAVTDMMHVEYTEHP ISINYRTEIDKPCQHHHHHH

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	cola de Cys con marcador de his)	
58	I1-GS10-E2: Tándem de I/E que tiene I1 (con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS_{10} a E2 (con extensión N-terminal (N+8) y cola de Cys con marcador de his)	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWDSGRGSY QYYRITYGETGGNSPVQEFTVPGPVHTAT ISGLKPGVDYTITVYAVTDHKPHADGPHT YHESPISINYRTEIDKPCQHHHHHH
59	Secuencia de bucle BC de agente de unión a EGFR E3	SWLPGKLRYQ
60	Secuencia de bucle BC de agente de unión a EGFR E3, donde X es cualquier aminoácido y s y t	$X_sLPGKLRYQX_t$

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	se seleccionan independientemente de 0 a 5 aminoácidos	
61	Secuencia de bucle DE de agente de unión a EGFR E3	PHDLRT
62	Secuencia de bucle DE de agente de unión a EGFR E3, donde X es cualquier aminoácido y u y w se seleccionan independientemente de 0 a 5 aminoácidos	X_uHDLRX_w
63	Secuencia de bucle FG de agente de unión a EGFR E3	TNMMHVEYSEYP
64	Secuencia de bucle DE de agente de unión a EGFR E3, donde X es cualquier	$X_yNMMHVEYSEYX_z$

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	aminoácido y y y z se seleccionan independientemente de 0 a 5 aminoácidos	
65	Secuencia central de monómero de IGF-IR I1: I1 sin extensión N-terminal o cola C-terminal	EVVAATPTSLLISWSARLKVARYYRITYG ETGGNSPVQEFTVPKNVYTATISGLKPGV DYTITVYAVTRFRDYQPISINYRT
66	Secuencia central de monómero de EGFR E1: E1 sin extensión N-terminal o cola C-terminal	EVVAATPTSLLISWVAGAEDYQYYRITYG ETGGNSPVQEFTVPHDLVTATISGLKPGV DYTITVYAVTDMMHVEYTEHPISINYRT
67	Secuencia central de monómero de EGFR E2: E2 sin extensión N-terminal o cola C-terminal	EVVAATPTSLLISWDSGRGSYQYYRITYG ETGGNSPVQEFTVPGPVHTATISGLKPGV DYTITVYAVTDHKPHADGPHTYHESPISI NYRT
68	Secuencia central de monómero de EGFR E3:	EVVAATPTSLLISWLPGKLRYQYYRITYG ETGGNSPVQEFTVPHDLRTATISGLKPGV

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	SEC ID N°: 82 sin extensión N-terminal o cola C-terminal	DYTITVYAVTNMMHVEYSEYPISINYRT
69	Ejemplo de extensión N-terminal (N+10)	MGVSDVPRDL
70	Ejemplo de extensión N-terminal	GVSDVPRDL
71	Ejemplo de extensión N-terminal (N+8)	VSDVPRDL
72	Ejemplo de extensión N-terminal, donde X es cualquier aminoácido y n es 0, 1 ó 2, preferiblemente cuando n=1, X es Met o Gly y cuando n=2, X es Met-Gly	X_nSDVPRDL
73	Ejemplo de extensión N-terminal, donde X es cualquier	X_nDVPRDL

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	aminoácido y n es 0, 1 ó 2, preferiblemente cuando n=1, X es Met o Gly y cuando n=2, X es Met-Gly	
74	Ejemplo de extensión N-terminal, donde X es cualquier aminoácido y n es 0, 1 ó 2, preferiblemente cuando n=1, X es Met o Gly y cuando n=2, X es Met-Gly	X_nVPRDL
75	Ejemplo de extensión N-terminal, donde X es cualquier aminoácido y n es 0, 1 ó 2, preferiblemente cuando n=1, X es Met	X_nPRDL

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	o Gly y cuando n=2, X es Met-Gly	
76	Ejemplo de extensión N-terminal, donde X es cualquier aminoácido y n es C, 1 ó 2, preferiblemente cuando n=1, X es Met o Gly y cuando n=2, X es Met-Gly	X_nRDL
77	Ejemplo de extensión N-terminal, donde X es cualquier aminoácido y n es C, 1 ó 2, preferiblemente cuando n=1, X es Met o Gly y cuando n=2, X es Met-Gly	X_nDL
78	Cola corta	EIDK

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79	Ejemplo de cola C-terminal	EIDKP
80	Ejemplo de cola C-terminal	EIDKPS
81	Ejemplo de cola C-terminal	EIDKPC
82	Monómero de EGFR E3 con extensión N-terminal (N+8) y sin cola	VSDVPRDLEVVAATPTSLLISWLPGKLRY QYYRITYGETGGNSPVQEFTVPHDLRTAT ISGLKPGVDYTITVYAVTNMMHVEYSEYP ISINYRT
87	E3-GS10-I1: Tándem de E/I que tiene E3 (con extensión N-terminal (N+8) y cola corta) fusionado a través del acaptador GS_{10} a I1 (con extensión N-terminal (N+8) y cola de Cys)	VSDVPRDLEVVAATPTSLLISWLPGKLRY QYYRITYGETGGNSPVQEFTVPHDLRTAT ISGLKPGVDYTITVYAVTNMMHVEYSEYP ISINYRTEIDK**GSGSGSGSGSGSGSGSGS GS**VSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDKPCQ
88	I1-GS10-E3: Tándem	VSDVPRDLEVVAATPTSLLISWSARLKVA

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	de I/E que tiene I1 (con extensión N-terminal (N+8) y cola corta) fusionado a través del adaptador GS_{10} a E3 (con extensión N-terminal (N+8) y cola de Cys)	RYYRITYGETGGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRFRDYQPISIN YRTEIDK**GSGSGSGSGSGSGSGSGSGS**VS DVPRDLEVVAATPTSLLISWLPGKLRYQY YRITYGETGGNSPVQEFTVPHDLRTATIS GLKPGVDYTITVYAVTNMMHVEYSEYPIS INYRTEIDKPCQ
89	E1-GS10-I1: Tándem de E/I que tiene E1 (con extensión N-terminal (N+8) y cola corta) fusionado a través del adaptador GS_{10} a I1 (con extensión N-terminal (N+8) y cola de Cys)	VSDVPRDLEVVAATPTSLLISWVAGAEDY QYYRITYGETGGNSPVQEFTVPHDLVTAT ISGLKPGVDYTITVYAVTDMMHVEYTEHP ISINYRTEIDK**GSGSGSGSGSGSGSGSGS GS**VSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDKPCQ
90	E2-GS10-I1: Tándem de E/I que tiene E2 (con extensión N-	VSDVPRDLEVVAATPTSLLISWDSGRGSY QYYRITYGETGGNSPVQEFTVPGPVHTAT ISGLKPGVDYTITVYAVTDHKPHADGPHT

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	terminal (N+8) y cola corta) fusionado a través del adaptador GS_{10} a I1 (con extensión N-terminal (N+8) y cola de Cys)	YHESPISINYRTEIDK**GSGSGSGSGSGSG SGSGSGS**VSDVPRDLEVVAATPTSLLISW SARLKVARYYRITYGETGGNSPVQEFTVP KNVYTATISGLKPGVDYTITVYAVTRFRD YQPISINYRTEIDKPCQ
91	I1-GS10-E1: Tándem de I/E que tiene I1 (con extensión N-terminal (N+8) y cola corta) fusionado a través del adaptador GS_{10} a E1 (con extensión N-terminal (N+8) y cola de Cys)	VSDVPRDLEVVAATPTSLLISWSARLKVA RYYRITYGETGGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRFRDYQPISIN YRTEIDK**GSGSGSGSGSGSGSGSGSGS**VS DVPRDLEVVAATPTSLLISWVAGAEDYQY YRITYGETGGNSPVQEFTVPHDLVTATIS GLKPGVDYTITVYAVTDMMHVEYTEHPIS INYRTEIDKPCQ
92	I1-GS10-E2: Tándem de I/E que tiene I1 (con extensión N-terminal (N+8) y cola corta)	VSDVPRDLEVVAATPTSLLISWSARLKVA RYYRITYGETGGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRFRDYQPISIN YRTEIDK**GSGSGSGSGSGSGSGSGSGS**VS DVPRDLEVVAATPTSLLISWDSGRGSYQY

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	fusionado a través del adaptador GS_{10} a E2 (con extensión N-terminal (N+8) y cola de Cys)	YRITYGETGGNSPVQEFTVPGPVHTATIS GLKPGVDYTITVYAVTDHKPHADGPHTYH ESPISINYRTEIDKPCQ
93	Adaptador PA3	PAPAPA
94	Adaptador PA6	PAPAPAPAPAPA
95	Adaptador PA9	PAPAPAPAPAPAPAPAPA
96	Cola de Ser modificada	EGSGS
97	Cola de Cys modificada	EGSGC
98	E3-$(PA)_n$-I1: Tándem de E/I que tiene E3 (con extensión N-terminal (N+8) y una cola E) fusionado a través del adaptador $(PA)_n$ a I1 (con extensión N-terminal (N+8) y una cola de	VSDVPRDLEVVAATPTSLLISWLPGKLRY QYYRITYGETGGNSPVQEFTVPHDLRTAT ISGLKPGVDYTITVYAVTNMMHVEYSEYP ISINYRTE**(PA)$_n$**VSDVPRDLEVVAATPT SLLISWSARLKVARYYRITYGETGGNSPV QEFTVPKNVYTATISGLKPGVDYTITVYA VTRFRDYQPISINYRTEGSGX

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	Ser o Cys modificada), donde n = 3, 6 ó 9, y X = Ser o Cys	
99	I1-$(PA)_n$-E3: Tándem de I/E que tiene I1 (con extensión N-terminal (N+8) y una cola E) fusionado a través del adaptador $(PA)_n$ a E3 (con extensión N-terminal (N+8) y una cola de Ser o Cys modificada), donde n = 3, 6 ó 9, y X = Ser o Cys	VSDVPRDLEVVAATPTSLLISWSARLKVA RYYRITYGETGGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRFRDYQPISIN YRTE**(PA)$_n$**VSDVPRDLEVVAATPTSLLI SWLPGKLRYQYYRITYGETGGNSPVQEFT VPHDLRTATISGLKPGVDYTITVYAVTNM MHVEYSEYPISINYRTEGSGX
100	E1-$(PA)_n$-I1: Tándem de E/I que tiene E1 (con extensión N-terminal (N+8) y una cola E) fusionado a	VSDVPRDLEVVAATPTSLLISWVAGAEDY QYYRITYGETGGNSPVQEFTVPHDLVTAT ISGLKPGVDYTITVYAVTDMMHVEYTEHP ISINYRTE**(PA)$_n$**VSDVPRDLEVVAATPT SLLISWSARLKVARYYRITYGETGGNSPV

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	través del adaptador $(PA)_n$ a I1 (con extensión N-terminal (N+8) y una cola de Ser o Cys modificada), donde n = 3, 6 ó 9, y X = Ser o Cys	QEFTVPKNVYTATISGLKPGVDYTITVYA VTRFRDYQPISINYRTEGSGX
101	E2-$(PA)_n$-I1: Tándem de E/I que tiene E2 (con extensión N-terminal (N+8) y una cola E) fusionado a través del adaptador $(PA)_n$ a I1 (con extensión N-terminal (N+8) y una cola de Ser o Cys modificada), donde n = 3, 6 ó 9, y X = Ser o Cys	VSDVPRDLEVVAATPTSLLISWDSGRGSY QYYRITYGETGGNSPVQEFTVPGPVHTAT ISGLKPGVDYTITVYAVTDHKPHADGPHT YHESPISINYRTE**(PA)$_n$**VSDVPRDLEVV AATPTSLLISWSARLKVARYYRITYGETG GNSPVQEFTVPKNVYTATISGLKPGVDYT ITVYAVTRFRDYQPISINYRTEGSGX
102	I1-$(PA)_n$-E1: Tándem	VSDVPRDLEVVAATPTSLLISWSARLKVA

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	de I/E que tiene I1 (con extensión N-terminal (N+8) y una cola E) fusionado a través del adaptador $(PA)_n$ a E1 (con extensión N-terminal (N+8) y una cola de Ser o Cys modificada), donde n = 3, 6 ó 9, y X = Ser o Cys	RYYRITYGETGGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRFRDYQPISIN YRTE(PA)$_n$VSDVPRDLEVVAATPTSLLI SWVAGAEDYQYYRITYGETGGNSPVQEFT VPHDLVCATISGLKPGVDYTITVYAVTDM MHVEYTEHPISINYRTEGSGX
103	I1-$(PA)_n$-E2: Tándem de I/E que tiene I1 (con extensión N-terminal (N+8) y una cola E) fusionado a través del adaptador $(PA)_n$ a E2 (con extensión N-terminal (N+8) y una cola de Ser o Cys	VSDVPRDLEVVAATPTSLLISWSARLKVA RYYRITYGETGGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRFRDYQPISIN YRTE(PA)$_n$VSDVPRDLEVVAATPTSLLI SWDSGRGSYQYYRITYGETGGNSPVQEFT VPGPVHTATISGLKPGVDYTITVYAVTDH KPHADGPHTYHESPISINYRTEGSGX

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	modificada), donde n = 3, 6 ó 9, y X = Ser c Cys	
104	E3-GS10-I1: Tánden de E/I que tiene E3 (con extensión N-terminal (N+8) y cola corta) fusicnado a través del adaptador GS_{10} a I1 (con extensión N-terminal (N+8) y cola de Ser)	VSDVPRDLEVVAATPTSLLISWLPGKLRY QYYRXTYGETCGNSPVQEFTVPHDLRTAT ISGLKPGVDYTITVYAVTNMMHVEYSEYP ISINYRTEIDK**GSGSGSGSGSGSGSGSGS GS**VSDVPRDLEVVAATPTSLXISWSAELK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDKPSQ
105	I1-GS10-E3: Tánden de I/E que tiene I1 con extensión N-terminal (N+8) y cola corta) fusicnado a través del adaptador GS_{10} a E3 (con extensión N-terminal (N+8) y	VSDVPRDLEVVAATPTSLLISWSARLKVA RYYRXTYGETCGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRFRDYQPISIN YRTEXDK**GSGSGSGSGSGSGSGSGSGS**VS DVPRDLEVVAATPTSLLISWXPGKLRYQY YRITYGETGGNSPVQEFTVPHDLRTATIS GXKPGVDYTITVYAVTNMMHVEYSEYPIS INYRTEIDKPSQ

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	cola de Ser)	
106	Monómero de EGFR E4 con extensión N-terminal (N+8) y sin cola	VSDVPRDLEVVAATPTSLLISWHERDGSR QYYRITYGETGGNSPVQEFTVPGGVRTAT ISGLKPGVDYTITVYAVTDYFNPTTHEYI YQTTPISINYRT
107	Monómero de EGFR E4 con extensión N-terminal (N+10) y una Ser con marcador de His	MGVSDVPRDLEVVAATPTSLLISWHERDG SRQYYRITYGETGGNSPVQEFTVPGGVRT ATISGLKPGVDYTITVYAVTDYFNPTTHE YIYQTTPISINYRTEIDKPSQHHHHHH
108	E4 secuencia central de monómero de EGFR: E4 sin extensión N-terminal o cola C-terminal	EVVAATPTSLLISWHERDGSRQYYRITYG ETGGNSPVQEFTVPGGVRTATISGLKPGV DYTITVYAVTDYFNPTTHEYIYQTTPISI NYRT
109	Secuencia de bucle BC de agente de unión a EGFR E4	SWHERDGSRQ
110	Secuencia de bucle DE de agente de unión a EGFR E4	PGGVRT

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111	Secuencia de bucle FG de agente de unión a EGFR E4	TDYFNPTTHEYIYQTTP
112	Monómero de EGFR E5 con extensión N-terminal (N+8) y sin cola	VSDVPRDLEVVAATPTSLLISWWAPVDRY QYYRITYGETGGNSPVQEFTVPRDVYTAT ISGLKPGVDYTITVYAVTDYKPHADGPHT YHESPISINYRT
113	Monómero de EGFR E5 con extensión N-terminal (N+10) y una cola de Ser o Cys modificada, donde X = Ser o Cys; puede comprender opcionalmente un marcador de 6X His	MGVSDVPRDLEVVAATPTSLLISWWAPVD RYQYYRITYGETGGNSPVQEFTVPRDVYT ATISGLKPGVDYTITVYAVTDYKPHADGP HTYHESPISINYRTEIDKPXQ
114	E5 secuencia central de monómero de EGFR: E5 sin extensión N-terminal o cola C-terminal	EVVAATPTSLLISWWAPVDRYQYYRITYG ETGGNSPVQEFTVPRDVYTATISGLKPGV DYTITVYAVTDYKPHADGPHTYHESPISI NYRT

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115	Secuencia de bucle BC de agente de unión a EGFR E5	SWWAPVDRYQ
116	Secuencia de bucle DE de agente de unión a EGFR E5	PRDVYT
117	Secuencia de bucle FG de agente de unión a EGFR E5	TDYKPHADGPHTYHESP
118	E4-GS10-I1: Tándem de E/I que tiene E4 (con extensión N-terminal (N+8) y cola corta) fusionado a través del adaptador GS10 a I1 (con extensión N-terminal (N+8) y sin cola)	VSDVPRDLEVVAATPTSLLISWHERDGSR QYYRITYGETGGNSPVQEFTVPGGVRTAT ISGLKPGVDYTITVYAVTDYFNPTTHEYI YQTTPISINYRTEIDK**GSGSGSGSGSGSG SGSGSGS**VSDVPRDLEVVAATPTSLLISW SARLKVARYYRITYGETGGNSPVQEFTVP KNVYTATISGLKPGVDYTITVYAVTRFRD YQPISINYRT
119	E4-GS10-I1: Tándem de E/I que tiene E4	VSDVPRDLEVVAATPTSLLISWHERDGSR QYYRITYGETGGNSPVQEFTVPGGVRTAT

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	(con extensión N-terminal (N+8) y cola corta) fusionado a través del adaptador GS10 a I1 (con extensión N-terminal (N+8) y cola de Ser o Cys modificada), donde X = Ser o Cys; puede comprender opcionalmente un marcador de 6X His	ISGLKPGVDYTITVYAVTDYFNPTTHEYI YQTTPISINYRTEIDK**GSGSGSGSGSGSG SGSGSGS**VSDVPRDLEVVAATPTSLLISW SARLKVARYYRITYGETGGNSPVQEFTVP KNVYTATISGLKPGVDYTITVYAVTRFRD YQPISINYRTEIDKPXQ
120	E4-GS10-I1: Tándem de E/I que tiene E4 (con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS10 a I1 (con extensión N-terminal (N+8) y	MGVSDVPRDLEVVAATPTSLLISWHERDG SRQYYRITYGETGGNSPVQEFTVPGGVRT ATISGLKPGVDYTITVYAVTDYFNPTTHE YIYQTTPISINYRTEIDK**GSGSGSGSGSG SGSGSGSGS**VSDVPRDLEVVAATPTSLLI SWSARLKVARYYRITYGETGGNSPVQEFT VPKNVYTATISGLKPGVDYTITVYAVTRF RDYQPISINYRTEIDKPCQHHHHHH

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	cola de Cys) con marcador de his	
121	E4-$(PA)_n$-I1: Tándem de E/I que tiene E4 (con extensión N-terminal (N+8) y una cola E) fusionado a través del adaptador $(PA)_n$ a I1 (con extensión N-terminal (N+8) y cola de Ser o Cys modificada), donde n = 3, 6 ó 9, y X = Ser o Cys; puede comprender opcionalmente un marcador de 6X His	VSDVPRDLEVVAATPTSLLISWHERDGSR QYYRITYGETGGNSPVQEFTVPGGVRTAT ISGLKPGVDYTITVYAVTDYFNPTTHEYI YQTTPISINYRTE**(PA)$_n$**VSDVPRDLEVV AATPTSLLISWSARLKVARYYRITYGETG GNSPVQEFTVPKNVYTATISGLKPGVDYT ITVYAVTRFRDYQPISINYRTEIDKPCCH HHHHH
122	I1-GS10-E4: Tándem de I/E que tiene I1 (con extensión N-terminal (N+8) y cola corta)	VSDVPRDLEVVAATPTSLLISWSARLKVA RYYRITYGETGGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRFRDYQPISIN YRTEIDK**GSGSGSGSGSGSGSGSGSGS**VS DVPRDLEVVAATPTSLLISWHERDGSRQY

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	fusionado a través del adaptador GS10 a E4 (que tiene extensión N-terminal (N+8) y sin cola)	YRITYGETGGNSPVQEFTVPGGVRTATIS GLKPGVDYTITVYAVTDYFNPTTHEYIYQ TTPISINYRT
123	I1-GS10-E4: Tándem de I/E que tiene I1 (con extensión N-terminal (N+8) y cola corta) fusionado a través del adaptador GS10 a E4 (con extensión N-terminal (N+8) y cola de Ser o Cys modificada), donde X = Ser o Cys; puede comprender opcionalmente un marcador de 6X His	VSDVPRDLEVVAATPTSLLISWSARLKVA RYYRITYGETGGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRFRDYQPISIN YRTEIDK**GSGSGSGSGSGSGSGSGSGS**VS DVPRDLEVVAATPTSLLISWHERDGSRQY YRITYGETGGNSPVQEFTVPGGVRTATIS GLKPGVDYTITVYAVTDYFNPTTHEYIYQ TTPISINYRTEIDKPXQ
124	I1-GS10-E4: Tándem de I/E que tiene I1	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT

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	(con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS10 a E4 (con extensión N-terminal (N+8) y a cola de Cys) con marcador de his	ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWHERDGSR QYYRITYGETGGNSPVQEFTVPGGVRTAT ISGLKPGVDYTITVYAVTDYFNPTTHEYI YQTTPISINYRTEIDKPCQHHHHHH
125	I1-$(PA)_n$-E4: Tándem de I/E que tiene I1 (con extensión N-terminal (N+8) y una cola E) fusionado a través del adaptador $(PA)_n$ a E4 (con extensión N-terminal (N+8) y cola de Ser o Cys modificada), donde n = 3, 6 ó 9, y X = Ser o Cys; puede comprender	VSDVPRDLEVVAATPTSLLISWSARLKVA RYYRITYGETGGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRFRDYQPISIN YRTE**(PA)$_n$**VSDVPRDLEVVAATPTSLLI SWHERDGSRQYYRITYGETGGNSPVQEFT VPGGVRTATISGLKPGVDYTITVYAVTDY FNPTTHEYIYQTTPISINYRTEIDKPXQ

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	opcionalmente un marcador de 6X His	
126	E5-GS10-I1: Tándem de E/I que tiene E5 (con extensión N-terminal (N+8) y cola corta) fusionado a través del adaptador GS10 I1 (con extensión N-terminal (N+8) y sin cola)	VSDVPRDLEVVAATPTSLLISWWAPVDRY QYYRITYGETGGNSPVQEFTVPRDVYTAT ISGLKPGVDYTITVYAVTDYKPHADGPHT YHESPISINYRTEIDK**GSGSGSGSGSGSG SGSGSGS**VSDVPRDLEVVAATPTSLLISW SARLKVARYYRITYGETGGNSPVQEFTVP KNVYTATISGLKPGVDYTITVYAVTRFRD YQPISINYRT
127	E5-GS10-I1: Tándem de E/I que tiene E5 (con extensión N-terminal (N+8) y cola corta) fusionado a través del adaptador GS10 a I1 (con extensión N-terminal (N+8) y cola de Ser o Cys	VSDVPRDLEVVAATPTSLLISWWAPVDRY QYYRITYGETGGNSPVQEFTVPRDVYTAT ISGLKPGVDYTITVYAVTDYKPHADGPHT YHESPISINYRTEIDK**GSGSGSGSGSGSG SGSGSGS**VSDVPRDLEVVAATPTSLLISW SARLKVARYYRITYGETGGNSPVQEFTVP KNVYTATISGLKPGVDYTITVYAVTRFRD YQPISINYRTEIDKPXQ

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	modificaca), donde X = Ser o Cys; puede comprender opcionalmente un marcador de 6X His	
128	E5-GS10-I1: Tándem de E/I que tiene E5 (con extensión N-terminal (N+10) y cola corta) fusionadc a través del adaptador GS10 a I1 (con extensión N-terminal (N+8) y a cola de Cys, con un marcador de His	MGVSDVPRDLEVVAATPTSLLISWWAPVD RYQYYRITYGETGGNSPVQEFTVPRDVYT ATISGLKPGVDYTITVYAVTDYKPHADGP HTYHESPISINYRTEIDK**GSGSGSGSGSG SGSGSGSGS**VSDVPRDLEVVAATPTSLLI SWSARLKVARYYRITYGETGGNSPVQEFT VPKNVYTATISGLKPGVDYTITVYAVTRF RDYQPISINYRTEIDKPCQHHHHHH
129	E5-$(PA)_n$-I1: Tándem de E/I que tiene E5 (con extensión N-terminal (N+8) y una cola E) fusionado a través del adaptadcr	VSDVPRDLEVVAATPTSLLISWWAPVDRY QYYRITYGETGGNSPVQEFTVPRDVYTAT ISGLKPGVDYTITVYAVTDYKPHADGPHT YHESPISINYRTE**(PA)$_n$**VSDVPRDLEVV AATPTSLLISWSARLKVARYYRITYGETG GNSPVQEFTVPKNVYTATISGLKPGVDYT

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	$(PA)_n$ a I1 (con extensión N-terminal (N+8) y cola de Ser o Cys modificada), donde n = 3, 6 ó 9, y X = Ser o Cys; puede comprender opcionalmente un marcador de 6X His	ITVYAVTRFRDYQPISINYRTEIDKPXQ
130	I1-GS10-E5: Tándem de I/E que tiene I1 (con extensión N-terminal (N+8) y cola corta) fusionado a través del adaptador GS10 a E5 (con extensión N-terminal (N+8) y sin cola)	VSDVPRDLEVVAATPTSLLISWSARLKVA RYYRITYGETGGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRFRDYQPISIN YRTEIDK**GSGSGSGSGSGSGSGSGSGS**VS DVPRDLEVVAATPTSLLISWWAPVDRYQY YRITYGETGGNSPVQEFTVPRDVYTATIS GLKPGVDYTITVYAVTDYKPHADGPHTYH ESPISINYRT
131	I1-GS10-E5: Tándem de I/E que tiene I1 (con extensión N-	VSDVPRDLEVVAATPTSLLISWSARLKVA RYYRITYGETGGNSPVQEFTVPKNVYTAT ISGLKPGVDYTITVYAVTRFRDYQPISIN

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	terminal (N+8) y cola corta) fusionado a través del adaptador GS10 a E5 (con extensión N-terminal (N+8) y cola de Ser o Cys modificada), donde X = Ser o Cys; puede comprender opcionalmente un marcador de 6X His	YRTEIDK**GSGSGSGSGSGSGSGSGSGS**VS DVPRDLEVVAATPTSLLISWWAPVDRYQY YRITYGETGGNSPVQEFTVPRDVYTATIS GLKPGVDYTITVYAVTDYKPHADGPHTYH ESPISINYRTEIDKPXQ
132	I1-GS10-E5: Tándem de I/E que tiene I1 (con extensión N-terminal (N+10) y cola corta) fusionado a través del adaptador GS10 a E5 (con extensión N-terminal (N+8) y a cola de Cys) con un	MGVSDVPRDLEVVAATPTSLLISWSARLK VAEYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWWAPVDRY QYYRITYGETGGNSPVQEFTVPRDVYTAT ISGLKPGVDYTITVYAVTDYKPHADGPHT YHESPISINYRTEIDKPCQHHHHHH

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	marcador de His	
133	I1-$(PA)_n$-E5: Tándem de I/E que tiene I1 (con extensión N-terminal (N+8) y una cola E) fusionado a través del adaptador $(PA)_n$ a E5 (con extensión N-terminal (N+8) y cola de Ser o Cys modificada), donde n = 3, 6 ó 9, y X = Ser o Cys; puede comprender opcionalmente un marcador de 6X His	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTE**(PA)$_n$**VSDVPRDLEVVAATPTSL LISWWAPVDRYQYYRITYGETGGNSPVQE FTVPRDVYTATISGLKPGVDYTITVYAVT DYKPHADGPHTYHESPISINYRTEIDKPX Q
134	Secuencia de bucle 3C de agente de unión a EGFR E4, donde X es cualquier aminoácido y g y h se seleccionan	X_gHERDGSRQX_h

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	independientemente de 0 a 5 aminoácidos	
135	Secuencia de bucle DE de agente de unión a EGFR E4, donde X es cualquier amincácido y i y j se seleccionan independientemente de 0 a 5 aminoácidos	X_iGCVRX_j
136	Secuencia de bucle FG de agente de unión a EGFR E4, donde X es cualquier amincácido y k y l se seleccionan independientemente de 0 a 5 aminoácidos	$X_kDYFNPTTHEYIYQTTX_l$
137	Secuencia de bucle BC de agente de unión a EGFR E5,	$X_gWAPVDRYQX_h$

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	donde X es cualquier aminoácido y g y h se seleccionan independientemente de 0 a 5 aminoácidos	
138	Secuencia de bucle DE de agente de unión a EGFR E5, donde X es cualquier aminoácido y i y j se seleccionan independientemente de 0 a 5 aminoácidos	X_iRDVYX_j
139	Secuencia de bucle FG de agente de unión a EGFR E5, donde X es cualquier aminoácido y k y l se seleccionan independientemente de 0 a 5 aminoácidos	X_kDYKPHADGPHTYHESX_l

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140	Monómero de EGFR E85 con extensión N-terminal (N+10) y cola de Ser con marcador de His	MGVSDVPRDLEVVAATPTSLLISWTQGST HYQYYRITYGETGGNSPVQEFTVPGMVYT ATISGLKPGVDYTITVYAVTDYFDRSTHE YKYRTTPISINYRTEIDKPSQHHHHHH
141	Núcleo de monómero de EGFR E85: monómero de E85 sin extensión N-terminal o cola C-terminal	EVVAATPTSLLISWTQGSTHYQYYRITYG ETGGNSPVQEFTVPGMVYTATISGLKPGV DYTITVYAVTDYFDRSTHEYKYRTTPISI NYRT
142	monómero de EGFR E85, donde X_1 se selecciona entre el grupo consistente en SEC ID N°: 69-77 y X_2 se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó	X_1EVVAATPTSLLISWTQGSTHYQYYRIT YGETGGNSPVQEFTVPGMVYTATISGLKP GVDYTITVYAVTDYFDRSTHEYKYRTTPI SINYRTX_2

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	10; puede comprender opcionalmente un marcador de his	
143	Secuencia de bucle BC de agente de unión a EGFR E85	SWTQGSTHYQ
144	Secuencia de bucle DE de agente de unión a EGFR E85	PGMVYT
145	Secuencia de bucle FG de agente de unión a EGFR E85	TDYFDRSTHEYKYRTTP
146	Secuencia de bucle BC de agente de unión a EGFR E85, donde X es cualquier aminoácido y g y h se seleccionan independientemente de 0 a 5 aminoácidos	$X_gTQGSTHYQX_h$
147	Secuencia de bucle	X_iGMVYX_j

SEC ID N°:	Descripción	Secuencia
	DE de agente de unión a EGFR E85, donde X es cualquier aminoácido y i y j se seleccionan independientemente de 0 a 5 amincácidos	
148	Secuencia de bucle FG de agente de unión a EGFR E85, donde X es cualquier aminoácido y k y l se seleccionan independientemente de 0 a 5 amincácidos	X_kDYFDRSTHEYKYRTTX_1
149	E85-GS10-I1: Tándem de E/I que tiene E85 (con extensión N-terminal (N+10) y una cola corta) fusionado a través del adaptador GS10 a	MGVSDVPRDLEVVAATPTSLLISWTQGST HYQYYRITYGETGGNSPVQEFTVPGMVYT ATISGLKPGVDYTITVYAVTDYFDRSTHE YKYRITTPISINYRTEIDK**GSGSGSGSGSG SGSGSGSGS**VSDVPRDLEVVAATPTSLLI SWSARLKVARYYRITYGETGGNSPVQEFT VPKNVYTATISGLKPGVDYTITVYAVTRF

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	I1 (con extensión N-terminal (N+8) y cola de Cys) con un marcador de 6X His	RDYQPISINYRTEIDKPCQHHHHHH
150	Núcleo de E85-GS10-I1, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	X_1EVVAATPTSLLISWTQGSTHYQYYRIT YGETGGNSPVQEFTVPGMVYTATISGLKP GVDYTITVYAVTDYFDRSTHEYKYRTTPI SINYRTEIDK**GSGSGSGSGSGSGSGSGSG SVSDVPRDL**EVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVYTA TISGLKPGVDYTITVYAVTRFRDYQPISI NYRTX_2

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151	núcleo de E85-$(PA)_n$-I1, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	X_1EVVAATPTSLLISWTQGSTHYQYYRIT YGETGGNSPVQEFTVPGMVYTATISGLKP GVDYTITVYAVTDYFDRSTHEYKYRTTPI SINYRTE**(PA)$_n$**VSDVPRDLEVVAATPTS LLISWSARLKVARYYRITYGETGGNSPVQ EFTVPKNVYTATISGLKPGVDYTITVYAV TRFRDYQPISINYRTX_2
152	I1-GS10-E85: Tándem de I/E que tiene I1 (con extensión N-terminal (N+10) y	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDK**GSGSGSGSGSGSGSGSGSGS**

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	una cola corta) fusionado a través del adaptador GS10 a E85 (con extensión N-terminal (N+8) y cola de Cys) con un marcador de 6X His	VSDVPRDLEVVAATPTSLLISWTQGSTHY QYYRITYGETGGNSPVQEFTVPGMVYTAT ISGLKPGVDYTITVYAVTDYFDRSTHEYK YRTTPISINYRTEIDKPCQHHHHHH
153	Núcleo de I1-GS10-E85, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLKP GVDYTITVYAVTRFRDYQPISINYRTEID KGSGSGSGSGSGSGSGSGSGSVSDVPRDL EVVAATPTSLLISWTQGSTHYQYYRITYG ETGGNSPVQEFTVPGMVYTATISGLKPGV DYTITVYAVTDYFDRSTHEYKYRTTPISI NYRTX_2

SEC ID N°:	Descripción	Secuencia
	SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	
154	Núcleo de I1-$(PA)_n$-E85, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	X_1EVVAATPTSLLISWSARIKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLKP GVDYTITVYAVTRFRDYQPISINYRT**(P A)$_n$**VSDVPRDLEVVAATPTSLLISWTQGS THYQYYRITYGETGGNSPVQEFTVPGMVY TATISGLKPGVDYTITVYAVTDYFDRSTH EYKYRTTPISINYRTX_2
155	Monómero de EGFR E90	MGVSDVPRDLEVVAATPTSLLISWYWEGL

SEC ID N°:	Descripción	Secuencia
	con extensión N-terminal (N+10) y cola de Ser con marcador de His	PYQYYRITYGETGGNSPVQEFTVPRDVNT ATISGLKPGVDYTITVYAVTDWYNPDTHE YIYHTIPISINYRTEIDKPSQHHHHHH
156	Núcleo de monómero de EGFR E90: monómero de E90 sin extensión N-terminal o cola C-terminal	EVVAATPTSLLISWYWEGLPYQYYRITYG ETGGNSPVQEFTVPRDVNTATISGLKPGV DYTITVYAVTDWYNPDTHEYIYHTIPISI NYRT
157	Monómero de EGFR E90, donde X_1 se selecciona entre el grupo consistente en SEC ID N°: 69-77 y X_2 se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10; puede comprender	X_1EVVAATPTSLLISWYWEGLPYQYYRIT YGETGGNSPVQEFTVPRDVNTATISGLKP GVDYTITVYAVTDWYNPDTHEYIYHTIPI SINYRTX_2

SEC ID N°:	Descripción	Secuencia
	opcionalmente un marcador de his	
158	Secuencia de bucle EC de agente de unión a EGFR E90	SWYWEGLPYQ
159	Secuencia de bucle DE de agente de unión a EGFR E90	PREVNT
160	Secuencia de bucle FG de agente de unión a EGFR E90	TDWYNPDTHEYIYHTIP
161	Secuencia de bucle BC de agente de unión a EGFR E90, donde X es cualquier aminoácido y g y h se seleccionan independientemente de 0 a 5 aminoácicos	$X_gYWEGLPYQX_h$
162	Secuencia de bucle DE de agente de	X_iRDVNX_j

SEC ID N°:	Descripción	Secuencia
	unión a EGFR E90, donde X es cualquier aminoácico y i y j se seleccionan independientemente de 0 a 5 aminoácidos	
163	Secuencia de bucle FG de agente de unión a EGFR E90, donde X es cualquier aminoácido y k y l se seleccionan independientemente de 0 a 5 aminoácidos	X_kDWYNPDTHEYIYHTIX$_l$
164	E90-GS10-I1: Tándem de E/I que tiene E90 (con extensión N-terminal (N+10) y una cola corta) fusionado a través del adaptador GS10 a I1 (con extensión N-	MGVSDVPRDLEVVAATPTSLLISWYWEGL PYQYYRITYGETGGNSPVQEFTVPRDVNT ATISGLKPGVDYTITVYAVTDWYNPDTHE YIYHTIPISINYRTEIDK**GSGSGSGSGSG SGSGSGSGS**VSDVPRDLEVVAATPTSLLI SWSARLKVARYYRITYGETGGNSPVQEFT VPKNVYTATISGLKPGVDYTITVYAVTRF RDYQPISINYRTEIDKPCQHHHHHH

SEC ID N°:	Descripción	Secuencia
	terminal (N+8) y cola de Cys) con un marcador de 6X His	
165	Núcleo de E90-GS10-[illegible]1, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	X_1EVVAATPTSLLISWYWEGLPYQYYR[illegible]T YGETGGNSPVQEFTVPRDVNTATISGLKP GVDYTITVYAVTDWYNPD[illegible]HEYIY[illegible]TIPI SINYRTEIDK**GSGSGSGSGSGSGSGSGSG SVSDVPRDL**EVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVYTA TISGLKPGVDYTITVYAV[illegible]RFRDYQPISI NYRTX_2
166	Núcleo de E90-$(PA)_n$-	X_1EVVAATPTSLLISWYWEGLPYQYYRIT

SEC ID N°:	Descripción	Secuencia
	I1, donde X1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	YGETGGNSPVQEFTVPRDVNTATISGLKP GVDYTITVYAVTDWYNPDTHEYIYHTIPI SINYRTE**(PA)**$_n$VSDVPRDLEVVAATPTS LLISWSARLKVARYYRITYGETGGNSPVQ EFTVPKNVYTATISGLKPGVDYTITVYAV TRFRDYQPISINYRTX_2
167	I1-GS10-E90: Tándem de I/E que tiene I1 (con extensión N-terminal (N+10) y una cola corta)	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWYWEGLPY

SEC ID N°:	Descripción	Secuencia
	fusionado a través del adaptador GS10 a E90 (con extensión N-terminal (N+8) y cola de Cys) con un marcador de 6X His	QYYRITYGETGGNSPVQEFTVPRDVNTAT ISGLKPGVDYTITVYAVTDWYNPDTHEYI YHTIPISINYRTEIDKPCQHHHHHH
168	Núcleo de I1-GS10-E90, donde X_1 es opcional y cuando está presente se seleccicna entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLKP GVDYTITVYAVTRFRDYQPISINYRTEID K**GSGSGSGSGSGSGSGSGSGS**VSDVPRDL EVVAATPTSLLISWYWEGLPYQYYRITYG ETGGNSPVQEFTVPRDVNTATISGLKPGV DYTITVYAVTDWYNPDTHEYIYHTIPISI NYRTX_2

SEC ID N°:	Descripción	Secuencia
	X_2 es SEC ID N°: 9 ó 10	
169	Núcleo de I1-$(PA)_n$-E90, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLKP GVDYTITVYAVTRFRDYQPISINYRTE**(P A)$_n$**VSDVPRDLEVVAATPTSLLISWYWEG LPYQYYRITYGETGGNSPVQEFTVPRDVN TATISGLKPGVDYTITVYAVTDWYNPDTH EYIYHTIPISINYRTX_2
170	Monómero de EGFR E96 con extensión N-	MGVSDVPRDLEVVAATPTSLLISWASNRG TYQYYRITYGETGGNSPVQEFTVPGGVST

SEC ID N°:	Descripción	Secuencia
	terminal (N+10) y cola de Ser con marcador de His	ATISGLKPGVDYTITVYAVTDAFNPITHE YNYFTTPISINYRTEIDKPSQHHHHHH
171	Núcleo de monómero de EGFR E96: monónero de E96 sin extensión N-terminal o cola C-terminal	EVVAATPTSLLISWASNRGTYQYYRITYG ETGGNSPVQEFTVPGGVSTATISGLKPGV DYTITVYAVTDAFNPTTHEYNYFTTPISI NYRT
172	Monómero de EGFR E96, donde X_1 se selecciona entre el grupo consistente en SEC ID N°: 69-77 y X_2 se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10; puede comprender opcionalmente un	X_1EVVAATPTSLLISWASNRGTYQYYRIT YGETGGNSPVQEFTVPGGVSTATISGLKP GVDYTITVYAVTDAFNPTTHEYNYFTTPI SINYRTX_2

SEC ID N°:	Descripción	Secuencia
	marcador de his	
173	Secuencia de bucle BC de agente de unión a EGFR E96	SWASNRGTYQ
174	Secuencia de bucle DE de agente de unión a EGFR E96	PGGVST
175	Secuencia de bucle FG de agente de unión a EGFR E96	TDAFNPTTHEYNYFTTP
176	Secuencia de bucle BC de agente de unión a EGFR E96, donde X es cualquier aminoácido y g y h se seleccionan independientemente de 0 a 5 aminoácidos	X_gASNRGTYQX_h
177	Secuencia de bucle DE de agente de unión a EGFR E96,	X_iGGVSX_j

SEC ID N°:	Descripción	Secuencia
	donde X es cualquier aminoácido y i y j se seleccionan independientemente de 0 a 5 aminoácidos	
178	Secuencia de bucle FG de agente de unión a EGFR E96, donde X es cualquier aminoácido y k y l se seleccionan independientemente de 0 a 5 aminoácidos	X_kDAFNPTTHEYNYFTTX$_l$
179	E96-GS10-I1: Tándem de E/I que tiene E96 (con extensión N-terminal (N+10) y una cola corta) fusionado a través del adaptador GS10 a I1 (con extensión N-terminal (N+8) y	MGVSDVPRDLEVVAATPTSLLISWASNRG TYQYYRITYGETGGNSPVQEFTVPGGVST ATISGLKPGVDYTITVYAVTDAFNPTTHE YNYFTTPISINYRTEIDK**GSGSGSGSGSG SGSGSGSGS**VSDVPRDLEVVAATPTSLLI SWSARLKVARYYRITYGETGGNSPVQEFT VPKNVYTATISGLKPGVDYTITVYAVTRF RDYQPISINYRTEIDKPCQHHHHHH

SEC ID N°:	Descripción	Secuencia
	cola de Cys) con un marcador de 6X His	
180	Núcleo de E96-GS10-I1, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	X_1EVVAATPTSLLISWASNRGTYQYYRIT YGETGGNSPVQEFTVPGGVSTATISGLKP GVDYTITVYAVTDAFNPTTHEYNYFTTPI SINYRTEIDK**GSGSGSGSGSGSGSGSGSG SVSDVPRDL**EVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVYTA TISGLKPGVDYTITVYAVTRFRDYQPISI NYRTX_2
181	Núcleo de E96-$(PA)_n$-I1, donde X1 es	X_1EVVAATPTSLLISWASNRGTYQYYRIT YGETGGNSPVQEFTVPGGVSTATISGLKP

SEC ID N°:	Descripción	Secuencia
	opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	GVDYTITVYAVTDAFNPTTHEYNYFTTPI SINYRTE**(PA)**$_n$VSDVPRDLEVVAATPTS LLISWSARLKVARYYRITYGETGGNSPVQ EFTVPKNVYTATISGLKPGVDYTITVYAV TRFRDYQPISINYRTX_2
182	I1-GS10-E96: Tándem de I/E que tiene I1 (con extensión N-terminal (N+10) y una cola corta) fusionado a través	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWASNRGTY QYYRITYGETGGNSPVQEFTVPGGVSTAT

SEC ID N°:	Descripción	Secuencia
	del adaptacor GS10 a E96 (con extensión N-terminal (N+8) y cola de Cys) con un marcador de 6X His	ISGLKPGVDYTITVYAVTDAFNPITHEYN YFTTPISINYRTEIDKPCQHHHHHH
183	Núcleo de I1-GS10-E96, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLKP GVDYTITVYAVTRFRDYQPISINYRTEID K**GSGSGSGSGSGSGSGSGSGS**VSDVPRDL EVVAATPTSLLISWASNRGTYQYYRITYG ETGGNSPVQEFTVPGGVSTATISGLKPGV DYTITVYAVTDAFNPTTHEYNYFTTPISI NYRTX_2

SEC ID N°:	Descripción	Secuencia
	10	
184	Núcleo de I1-$(PA)_n$-E96, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLKP GVDYTITVYAVTRFRDYQPISINYRTE**(PA)$_n$**VSDVPRDLEVVAATPTSLLISWASNR GTYQYYRITYGETGGNSPVQEFTVPGGVS TATISGLKPGVDYTITVYAVTDAFNPTTH EYNYFTTPISINYRTX_2
185	Monómero de EGFR E105 con extensión N-terminal (N+10) y	MGVSDVPRDLEVVAATPTSLLISWDAPTS RYQYYRITYGETGGNSPVQEFTVPGGLST ATISGLKPGVDYTITVYAVTDYKPHADGP

SEC ID N°:	Descripción	Secuencia
	cola de Ser con marcador de His	HTYHESPISINYRTEIDKPSQHHHHHH
186	Núcleo de monómero de EGFR E105: monómero de E105 sin extensión N-terminal o cola C-terminal	EVVAATPTSLLISWDAPTSRYQYYRITYG ETGGNSPVQEFTVPGGLSTATISGLKPGV DYTITVYAVTDYKPHADGPHTYHESPISI NYRT
187	Monómero de EGFR E105, donde X_1 se selecciona entre el grupo consistente en SEC ID N°: 69-77 y X_2 se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10; puede comprender opcionalmente un marcador de his	X_1EVVAATPTSLLISWDAPTSRYQYYRIT YGETGGNSPVQEFTVPGGLSTATISGLKP GVDYTITVYAVTDYKPHADGPHTYHESPI SINYRTX_2

SEC ID N°:	Descripción	Secuencia
188	Secuencia de bucle EC de agente de unión a EGFR E105	SWDAPTSRYQ
189	Secuencia de bucle DE de agente de unión a EGFR E105	PGGLST
117	Secuencia de bucle FG de agente de unión a EGFR E105	TDYKPHADGPHTYHESP
190	Secuencia de bucle EC de agente de unión a EGFR E105, conde X es cualquier aminoácido y g y h se seleccionan independientemente de 0 a 5 aminoácidos	X_gDAPTSRYQX_h
191	Secuencia de bucle DE de agente de unión a EGFR E105, conde X es cualquier	X_iGGLSX$_j$

SEC ID N°:	Descripción	Secuencia
	aminoácido y i y j se seleccionan independientemente de 0 a 5 aminoácidos	
139	Secuencia de bucle FG de agente de unión a EGFR E105, donde X es cualquier aminoácido y k y l se seleccionan independientemente de 0 a 5 aminoácidos	X_kDYKPHADGPHTYHESX$_l$
192	E105-GS10-I1: Tándem de E/I que tiene E105 (con extensión N-terminal (N+10) y una cola corta) fusionado a través del adaptador GS10 a I1 (con extensión N-terminal (N+8) y cola de Cys) con un	MGVSDVPRDLEVVAATPTSLLISWDAPTS RYQYYRITYGETGGNSPVQEFTVPGGLST ATISGLKPGVDYTITVYAVTDYKPHADGP HTYHESPISINYRTEIDK**GSGSGSGSGSG SGSGSGSGS**VSDVPRDLEVVAATPTSLLI SWSARLKVARYYRITYGETGGNSPVQEFT VPKNVYTATISGLKPGVDYTITVYAVTRF RDYQPISINYRTEIDKPCQHHHHHH

SEC ID N°:	Descripción	Secuencia
	marcador de 6X His	
193	Núcleo de E105-GS10-I1, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	X_1EVVAATPTSLLISWDAPTSRYQYYRIT YGETGGNSPVQEFTVPGGLSTATISGLKP GVDYTITVYAVTDYKPHADGPHTYHESPI SINYRTEIDKGSGSGSGSGSGSGSGSGSG SVSDVPRDLEVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVYTA TISGLKPGVDYTITVYAVTRFRDYQPISI NYRTX_2
194	Núcleo de E105-$(PA)_n$-I1, donde X1 es opcional y cuando	X_1EVVAATPTSLLISWDAPTSRYQYYRIT YGETGGNSPVQEFTVPGGLSTATISGLKP GVDYTITVYAVTDYKPHADGPHTYHESPI

SEC ID N°:	Descripción	Secuencia
	está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	SINYRTE**(PA)**$_n$VSDVPRDLEVVAATPTS LLISWSARLKVARYYRITYGETGGNSPVQ EFTVPKNVYTATISGLKPGVDYTITVYAV TRFRDYQPISINYRTX$_2$
195	I1-GS10-E105: Tándem de I/E que tiene I1 (con extensión N-terminal (N+10) y una cola corta) fusionado a través del adaptador GS10 a	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWDAPTSRY QYYRITYGETGGNSPVQEFTVPGGLSTAT ISGLKPGVDYTITVYAVTDYKPHADGPHT

SEC ID N°:	Descripción	Secuencia
	E105 (con extensión N-terminal (N+8) y cola de Cys) con un marcador de 6X His	YHESPISINYRTEIDKPCQHHHHHH
196	Núcleo de I1-GS10-E105, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLKP GVDYTITVYAVTRFRDYQPISINYRTEID KGSGSGSGSGSGSGSGSGSGSVSDVPRDL EVVAATPTSLLISWDAPTSRYQYYRITYG ETGGNSPVQEFTVPGGLSTATISGLKPGV DYTITVYAVTDYKPHADGPHTYHESPISI NYRTX_2

SEC ID N°:	Descripción	Secuencia
197	Núcleo de I1-$(PA)_n$-E105, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLKP GVDYTITVYAVTRFRDYQPISINYRTE**(P A)$_n$**VSDVPRDLEVVAATPTSLLISWDAPT SRYQYYRITYGETGGNSPVQEFTVPGGLS TATISGLKPGVDYTITVYAVTDYKPHADG PHTYHESPISINYRTX_2
198	Monómero de EGFR E112 con extensión N-terminal (N+10) y cola de Ser con	MGVSDVPRDLEVVAATPTSLLISWDAGAV TYQYYRITYGETGGNSPVQEFTVPGGVRT ATISGLKPGVDYTITVYAVTDYKPHADGP HTYHEYPISINYRTEIDKPSQHHHHHH

SEC ID N°:	Descripción	Secuencia
	marcador de His	
199	Núcleo de monómero de EGFR E112: monómero de E112 sin extensión N-terminal c cola C-terminal	EVVAATPTSLLISWDAGAVTYQYYRITYG ETGGNSPVQEFTVPGGVRTATISGLKPGV DYTITVYAVTDYKPHADGPHTYHEYPISI NYRT
200	Monómero de EGFR E112, donde X_1 se selecciona entre el grupo consistente en SEC ID N°: 69-77 y X_2 se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10; puede comprender opcionalmente un marcador de his	X_1EVVAATPTSLLISWDAGAVTYQYYRIT YGETGGNSPVQEFTVPGGVRTATISGLKP GVDYTITVYAVTDYKPHADGPHTYHEYPI SINYRTX_2

SEC ID N°:	Descripción	Secuencia
201	Secuencia de bucle BC de agente de unión a EGFR E1:2	SWDAGAVTYQ
110	Secuencia de bucle DE de agente de unión a EGFR E1:2	PGGVRT
202	Secuencia de bucle FG de agente de unión a EGFR E1:2	TDYKPHADGPHTYHEYP
203	Secuencia de bucle BC de agente de unión a EGFR E1:2, donde X es cualquier aminoácido y g y h se seleccionan independientemente de 0 a 5 aminoácidos	$X_gDAGAVTYQX_h$
135	Secuencia de bucle DE de agente de unión a EGFR E1:2, donde X es cualquier	X_iGGVRX_j

SEC ID N°:	Descripción	Secuencia
	aminoácido y i y j se seleccionan independientemente de 0 a 5 aminoácidos	
204	Secuencia de bucle FG de agente de unión a EGFR E112, donde X es cualquier aminoácido y k y l se seleccionan independientemente de 0 a 5 aminoácidos	$X_kDYKPHADGPHTYHEYX_l$
205	E112-GS10-I1: Tándem de E/I que tiene E112 (con extensión N-terminal (N+10) y una cola corta) fusionado a través del adaptador GS10 a I1 (con extensión N-terminal (N+8) y cola de Cys) con un	MGVSDVPRDLEVVAATPTSLLISWDAGAV TYQYYRITYGETGGNSPVQEFTVPGGVRT ATISGLKPGVDYTITVYAVTDYKPHADGP HTYHEYPISINYRTEIDK**GSGSGSGSGSG SGSGSGSGS**VSDVPRDLEVVAATPTSLLI SWSARLKVARYYRITYGETGGNSPVQEFT VPKNVYTATISGLKPGVDYTITVYAVTRF RDYQPISINYRTEIDKPCQHHHHHH

SEC ID N°:	Descripción	Secuencia
	marcador de 6X His	
206	Núcleo de E112-GS10-I1, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	X_1EVVAATPTSLLISWDAGAVTYQYYRIT YGETGGNSPVQEFTVPGGVRTATISGLKP GVDYTITVYAVTDYKPHADGPHTYHEYPI SINYRTEIDK**GSGSGSGSGSGSGSGSGSG SVSDVPRDL**EVVAATPTSLLISWSARLKV ARYYRITYGETGGNSPVQEFTVPKNVYTA TISGLKPGVDYTITVYAVTRFRDYQPISI NYRTX_2
207	Núcleo de E112-$(PA)_n$-I1, donde X1 es opcional y cuando	X_1EVVAATPTSLLISWDAGAVTYQYYRIT YGETGGNSPVQEFTVPGGVRTATISGLKP GVDYTITVYAVTDYKPHADGPHTYHEYPI

SEC ID N°:	Descripción	Secuencia
	está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 5 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	SINYRTE**(PA)**$_n$VSDVPRDLEVVAATPTS LLISWSARLKVARYYRITYGETGGNSPVQ EFTVPKNVYTATISGLKPGVDYTITVYAV TRFRDYQPISINYRTX$_2$
208	I1-GS10-E112: Tándem de I/E que tiene I1 (con extensión N-terminal (N+10) y una cola corta) fusionado a través del adaptador GS10 a	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIDK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWDAGAVTY QYYRITYGETGGNSPVQEFTVPGGVRTAT ISGLKPGVDYTITVYAVTDYKPHADGPHT

SEC ID N°:	Descripción	Secuencia
	E112 (con extensión N-terminal (N+8) y cola de Cys) con un marcador de 6X His	YHEYPISINYRTEIDKPCCHHHHHH
209	Núcleo de I1-GS10-E112, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLKP GVDYTITVYAVTRFRDYQPISINYRTEID KGSGSGSGSGSGSGSGSGSGSVSDVPRDL EVVAATPTSLLISWDAGAVTYQYYRITYG ETGGNSPVQEFTVPGGVRTATISGLKPGV DYTITVYAVTDYKPHADGPHTYHEYPISI NYRTX_2

SEC ID N°:	Descripción	Secuencia
210	Núcleo de I1-$(PA)_n$-E112, donde X_1 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 69-77, X_2 es opcional y cuando está presente se selecciona entre el grupo consistente en SEC ID N°: 9, 10, ó 78-81, y n = 3, 6 ó 9; en ejemplos de modalidades, X_1 es SEC ID N°: 69 ó 71 y X_2 es SEC ID N°: 9 ó 10	X_1EVVAATPTSLLISWSARLKVARYYRIT YGETGGNSPVQEFTVPKNVYTATISGLKP GVDYTITVYAVTRFRDYQPISINYRTE**(P A)$_n$**VSDVPRDLEVVAATPTSLLISWDAGA VTYQYYRITYGETGGNSPVQEFTVPGGVR TATISGLKPGVDYTITVYAVTDYKPHADG PHTYHEYPISINYRTX_2
211	I1-GSGCGS8-E5: Tándem de I/E que tiene I1 (con extensión N-terminal	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIEK**GSGCGSGSGSGSGSGSGS**

SEC ID N°:	Descripción	Secuencia
	(N+10) y una cola corta modificada) fusionado a través del adaptador GSGCGS8 a E5 (con extensión N-terminal (N+8) y una cola E) con un marcador de 6X His opcional	VSDVPRDLEVVAATPTSLLISWWAPVDRY QYYRITYGETGGNSPVQEFTVPRDVYTAT ISGLKPGVDYTITVYAVTDYKPHADGPHT YHESPISINYRTEHHHHHH
212	I1-GS10-E5-GSGC: Tándem de I/E que tiene I1 (con extensión N-terminal (N+10) y una cola corta modificada) fusionado a través del adaptador GS10 a E5 (con extensión N-terminal (N+8) y una cola de Cys modificada) con un marcador de 6X His	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTEFRDYQPIS INYRTEIEK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWWAPVDRY QYYRITYGETGGNSPVQEFTVPRDVYTAT ISGLKPGVDYTITVYAVTDYKPHADGPHT YHESPISINYRTEGSGCHHHHHH

SEC ID N°:	Descripción	Secuencia
	opcional	
213	I1(S62C)-GS10-E5: Tándem de I/E que tiene I1 (con extensión N-terminal (N+10), una sustitución S62C (recuadrada), y una cola corta modificada) fusionado a través del adaptador GS10 a E5 (con extensión N-terminal (N+8) y una cola E) con un marcador de 6X His opcional; la posición 62 se refiere al aminoácido que corresponde a la posición 62 de la	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATI[C]GLKPGVDYTITVYAVTRFRDYQPIS INYRTEIEK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWWAPVDRY QYYRITYGETGGNSPVQEFTVPRDVYTAT ISGLKPGVDYTITVYAVTDYKPHADGPHT YHESPISINYRTEHHHHHH

SEC ID N°:	Descripción	Secuencia
	SEC ID N°:1	
214	I1-GS10-E5(S62C): Tándem de I/E que tiene I1 (con extensión N-terminal (N+10) y una cola corta modificada) fusionado a través del adaptador GS10 a E5 (con extensión N-terminal (N+8), una sustitución S62C (recuadrada), y una cola E) con un marcador de 6X His opcional; la posición 62 se refiere al aminoácido que corresponde a la posición 62 de la SEC ID N°:1	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIEK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWWAPVDRY QYYRITYGETGGNSPVQEFTVPRDVYTAT ICCLKPGVDYTITVYAVTDYKPHADGPHT YHESPISINYRTEHHHHHH

SEC ID N°:	Descripción	Secuencia
215	I1(S91C)-GS10-E5: Tándem de I/E que tiene I1 (con extensión N-terminal (N+10), una sustitución S91C (recuadrada), y una cola corta modificada) fusionado a través del adaptador GS10 a E5 (con extensión N-terminal (N+8) y una cola E) con un marcador de 6X His opcional; la posición 91 se refiere al aminoácido correspondiente a la posición 91 de la SEC ID N°:1	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIC INYRTEIEKGSGSGSGSGSGSGSGSGSGS VSDVPRDLEVVAATPTSLLISWWAPVDRY QYYRITYGETGGNSPVQEFTVPRDVYTAT ISGLKPGVDYTITVYAVTDYKPHADGPHT YHESPISINYRTEHHHHHH

SEC ID N°:	Descripción	Secuencia
216	I1-GS10-E5(S91C): Tándem de I/E que tiene I1 (con extensión N-terminal (N+10) y una cola corta modificada) fusionado a través del adaptador GS10 a E5 (con extensión N-terminal (N+8), una sustitución S91C (recuadrada), y una cola E) con un marcador de 6X His opcional; la posición 91 se refiere al aminoácido correspondiente a la posición 91 de la SEC ID N°:1	MGVSDVPRDLEVVAATPTSLLISWSARLK VARYYRITYGETGGNSPVQEFTVPKNVYT ATISGLKPGVDYTITVYAVTRFRDYQPIS INYRTEIEK**GSGSGSGSGSGSGSGSGSGS** VSDVPRDLEVVAATPTSLLISWWAPVDRY QYYRITYGETGGNSPVQEFTVPRDVYTAT ISGLKPGVDYTITVYAVTDYKPHADGPHT YHESPICINYRTEHHHHHH
217	Cola corta	EIEK

SEC ID N°:	Descripción	Secuencia
	modificada	
218	Adaptador GSGCGS8	GSGCGSGSGSGSGSGSGS

Ejemplo 1: Ensayo de In Cell Western para Explorar para Actividad de EGFR

Se desarrollaron ensayos In Cell Western para explorar diversos clones de ^{10}Fn3 únicos para la capacidad de inhibir la actividad de EGFR para identificar los que se podrían unir con agentes de unión a IGF1R de ^{10}Fn3 para construir agentes de unión a E/I. Los ensayos In Cell Western también se usaron para explorar y determinar la potencia relativa de agentes de unión a E/I de ^{10}Fn3 específicos. Se desarrollaron dos ensayos de In Cell Western para medir 1) inhibición de fosforilación de EGFR estimulada por EGF o 2) inhibición de fosforilación de ERK estimulada por EGF. Las células se sembraron en placas de microtitulación de 96 pocillos revestidas con poli-D-lisina (Becton Dickinson, Franklin Lakes, NJ) a 24.000 células/pocillo para células de carcinoma epidermoide A431 o de carcinoma de cabeza y cuello FaDu y se dejó que se adhirieran durante una noche. Las células se lavaron una vez y después se incubaron durante 24 horas en medio sin suero.

A continuación se aplicaron diluciones seriadas de clones de los agentes de unión basados en ^{10}Fn3 a las células y se incubaron durante 2-3 horas antes de la estimulación con 100 ng/ml de EGF durante 10 minutos. Después de la estimulación, las células se fijaron durante 20 minutos en PBS que contenía formaldehído al 3.7% y después se permeabilizaron en PBS que contenía triton-X-100 al 0.1% durante 15 minutos. Las células se bloquearon durante una hora en bloqueante Odyssey (Li-Cor Biosciences, Lincoln, Nebraska) y se incubaron con anticuerpos para detectar EGFR fosforilado en tirosina 1068 (Cell Signaling, Beverly, MA) y β-actina (Sigma, St. Louis, MO) o pERK (MAP cinasa fosforilada en tirosina 202/treonina 204) y ERK total (Santa Cruz Biotechnology, Santa Cruz, CA). Después de lavar tres veces en PBS que contenía tween-20 al 0.1%, se añadieron anticuerpos secundarios (Invitrogen, Carlsbad, CA o Rockland, Gilbertsville, PA). Las células se lavaron tres veces en PBS que contenía tween-20 al 0.1% y se visualizaron en un Sistema de Formación de Imágenes por Infrarrojos Li-Cor Odyssey (Li-Cor Biosciences, Lincoln, Nebraska). Cada clon se ensayó por duplicado o triplicado y los valores se normalizaron para β-actina para el ensayo de pEGFR y ERK total para el ensayo de pERK. Se calcularon valores de CI50 a partir del análisis de regresión lineal del porcentaje de inhibición de la señal máxima menos el fondo.

Los resultados produjeron diversos clones de ^{10}Fn3

que tenían la capacidad de inhibir la actividad de EGFR y mostraron que ciertos agentes de unión a E/I de ^{10}Fn3 específicos poseían actividad similar al ejemplo mostrado en la Figura 9.

Ejemplo 2: Expresión de agentes de unión basados en ^{10}Fn3

Se produjeron agentes de unión a E/I uniendo covalentemente un ^{10}Fn3 de unión a EGFR a un ^{10}Fn3 de unión a IGFIR usando un adaptador glicina-serina, generando de este modo dímeros de ^{10}Fn3, en los que cada dominio de ^{10}Fn3 se une a una diana diferente. El ^{10}Fn3 de unión a IGFIR (I1) se describió propiamente como la SEC ID N°: 226 en la Publicación PCT N° WO 2008/066752. Se identificaron dos ^{10}Fn3 de unión a EGFR novedosos (E2 y E1) explorando una biblioteca de fusión de ARN-proteína, como se describe en la Publicación PCT N° WO 2008/066752, para agentes de unión a EGFR-Fc (R&D Systems, Minneapolis, MN). Los siguientes ejemplos describen resultados usando una diversidad de agentes de unión a E/I basados en ^{10}Fn3 marcados con His diferentes (no pegilados): E2-GS10-I1 (SEC ID N°: 25), E1-GS10-I1 (SEC ID N°: 31), I1-GS10-E1 (SEC ID N°: 28) e I1-GS10-E2 (SEC ID N°: 22).

Los siguientes ejemplos también describen resultados con los siguientes agentes de unión a E/I basados en ^{10}Fn3, marcados con His, pegilados: E1-GS10-I1 (SEC ID N°: 55), E2-GS10-I1 (SEC ID N°: 56), E3-GS10-I1 (SEC ID N°: 53), I1-GS10-E1 (SEC ID N°: 57), I1-GS10-E2 (SEC ID N°: 58), I1-

GS10-E3 (SEC ID N°: 54), E4-GS10-I1 (SEC ID N°: 120), I1-GS10-E4 (SEC ID N°: 124), E5-GS10-I1 (SEC ID N°: 128), I1-GS10-E5 (SEC ID N°: 132), E85-GS10-I1 (SEC ID N°: 149), I1-GS10-E85 (SEC ID N°: 152), E90-GS10-I1 (SEC ID N°: 164), E96-GS10-I1 (SEC ID N°: 179), E105-GS10-I1 (SEC ID N°: 192), I1-GS10-E105 (SEC ID N°: 195), E112-GS10-I1 (SEC ID N°: 205), I1-GS10-E112 (SEC ID N°: 208), I1-GSGCGS8-E5 (SEC ID N°: 211), I1-GS10-E5-GSGC (SEC ID N°: 212), I1(S62C)-GS10-E5 (SEC ID N°: 213), I1-GS10-E5(S62C) (SEC ID N°: 214), I1(S91C)-GS10-E5 (SEC ID N°: 215), and I1-GS10-E5(S91C) (SEC ID N°: 216).

Los ejemplos también describen resultados usando un agente de unión a IGFRIR basado en ^{10}Fn3 marcado con His, I1 (SEC ID N°: 4) y diez agentes de unión a EGFR basados en ^{10}Fn3 marcados con His, E2 (SEC ID N°: 6), E1 (SEC ID N°: 8), E3 (SEC ID N°: 52), E4 (SEC ID N°: 107), E5 (SEC ID N°: 113, donde X = Ser y con un marcador de His en el C-terminal-terminal), E5 pegilado (SEC ID N°: 113, donde X = Cys y con un marcador de His en el C-terminal-terminal), E85 (SEC ID N°: 140), E90 (SEC ID N°: 155), E96 (SEC ID N°: 170), E105 (SEC ID N°: 185) y E112 (SEC ID N°: 198). El ejemplo 32 también describe una diversidad de monómeros de E que tienen las secuencias expuestas en la Figura 45 y que incluye un marcador de His en el C-terminal-terminal.

Los diversos agentes de unión basados en ^{10}Fn3 se

purificaron usando un procedimiento de producción de proteína de alto rendimiento (HTPP). Los agentes de unión seleccionados se clonaron en el vector pET9d para generar fusiones de marcador His_6. Se transformó el ADN en *E. coli* HMS174(DE3) y las células se inocularon en 5 ml de medio LB que contenía 50 µg/ml de kanamicina en un formato de 24 pocillos y se cultivaron a 37°C durante una noche. Se prepararon cultivos frescos de 5 ml de medio LB (50 µg/ml de kanamicina) para expresión inducible aspirando 200 µl del cultivo de la noche y distribuyendo los mismos en el pocillo apropiado. Los cultivos se desarrollaron a 37°C hasta A_{600} 0.6-0.9. Después de la inducción con isopropil-β-tiogalactósido (IPTG) 1 mM, el cultivo se desarrolló durante otras 6 horas a 30°C y se recogió por centrifugación durante 10 minutos a 3220 x g a 4°C. Los sedimentos celulares se congelaron a 80°C.

Los sedimentos celulares (en el formato de 24 pocillos) se lisaron por resuspensión en 450 µl de amortiguador de Lisis (NaH_2PO_4 50 mM, NaCl 0.5 M, Combinado de Inhibidor de Proteasa Complete™ 1x sin EDTA (Roche), PMSF 1 mM, CHAPS 10 mM, imidazol 40 mM, 1 mg/ml de lisozima, 30 µg/ml de ADNasa, 2 µg/ml de aprotonina, pH 8.0) y se agitaron a temperatura ambiente durante 1 hora. Los lisados se aclararon y re-dispusieron en un formato de 96 pocillos por transferencia a un Unifilter Whatman GF/D de 96 pocillos

equipado con una placa de captura de 650 µl de 96 pocillos y se centrifugaron durante 5 minutos a x 200 g. Los lisados aclarados se transfirieron a un Placa de Quelación con Ni de 96 pocillos que se había equilibrado con amortiguador de equilibrado (NaH_2PO_4 50 mM, NaCl 0.5 M, CHAPS 10 mM, imidazol 40 mM, pH 8.0) y se incubaron durante 5 minutos. El material no unido se eliminó por vacío. La resina se lavó 2 x 0.3 ml/pocillo con amortiguador de Lavado N° 1 (NaH_2PO_4 50 mM, NaCl 0.5 M, CHAPS 5 mM, imidazol 40 mM, pH 8.0) eliminándose cada lavado con vacío. A continuación, la resina se lavó con 3 x 0.3 ml/pocillo con PBS eliminándose cada etapa de lavado con vacío. Antes de la elución, cada pocillo se lavó con 50 µl de amortiguador de Elución (PBS + EDTA 20 mM), se incubó durante 5 minutos y el lavado se desechó con vacío. La proteína se eluyó aplicando 100 µl adicionales de amortiguador de Elución a cada pocillo. Después de una incubación durante 30 minutos a temperatura ambiente, la placa o las placas se centrifugaron durante 5 minutos a 200 x g y la proteína eluída se recogió en placas de captura de 96 pocillos que contenían 5 µl de $MgCl_2$ 0.5 M fijado al fondo de las placas de Ni. La proteína eluída se cuantificó usando un ensayo de Proteína BCA con la SEC ID N°: 2 como el patrón de proteína.

La HTPP produjo agentes de unión basados en ^{10}Fn3 activos que se expresaron en una forma soluble y se

purificaron de la fracción soluble del citosol bacteriano. La figura 1 ilustra un análisis de SDS-PAGE ejemplar de uno de los agentes de unión a E/I basados en ^{10}Fn3. El análisis de SEC en una Superdex 200 5/150 GL en una fase móvil de $NaPO_4$ 100 mM, $NaSO_4$ 100 mM, NaCl 150 mM, pH 6.8 (GE Healthcare) demostró proteínas predominantemente monoméricas (véase el Ejemplo 4).

Además, se realizó la expresión y purificación a media escala de agentes de unión basados en ^{10}Fn3 seleccionados. Los agentes de unión seleccionados, fusionados con un marcador His_6, se clonaron en un vector pET9d o pET29 y se expresaron en células de *E. coli* HMS174(DE3) o BL212(DE3) (EMD Biosciences, San Diego, CA). Se usaron 20 ml de un cultivo de inóculo (generado a partir de una única colonia sembrada) para inocular 1 litro de medio LB que contenía 50 µg/ml de kanamicina. El cultivo se desarrolló a 37°C hasta A_{600} 0.6-1.0. Después de la inducción con isopropil-β-tiogalactósido (IPTG) 1 mM, el cultivo se desarrolló durante otras 6 horas a 30°C. Como alternativa, la expresión se realizó a 18°C después de cultivo inicial a 37°C usando medio de autoinducción (medio "ONE", EMD Biosciences, San Diego, CA). Los sedimentos celulares se recogieron por centrifugación durante 30 minutos a ≥10.000 x g a 4°C y se congelaron a 80°C. El sedimento celular se resuspendió en 25 ml de amortiguador de lisis (NaH_2PO_4 20 mM,

NaCl 0.5 M, Combinado de Inhibidor de Proteasa Complete™ 1x sin EDTA (Roche), pH 7.4) usando un homogeneizador Ultra-turrax en hielo. La lisis celular se consiguió por homogeneización a alta presión (≥124.07 MPa (≥18.000 psi)) usando un Microfluidizador Modelo M-110S (Microfluidics). La fracción soluble se separó por centrifugación durante 30 minutos a 23.300 x g a 4°C. El sobrenadante se aclaró por un filtro de 0.45 µm. El lisado aclarado se cargó en una columna HisTrap (GE) pre-equilibrada con NaH_2PO_4 20 mM, NaCl 0.5 M, pH 7.4. Después, la columna se lavó con 25 volúmenes de columna de NaH_2PO_4 20 mM, NaCl 0.5 M, pH 7.4, seguido de 20 volúmenes de columna de NaH_2PO_4 20 mM, NaCl 0.5 M, imidazol 25 mM, pH 7.4 y después 35 volúmenes de columna de NaH_2PO_4 20 mM, NaCl 0.5 M, imidazol 40 mM, pH 7.4. La proteína se eluyó con 15 volúmenes de columna de NaH_2PO_4 20 mM, NaCl 0.5 M, imidazol 500 mM, pH 7.4, las fracciones se combinaron basándose en absorbancia a A_{280} y se dializaron frente a PBS 1x, Tris 50 mM, NaCl 150 mM, pH 8.5 o NaOAc 50 mM, NaCl 150 mM, pH 4.5. Cualquier precipitado se eliminó filtrando con 0.22 µm.

La expresión y purificación a media escala produjo proteínas altamente puras y activas que se expresaron en una forma soluble y se purificaron de la fracción soluble del citosol bacteriano. El análisis de SEC en una Superdex 200 10/30GL en una fase móvil de $NaPO_4$ 100 mM, $NaSO_4$ 100 mM, NaCl 150 mM, pH 6.8 (GE Healthcare) demostró proteínas

predominantemente monoméricas (véase el Ejemplo 4).

Ejemplo 3: Pegilación de Agentes de Unión a E/I basados en ^{10}Fn3

Las proteínas de armazón basadas en fibronectina multivalentes, tales como agentes de unión a E/I basados en ^{10}Fn3, se pueden pegilar con diversos tamaños y tipos de PEG. Para permitir la pegilación, la proteína se modifica típicamente cerca del C-terminal por una única mutación puntual de un aminoácido, típicamente una serina, a una cisteína. La PEGilación de la proteína en el único resto de cisteína se consigue mediante conjugación con diversas formas de PEG derivatizadas con maleimida combinando el reactivo de PEG derivatizado con la solución de proteína e incubando. El progreso y la confirmación de la reacción de conjugación de PEGilación se pueden confirmar por SDS-PAGE y/o procedimientos de SE-HPLC que separan la proteína no PEGilada de la proteína PEGilada.

Por ejemplo, la construcción E2-GS10-I1 (SEC ID N°: 25) se pegiló sustituyendo una serina que estaba en la posición 221 con una cisteína. La construcción resultante, SEC ID N°: 56, después se conjugó con un PEG ramificado de 40 kDa derivatizado con maleimida (NOF America Corporation, White Plains, NY). El reactivo de PEG derivatizado se mezcló con la construcción de proteína en solución y se incubó a pH 7.40 a temperatura ambiente hasta que la reacción hubiera

terminado, típicamente 30 minutos o durante una noche a 4°C. El pH se disminuyó a pH 4.5 o pH 5.0 por diálisis o desalación rápida usando cromatografía en columna de exclusión por tamaño en amortiguador NaOAc 50, NaCl 150 mM. La mezcla de productos y el exceso de reactivos de la reacción PEGilación después se cargaron en una columna de cromatografía de intercambio catiónico al pH disminuido y se eluyó con un gradiente de NaCl de 150 mM a 1 M. También se realizaron estudios para confirmar la pegilación como se ha descrito en el anterior párrafo. Las conjugaciones se pueden realizar con las versiones marcadas con His o sin marcador His de la proteína.

En las ocasiones en las que se tiene que agotar la contaminación de endotoxina de *E. coli* en la muestra, se emplearon dos procedimientos usados por separado o en combinación entre sí. El primero era lavar la columna de intercambio catiónico con típicamente 5 volúmenes de columna de amortiguador NaOAc complementado con Triton X-100 al 0.5%, seguido de 20 volúmenes de columna (o más) del mismo amortiguador sin Triton X-100. Adicionalmente o en lugar de este procedimiento, la proteína se pasó muy lentamente a través de un filtro Sartorius Sartobind® Q (Sartorius Stedim Biotech Bohemia, Nueva York).

Dos de los agentes de unión a E/I basados en ^{10}Fn3, E2-GS10-I1-cys (con his) (SEC ID N°: 56) y E3-GS10-I1-Cys

(con his) (SEC ID N°: 53), se pegilaron usando un procedimiento alternativo. Cinco ml de un cultivo de inóculo de células de *E. coli* BL21(DE3) que contenían un plásmido pET29 dirigido por T7 polimerasa que codifica E2-GS10-I1-cys (con his) o E3-GS10-I1-Cys (con his), se generaron a partir de una única colonia sembrada y se usaron para inocular 1 litro de medio de auto-inducción (medio "ONE", EMD Biosciences, San Diego, CA) que contenía 50 μg/ml de kanamicina. La expresión se realizó a 18°C después de cultivo inicial a 37°C y se recogió por centrifugación durante 10 minutos a ~10.000 x g a 4°C. Los sedimentos celulares se congelaron a 80°C. El sedimento celular se resuspendió en 10 ml de amortiguador de lisis (NaH_2PO_4 20 mM, NaCl 0.2 mM, Imidazol 5 mM, pH 7.4) y se lisó mecánicamente usando un homogeneizador Avestin. La fracción soluble se separó por centrifugación durante 15 minutos a 23.300 x g a 4°C. El sobrenadante se decantó y el sedimento se solubilizó en amortiguador de Lisis (anteriormente) complementado con clorhidrato de guanidina (GdnHCl) de 4 M a 6 M. Después, la proteína solubilizada se purificó en una columna NiNTA dimensionada de forma adecuada (Qiagen, Inc.) pre-equilibrada con el Amortiguador de Lisis complementado con GdnHCl. Después, la columna se lavó con 5 a 10 volúmenes de columna del mismo amortiguador, seguido de elución con el mismo amortiguador complementado con Imidazol 300 mM. Las

fracciones eluídas de la columna que contenía la proteína de interés se diluyeron a 2-3 mg/ml de proteína y después se combinaron con un exceso molar de 1.2-1.5 de NEM-PEG sólido (ramificado de 40 kDa u otro). Se dejó que la mezcla reaccionara a temperatura ambiente durante 30 minutos o hasta que la reacción hubiese finalizado. Después, todo el volumen de reacción se puso en una bolsa de diálisis (límite de Peso Molecular 5.000 Da) y la mezcla se sometió a un procedimiento de replegamiento por diálisis. Por ejemplo, este procedimiento puede consistir en dos intercambios de diálisis de 10-16 horas 500:1 (amortiguador: dializado) frente a NaOAc 50 mM, NaCl 150 mm, pH 4.5. El dializado de este procedimiento contiene materiales PEGilados plegados apropiadamente más exceso de reactivos. La mezcla de productos y el exceso de reactivos de la reacción de PEGilación se aclararon por centrifugación o filtración antes de cargar los mismos en una columna de cromatografía de intercambio catiónico (SP Sepharose o Resource S, GE Healthcare). La columna se desarrolló con un gradiente de NaCl de 150 mM a 1 M en el amortiguador de fondo NaOAc. Se realizaron estudios para confirmar la pegilación como se ha descrito anteriormente.

Ejemplo 4: Caracterización biofísica de agentes de unión basados en ^{10}Fn3

Se realizó cromatografía de exclusión por tamaño

(SEC) convencional en las proteínas purificadas de la HTPP y los procedimientos a media escala (de 0.1 a 1 µg de proteína para HTPP y 10-50 µg para media escala). La SEC del material obtenido de HTPP se realizó usando una columna Superdex 200 5/150 (GE Healthcare) o en una columna Superdex 200 10/30 (GE Healthcare) para material de media escala en un sistema de HPLC Agilent 1100 ó 1200 con detección de UV a A_{214}nm y A_{280}nm y con detección de fluorescencia (excitación = $_{280}$nm, emisión = $_{350}$nm). Se empleó un amortiguador de sulfato sódico 100 mM, fosfato sódico 100 mM, cloruro sódico 150 mM, pH 6.8 a un caudal apropiado de la columna de SEC. Se usaron patrones de filtración en gel (Bio-Rad Laboratories, Hercules, CA) para el calibrado de peso molecular.

Los resultados de la SEC sobre los agentes de unión basados en ^{10}Fn3 purificados por HTPP mostraron proteínas predominantemente monoméricas y elución en el intervalo aproximado de 25 kDa frente a patrones de Filtración en Gel globulares (BioRad).

Los resultados de la SEC sobre los agentes de unión basados en ^{10}Fn3 purificados de media escala mostraron proteínas predominantemente monoméricas y elución en el intervalo aproximado de 25 kDa frente a patrones de Filtración en Gel globulares (BioRad). La Figura 2 ilustra perfiles de SEC ejemplares para agentes de unión a E/I basados en ^{10}Fn3 (I1-GS10-E2 en la Figura 2A y E2-GS10-I1 en

la Figura 2B).

Los agentes de unión basados en ^{10}Fn3 de media escala seleccionados se analizaron adicionalmente por EM-CL (sistema de HPLC de cromatografía líquida de Water 2695 acoplado con un espectrómetro de masas Waters Q-TOF API, Waters Corporation, Milford, MA). Las muestras se diluyeron hasta aproximadamente 0.5 mg/ml con agua de calidad HPLC. Aproximadamente 5 µl de la muestra diluida se inyectaron en una columna Jupiter C18 (número de Catálogo 00G-4053-80, Phenomenex). Amortiguador A: TFA al 0.02% + ácido fórmico al 0.08% en agua de calidad HPLC. Amortiguador B: TFA al 0.02% + ácido fórmico al 0.08% en acetonitrilo de calidad HPLC. La muestra se eluyó con un gradiente (Tabla 1) a un caudal de 0.2 ml/minutos.

Tabla 1

Tiempo	%A	%B
0	95	5
5.00	75	25
25.00	55	45
30.00	5	95
32.00	95	5
45.00	95	5

La elución de HPLC se dividió a una proporción de aproximadamente 1:1 y la mitad se envió al detector de UV y

la otra mitad, al espectrómetro de masas. El espectrómetro de masas tenía los siguientes ajustes de instrumento: tensión capilar 3.5 KV, tensión de cono 40, temperatura de fuente 80°C, temperatura de desolvatación 250°C, flujo de gas de desolvatación 450 y tensión de fotodetector multicanal 2200. Los espectros sin procesar se deconvolujeron con MaxEn1 (Waters Corporation).

El peso molecular de I1-GS10-E2 (SEC ID N°: 22) medido por EM-CL es 24.445 Dalton, que está en el intervalo de 1 Dalton del peso molecular calculado a partir de la composición de aminoácidos. Esto indica que la proteína tiene la composición de aminoácidos correcta y se procesa la metionina N-terminal. No hay ninguna otra modificación post-traducción en la proteína.

Se realizó análisis de Calorimetría de Exploración Diferencial (DSC) del I1-GS10-E2 de media escala para determinar la T_m. Se exploró una solución de 1 mg/ml en un calorímetro N-DSC II (Calorimetry Sciences Corp) incrementando la temperatura de 5°C a 95°C a una velocidad de 1 grado por minuto a una presión de 303.98 kPa (3 atm). El dato se analizó frente a un procesamiento de control del amortiguador apropiado usando el mejor ajuste usando un Software Orgin (OrginLab Corp). Los resultados de este ensayo demuestran que el agente de unión a E/I tiene una T_m de 50.69°C (véase la Figura 3). Usando los mismos

procedimientos, se determinó que la T_m de E2-GS10-I1 (con Peg) es 50.72°C y se determinó que la T_m de E2-GS10-I1 (sin Peg) es 56.82°C (véase la Figura 3B).

Ejemplo 5: Determinación de la afinidad de unión

Se realizó análisis de resonancia de plasmón superficial (BIAcore) en agentes de unión basados en ^{10}Fn3 en fase solución para determinar las velocidades de disociación y/o afinidades de unión usando EGFR-Fc e IGF1R-Fc capturados. El dominio extracelular de IGF1R humano (aa 1-932) se clonó en un vector de expresión de mamífero que contenía las regiones bisagra y constante de IgG1 humana. La transfección transitoria del plásmido produjo una proteína de fusión, IGF1R-Fc, que se purificó posteriormente por cromatografía de Proteína A. El EGFR-Fc humano recombinante (aa 1-645 del dominio extracelular de EGFR humano fusionado con Fc humano) se adquirió en R&D systems (Minneapolis, MN). Se capturó IGF1R-Fc en Proteína A inmovilizada mientras que EGFR-Fc se capturó con anticuerpo anti- ser humano inmovilizado.

En un experimento típico se inmovilizó IgG anti-ser humano en celdas de flujo 1 y 2 de un chip CM5 siguiendo las recomendaciones del fabricante (GE Healthcare, Piscataway, NJ). Se inyectó EGFR-Fc (50 nM) a 5 µl durante 2 minutos en la celda de flujo 2 (Fc2). Se usaron dos inyecciones de 30 segundos de $MgCl_2$ 3 M para la regeneración del EGFR-Fc unido de la superficie de IgG anti-ser humano.

La Proteína A se diluyó hasta 80 µg/ml en acetato pH 4.5 y se inmovilizó a ~3000 UR en las celdas de flujo 3 y 4 de la superficie del chip CM5. Aproximadamente 1300 UR de IGF1R-Fc se capturaron en la Fc 4. Se usaron dos inyecciones de 30 segundos de glicina 50 mM pH 1.5 para regenerar la superficie entre muestras.

Una serie de concentración de 100 nM a 1 nM de proteína purificada por HTPP (tres puntos de datos recogidos) o de 300 nM a 0.05 nM de proteína purificada a media escala (once puntos de datos recogidos) se evaluó para la unión a EGFR-Fc o IGF1R-Fc. Los sensogramas se obtuvieron a cada concentración y se evaluaron usando el Software de Evaluación Biacore T100, Versión 1.1.1 (GE healthcare/Biacore) para determinar las constantes de velocidad k_a (k_{on}) y k_d (k_{off}). Para la evaluación de HTPP, la velocidad de disociación se ajustó a partir de las curvas de 3 puntos. La K_D de afinidad se calculó a partir de la proporción de las constantes de velocidad k_{off}/k_{on}.

Los agentes de unión a EGFR basados en ^{10}Fn3 se evaluaron para especificidad en un formato similar usando IgG anti-ser humano para capturar HER2-Fc. Los agentes de unión basados en ^{10}Fn3 no mostraron ninguna unión apreciable a HER2-Fc capturado en condiciones en las que se observó una unión robusta para EGFR-Fc.

Como se muestra en la Tabla 2, ambos dominios de los agentes de unión a E/I basados en ^{10}Fn3 son funcionales,

conservando sus propiedades de unión a las respectivas dianas. Las velocidades de disociación mostradas en la Tabla 2 son para material de media escala y son similares a los resultados cualitativos obtenidos con el material de HTPP.

Tabla 2:

Resumen de las constantes de unión para agentes de unión basados en ^{10}Fn3

Diana	Proteína	ka (1/Ms)	kd (1/s)	K_D (nM)
EGFR-Fc	E1	1.19E+05	1.18E-03	9.92
		1.43E+05	1.89E-03	13.2
	E1-GS10-I1	6.29E+04	4.74E-04	7.53
		3.82E+04	3.89E-04	10.17
	I1-GS10-E1	1.26E+05	6.03E-04	4.8
		4.13E+04	4.25E-04	10.28
	E2	3.73E+05	2.72E-04	0.73
		3.27E+05	3.2E-04	0.98
	E2-GS10-I1	3.93E+05	1.75E-04	0.45
		3.75E+05	1.67E-04	0.45
	I1-GS10-E2	6.47E+05	1.42E-04	0.22
		3.90E+05	1.14E-04	0.29
	E3	2.83E+05	3.98E-04	3.4
				1.4
	E3-GS10-I1	3.49E+05	2.29E-04	0.66

Diana	Proteína	ka (1/Ms)	kd (1/s)	K_D (nM)
	I1-GS10-E3	1.17E+05	2.91E-04	2.48
IGF1R-Fc	I1	3.84E+06	4.34E-04	0.11
	E1-GS10-I1	5.13E+05	3.38E-04	0.66
	I1-GS10-E1	1.47E+06	3.98E-04	0.27
	E2-GS10-I1	1.24E+06	3.95E-04	0.32
	I1-GS10-E2	3.82E+06	4.79E-04	0.13
	E3-GS10-I1	1.8E+06	2.09E-04	0.12
	I1-GS10-E3	1.37E+06	4.54E-05	0.03

Ejemplo 6: Inhibición de actividad de IGFR en células H292

Se determinó la capacidad de agentes de unión a E/I basados en ^{10}Fn3 de inhibir la fosforilación de IGF1R en la tirosina 1131 usando un ensayo *in vitro* de células H292. En resumen, 65 X 10^3 células H292 se sembraron en microplacas de

96 pocillos (placa de 96 pocillos revestida con Poli-D-Lisina Biocoat, N° de cat 356640, Becton Dickinson, Franklin Lakes, NJ) en medio de cultivo RPMI-1640 que contenía Hepes 10 mM pH 7.4 y suero fetal bovino al 10%. Se dejó que las células se adhirieran durante 24 horas a 37°C, CO2 al 5%. Al siguiente día, las células se lavaron una vez con 200 microlitros por pocillo de RPMI-1640 sin suero y se incubaron durante una noche en 100 µl por pocillo de RPMI-1640 sin suero. Se añadieron diluciones seriadas del material de HTPP y las células se incubaron durante 3 horas adicionales. Las células se estimularon con 10 ng/ml de IGF-1 (N° de cat 500-P11, PeproTech, Rocky Hill, NJ) durante 10 minutos a 37°C. El medio se vertió de la placa y se añadieron 100 µl de amortiguador de lisis celular (Cell Signaling N° cat 9803, Beverly, MA) a cada pocillo. Las células se incubaron a temperatura ambiente durante 15 minutos para permitir la lisis y el lisado se transfirió a un ELISA de fosfo-IGFR (N° cat 7302, Cell Signaling, Beverly, MA). Se siguió el procedimiento del fabricante para realizar el ELISA.

Como se demuestra en la Figura 4, el E1-GS10-I1 marcado con His inhibió la fosforilación estimulada por IGF1 del IGF1R (CI_{50} = 0.004 µM) con una potencia comparable al agente de unión de IGF1R aislado, I1 (CI_{50} = 0.018 µM). El agente de unión de EGFR, E1, sólo tenía muy poco efecto sobre la fosforilación de IGF1R (CI_{50} > 3.5 µM). Como se muestra en

la Figura 9, los agentes de unión a E/I adicionales demostraron capacidad de inhibir la fosforilación estimulada por IGF1R con una CI50 en el intervalo de 0.1 nM a 19 nM, incluyendo varios agentes de unión a E/I pegilados que se ensayaron. En particular, para los agentes de unión a E/I pegilados E1-GS10-I1 e I1-GS10-E1 la inhibición de pIGFR se mostró a 0.9 nM y 4 nM, respectivamente. Para los agentes de unión a E/I pegilados E2-GS10-I1 e I1-GS10-E2, la inhibición de pIGFR se mostró a 0.3 nM y 0.8 nM, respectivamente.

Ejemplo 7: Inhibición de la actividad de EGFR en células H292

Se determinó la capacidad de agentes de unión a E/I basados en ^{10}Fn3 de inhibir la fosforilación del EGFR en la tirosina 1068 usando un ensayo *in vitro* de células H292. El ensayo se realizó como se ha descrito en el Ejemplo 6, excepto porque las células se estimularon con 100 ng/ml de EGF (N° de cat 236-EG-200, R & D Systems, Minneapolis, MN) y se realizó un ELISA de fosfo-EGFR (N° cat 7240, Cell Signaling, Beverly, MA). Se siguió el procedimiento del fabricante para realizar el ELISA.

Como se ha demostrado en la Figura 5, el E1-GS10-I1 marcado con His inhibió la fosforilación estimulada por EGF del EGFR (CI_{50} = 0.020 μM) con una potencia comparable al agente de unión de EGFR aislado, E1 (CI_{50} = 0.007 μM). El agente de unión de IGF1R, I1, sólo tenía muy poco efecto sobre la fosforilación de EGFR (CI_{50} > 6.21 μM). Como se

muestra en la Figura 9, los agentes de unión a E/I adicionales demostraron capacidad de inhibir la fosforilación estimulada con EGF con una CI50 en el intervalo de 7 nM a 127 nM, incluyendo varios agentes de unión a E/I pegilados que se ensayaron. En particular, para E2-GS10-I1 e I1-GS10-E2, pegilados, la inhibición de pEGFR se mostró a 32 nM y 47 nM, respectivamente. Se muestran datos similares en la Figura 11 para los agentes de unión a E/I pegilados E2-GS10-I1 e I1-GS10-E2.

Ejemplo 8: Inhibición de pAKT inducida por EGF+IGF1 en células H292

Se determinó la capacidad de agentes de unión a E/I basados en ^{10}Fn3 de inhibir la fosforilación de AKT en la serina 473 usando un ensayo *in vitro* de células H292. El ensayo se realizó como se ha descrito en el Ejemplo 6, excepto porque las células se estimularon simultáneamente tanto con EGF como con IGF1 como se ha descrito anteriormente y los lisados se analizaron con un ELISA fosfo-AKT (N° cat 7160, Cell Signaling, Beverly, MA). Se siguió el procedimiento del fabricante para realizar el ELISA.

La transducción de señal en EGFR e IGF1R se introduce en la ruta de señalización de PI3K-AKT y estimula la fosforilación de AKT. Como se demuestra en la Figura 6, E1-GS10-I1 inhibió la fosforilación estimulada por EGF e IGF1 de AKT en células H292. El agente de unión a E/I basado en

^{10}Fn3 era ligeramente más potente en su capacidad de bloquear la activación de AKT (CI_{50} = 0.004 μM) que el propio agente de unión de IGF1R, I1, (CI_{50} = 0.031 μM). El agente de unión de EGFR, E1, mostró una actividad solamente modesta en su capacidad de bloquear la activación de AKT por ambos ligandos (CI_{50} = 1.28 μM). Como se muestra en la Figura 9, los agentes de unión a E/I adicionales demostraron capacidad de inhibir la fosforilación de AKT estimulada por EGF e IGF1 con una CI50 en el intervalo de 0.1 nM a 26 nM, incluyendo varios agentes de unión a E/I pegilados que se ensayaron.

Ejemplo 9: Inhibición de proliferación celular en células RH41 y H292

Los agentes de unión a E/I basados en ^{10}Fn3 se evaluaron para actividad antiproliferativa en la línea celular de carcinoma pulmonar no microcítico H292, que depende de la señalización de EGFR para el crecimiento, o la línea celular de sarcoma de Ewing RH41, que depende de la señalización de IGF1R para el crecimiento. La actividad antiproliferativa de los agentes de unión se evaluó en cultivos monocapa tiñendo el ADN celular con la tinción fluorescente CyQuantNF (N° de cat C35006, Invitrogen, Carlsbad, CA). En resumen, 2 X 10^3 células H292 o 5 X 10^3 de RH41 se sembraron en microplacas de 96 pocillos (View Plates 96F cat#6005225, Perkin-Elmer, Waltham, MA) en medio de cultivo RPMI-1640 que contenía Hepes 10 mM pH 7.4 y suero

fetal bovino al 10% y se dejó que se adhirieran durante 24 horas a 37°C, CO_2 al 5%. Las células se mantuvieron como monocapas que crecían exponencialmente y permanecieron en la fase de crecimiento logarítmico durante el periodo del ensayo sin alcanzar confluencia durante el curso del ensayo. Veinticuatro horas después del sembrado se añadieron diluciones seriadas de material de media escala y las células se incubaron durante 72 horas adicionales. Después de esta incubación, las células se trataron con reactivo CyQuantNF y se dejó que el colorante se incorporara en ADN celular durante 1 hora a 37°C. El ADN total se cuantificó leyendo la fluorescencia a una excitación de 485 nm y emisión de 530 nm en un instrumento CytoFluor 4000 (Applied Biosystems, Framingham, MA). El tiempo total que las células se expusieron al fármaco fue 72 horas. Se incluyeron compuestos de patrón en cada experimento para verificar el rendimiento y la reproducibilidad del ensayo. Se usó análisis de regresión lineal del porcentaje de inhibición por el compuesto de ensayo para determinar los valores de CI_{50}.

Como se demuestra en la Figura 7, en células RH41, E1-GS10-I1 marcado con His inhibió la proliferación con una potencia comparable (CI_{50} = 0.009 μM) al agente de unión de IGFR, I1 (CI_{50} = 0.028 μM). El agente de unión de EGFR, E1, por sí mismo tenía muy poco efecto sobre la proliferación en esta línea celular (CI_{50} > 12.5 μM).

Como se demuestra en la Figura 8, en células H292, E2-GS10-I1 marcado con His inhibió la proliferación con una mayor potencia (CI_{50} = 0.329 μM) que el agente de unión de IGFR, I1, (CI_{50} = 0.699 μM) o el agente de unión de EGFR, E2 (CI_{50} = 0.553 μM). Véase la siguiente Tabla 4 para los valores de CI50 para los monómeros de E e I.

Ejemplo 10: Ensayo de unión de ligando EGF de competencia

Los agentes de unión a E/I E1-GS10-I1, I1-GS10-E1, E2-GS10-I1 e I1-GS10-E2 (material de HTPP) se ensayaron en un ensayo de competición basado en células de unión de ligando EGF en células A431 y se comparó con los agentes de unión a EGFR basados en ^{10}Fn3 E1 y E2 (material de media escala). Las células A431 se sembraron a 15000 células/pocillo en placas de 96 pocillos en DMEM + FBS al 10% y se incubaron durante 48 horas. Las células se lavaron con medio de privación (DMEM + BSA al 0.1%) y se incubaron en medio de privación durante 1 hora. El medio de privación se retiró y se sustituyó con agentes de unión basados en ^{10}Fn3 que se diluyeron en medio de privación y las células se pre-incubaron durante 30 minutos a 37°C para permitir que las proteínas se unieran a los receptores de EGF sobre las superficies celulares. Se añadió una concentración final de 10 nM de EGF marcado con Europio (Eu) (Perkin Elmer, Boston, MA) diluido en medio de privación a las células pre-incubadas y las placas se incubaron durante 3 horas a 4°C en oscuridad. Las células se lavaron dos veces con PBS frío y se añadieron 50

µl/pocillo de solución de Mejora (Perkin Elmer, Boston, MA) a las placas y se incubó durante 1 hora a 37°C. Las placas se leyeron en el Flexstation II (Molecular Devices). Los datos se representaron con software Softmax plus y se calcularon los valores de CI50, es decir, la concentración de agentes de unión basados en ^{10}Fn3 que se requería para inhibir al 50% del ligando Eu-EGF de la unión al receptor de EGF sobre las superficies celulares.

Los resultados para E2 y E1 comparados con E2-GS10-I1, I1-GS10-E2, E1-GS10-I1 e I1-GS10-E1 se resumen en la Tabla 3. Este dato indica que los agentes de unión a E/I basados en ^{10}Fn3 compiten con, e inhiben la unión de, EGF al receptor EGFR en células A431 con potencia similar a los agentes de unión a EGFR basados en ^{10}Fn3. Véase la siguiente Tabla 4 para los valores de CI50 para los monómeros de E e I.

Tabla 3

Resumen de los valores de CI50 para la inhibición de la Unión de EGF a EGFR sobre las superficies de células A431

Proteína	CI50 (nM)
E2	.7
E1	14
E2-GS10-I1	1.8
I1-GS10-E2	1.4
E1-GS10-I1	14.6
I1-GS10-E1	7

Ejemplo 11: Activación y Actividad de Señalización en Ensayos Basados en Células

Se evaluaron los efectos diana de los diversos agentes de unión a E/I basados en ^{10}Fn3 en células de carcinoma de colon DiFi por inmunotransferencia. Las células se sembraron a 4 x 10^5 células en cada matraz de 25 cm^2 y se incubaron durante una noche a 37°C en CO_2 al 5%. Al siguiente día, los tratamientos se iniciaron y las células se incubaron adicionalmente durante diversos tiempos de 1.5 a 120 horas. Después, las células se lisaron en HNTG (Hepes 50 mM, NaCl 150 mM, triton-X-100 al 0.5%, glicerol al 8%, Na_3VO_4 2 mM, $MgCl_2$ 1.5 mM, EDTA 1 mM que contenía los inhibidores de proteasa AEBSF, aprotinina, leupeptina, bestatina, pepstatina-A y E64) y la proteína total se cuantificó con el ensayo de proteína de BCA (Pierce, Waltham, MA). Los niveles de EGFR total, IGF1R total y el estado de fosforilación del EGFR, isoformas ERK1/2 de proteína MAP cinasa, se detectó por análisis SDS-PAGE de 20 microgramos de proteína total seguido de transferencia de proteínas a nitrocelulosa e inmunotransferencia con anticuerpos específicos. Las transferencias también se sondaron con β-actina para demostrar carga igual de cada muestra.

Los agentes de unión a E/I basados en ^{10}Fn3 pegilados E1-GS10-I1 (SEC ID N°: 55), E2-GS10-I1 (SEC ID N°: 56) y E3-GS10-I1 (SEC ID N°: 53) demostraron la capacidad de

degradar EGFR en este ensayo. Además, para E3-GS10-I1 (SEC ID N°: 53), también se observó degradación de IGF1R. El efecto sobre la degradación de EGFR para el agente pegilado E2-GS10-I1 se muestra en la Figura 10, así como otros efectos sobre moléculas de señalización. Adicionalmente, la versión no pegilada del agente de unión E2-GS10-I1 demostró degradación de EGFR similar (datos no mostrados). La Figura 9 muestra que para el agente de unión pegilado I1-GS10-E2, no había degradación de EGFR. La siguiente Tabla 4 resume diversas propiedades de los monómeros de E.

Tabla 4

Resumen de propiedades de monómeros de E.

EGFR					
Monómero	BIAcore KD CI50	Neutraliza unión de EGF CI50	Inhibición de pEGFR CI50	Inhibición de pERK CI50	Inhibición de Proliferación de H292 CI50
E1	14.6 nM	0.53 nM	18 nM	17 nM	18 nM
E2	1.4 nM	1.46 nM	20 nM	40 nM	30 nM
E3	0.72 nM	0.87 nM	11 nM	97 nM	26 nM

Ejemplo 12: Evaluación de Ciertos Agentes de Unión a E/I Basados en ^{10}Fn3 sobre Xenoinjertos de Tumor H292 Desarrollado en Ratones Desnudos

Los agentes de unión a E/I pegilados E2-GS10-I1 y E3-GS10-I1 así como el anticuerpo monoclonal panitumumab se evaluaron en un modelo de xenoinjerto de tumor H292. Para modelos *in vivo*, se obtuvo panitumumab como el fármaco comercializado y los agentes de unión a E/I se purificaron como se ha descrito anteriormente. La actividad *in vitro* de todos los agentes de unión a E/I se validó antes de la administración en animales ensayando la funcionalidad de cada extremo en el ensayo de pEGFR estimulado con EGF y pIGFR estimulado con IGF1 en células H292. Los agentes de unión a E/I se diluyeron en solución salina amortiguada con fosfato (PBS) al comienzo del experimento y se almacenaron a 2-4°C durante la duración de cada estudio. Ambos compuestos se administraron i.p. en un volumen total de 500 µl/iny/ratón y se equilibraron a temperatura ambiente antes de la administración.

Ratones y propagación de tumor. Se obtuvieron ratones atímicos (desnudos) hembra de 5-6 semanas de edad de Harlan Sprague-Dawley Co. (Indianapolis, IN) y se mantuvieron en cuarentena durante aproximadamente 3 semanas antes de su uso para la propagación de tumor o ensayo de eficacia de fármaco. A los animales se proporcionó alimento

y agua *ad libitum*. Se realizó el cuidado animal en concordancia con las directrices de AAALAC y Bristol-Myers Squibb. Los tumores se propagaron por implante subcutáneo (s.c.) en ratones desnudos. Los pases de tumor tuvieron lugar aproximadamente cada dos a cuatro semanas.

Ensayo antitumoral in vivo. El peso estimado del tumor se calculó usando la fórmula: Peso de tumor (mg) = (w^2 * l)/2; donde w = anchura y l = longitud en mm. La actividad antitumoral se evaluó en términos de % de inhibición de crecimiento del tumor (TGI) donde un %TGI de >50% se consideró activo. La inhibición relativa de % de crecimiento de tumor se calculó como $\%TGI=[(C_t-T_t)/(C_t-C_0)] \times 100$ donde C_t = peso mediano de tumor de ratones de control en el momento t en días después del implante del tumor, T_t = peso mediano de tumor de ratones tratados en el momento t, C_0 = peso mediano de tumor de ratones de control en el momento 0. El valor de %TGI se calculó en diversos puntos de tiempo comenzando después de 1.5 tiempos de duplicación de volumen de tumor y se sostuvo a lo largo de un periodo de tiempo de 3 tiempos de duplicación de volumen de tumor (TVDT), cuando fue posible. Cuando, TVDT = tiempo mediano (días) para que los tumores de control alcancen el tamaño diana - tiempo mediano (días) para que los tumores de control alcancen la mitad del tamaño diana. La definición de un ratón curado era uno cuyo tumor era indetectable o <35 mg, cuando se evaluó más de 10 TVDT

post-tratamiento. La dosis de un compuesto que produjo el máximo efecto terapéutico se denominó la dosis óptima (DO). Se consideraron que los grupos de tratamiento (típicamente 8 ratones) con más de una muerte atribuible a toxicidad de fármaco tenían tratamientos excesivamente tóxicos y sus datos no se usaron en la evaluación de actividad antitumoral. La dosis máxima tolerada (MTD) se define como el nivel de dosis inmediatamente inferior a la que tiene lugar toxicidad excesiva (es decir, más de una muerte). Se consideró que los ratones tratados que mueren antes de que sus tumores alcanzaran el tamaño diana habían muerto de toxicidad del fármaco. Se realizaron evaluaciones estadísticas de los datos usando el ensayo de Wilcoxon generalizado de Gehan (Gehan, EA, A Generalized Wilcoxon Test for Comparing Arbitrarily Slightly-Censored Samples, Biometrika 52: 203-223, 1965).

Medición de criterios de valoración farmacodinámicos en tumores. Los tumores se recogieron de ratones no tratados o tratados con fármaco y se congelaron instantáneamente en nitrógeno líquido. Las muestras se pesaron y homogeneizaron en 10 µl de amortiguador de lisis (Hepes 50 mM, NaCl 150 mM, triton-X-100 al 0.5%, glicerol al 8%, Na_3VO_4, 2 mM, $MgCl_2$ 1.5 mM, EDTA 1 mM que contenía un comprimido completo de inhibidor de mini proteasa Sigma N° S8820 por 15 ml de amortiguador y combinado de inhibidor de

fosfatasa Sigma N° P5726) para cada mg de tejido. Los tejidos se trituraron en una placa de petri de 100 mm con dos bisturís, se transfirieron a tubos de fondo de redondo de polipropileno Falcon N° 2059 y se maceraron con un homogeneizador manual durante 30 segundos. El homogeneizado se transfirió a tubos eppendorf de 1.5 ml y se centrifugó a 15000 x g durante 2 minutos en una microcentrífuga. El sobrenadante aclarado se transfirió a un nuevo tubo y se determinó la concentración de proteína total con el ensayo de proteína Pierce BCA (Pierce Biotechnology). Las muestras se analizaron por inmunotransferencia o en un Sistema de Ensayo multi punto Meso scale MSD Sector Imager 6000 como se recomienda por el fabricante (Meso Scale Discovery, Gaithersburg, MD).

Los agentes de unión a E/I pegilados E2-GS10-I1 y E3-GS10-I1 se ensayaron en un NSCLC H292 en ratones atímicos. Los tumores se implantaron por vía subcutánea con fragmentos de tumor H292 de 1 mm^3 en el flanco posterior y se dejaron establecer hasta un tamaño de 50-150 mg antes del inicio del tratamiento el Día 6 post-implante de tumor. Los agentes de unión a E/I pegilados se administraron i.p. a una dosis de 100 mg/kg con un programa TIWX3 para evaluar la actividad antitumoral. Se obtuvo panitumumab como fármaco comercializado y se administró i.p. a su dosis óptima de 1 mg/ratón y a una dosis menor de 0.1 mg/ratón con un programa

Q3DX5. Los tamaños medios de tumor calculados en grupos de 8 ratones se muestran en la Figura 12A. Las dosis de 1 mg/ratón y 0.1 mg/ratón de panitumumab eran ambas activas en %TGI con valores del 101% y 100%, respectivamente y estos valores eran significativamente diferentes de los animales de control ($p = 0.0002$, Tabla 5). El E2-GS10-I1 pegilado también era significativamente activo en %TGI con un valor del 96% ($p = 0.0005$). El E3-GS10-I1 pegilado no era activo en este estudio con un valor de %TGI del 31% que no era estadísticamente diferente del grupo del grupo control ($p = 0.416$). Los análisis post-dosificación indicaron que aproximadamente dos tercios del E3-GS10-I1 pegilado se agregó (66.64% de agregación/33.36% de monómero para un lote y 72.53% de agregación/27.47% de monómero para otro lote) que podría explicar la mala actividad del E3-GS10-I1 pegilado en este ensayo. Por el contrario, el E2-GS10-I1 pegilado mostró solamente un pequeño porcentaje de agregación en estudios post-dosificación (1.79% de agregación/98.21% de monómero).

Todos los tratamientos se toleraron bien sin ninguna muerte relacionada con tratamiento o pérdida de peso excesiva a lo largo del curso del estudio. Las observaciones clínicas no pusieron de manifiesto ninguna evidencia de toxicidad y el cambio promedio de peso a lo largo del curso de la terapia estaba dentro de límites aceptables (Figura 12B).

Tabla 5

Resultados del estudio de xenoinjerto de tumor humano H292

Grupo	Compuesto	Programa, Vía	Dosis (mg/kg)	Cambio PRO de peso (g)	%TGI	valor p para %TGI	Resultado en %TGI
1	Control (no tratado)	---	---	5.3	---	1.0	---
2	panitumumab	q3dx5;6 ip[a]	1 mg/ratón	9.6	101	0.0002	A
3	panitumumab	q3dx5;6 ip[a]	0.1 mg/ratón	6.3	100	0.0002	A
4	E2-GS10-I1 (con PEG)	TIWx3;6 ip[a]	100	-0.1	94	0.0005	A
5	E3-GS10-I1 (con PEG)	TIWx3;6 ip[a]	100	9.5	28	0.416	I

[a] El vehículo era solución salina amortiguada con fosfato. Las abreviaturas usadas son las siguientes: ip, vía intraperitoneal; %TGI, inhibición relativa de % de

crecimiento de tumor calculada como %TGI=[(Ct-Tt)/(Ct-C0)] x 100 donde Ct = peso mediano de tumor de ratones de control en el momento t en días después del implante de tumor, Tt = peso mediano de tumor de ratones tratados en el momento t, C0 = peso mediano de tumor de ratones de control en el momento 0. El valor %TGI se calculó en dos momentos como la inhibición promedio del Día 12 y Día 20. Resultado, un régimen de tratamiento se consideró activo si produjo un valor estadísticamente significativo de %TGI de >50%; q3dx5;6, el compuesto se administró cada tres días durante cinco dosis comenzando el sexto día después del implante de tumor; TIWx3;6, el compuesto se administró tres veces por semana durante tres semanas comenzando el sexto día después del implante de tumor. Los valores p se calcularon el Día 20 con respecto al grupo de control en un análisis emparejado de dos colas con 8 mediciones por grupo. Resultado en %TGI, A= activo e I= inactivo.

Criterios de valoración farmacodinámicos del estudio del tumor H292. Las muestras de tumores de grupos de control no tratados, tratados con panitumumab y con agente de unión a E/I se analizaron para niveles de EGFR, ErbB2 e IGFR fosforilado que indicarían supresión de diana. Los tumores también se analizaron para niveles de EGFR total para determinar si tuvo lugar la degradación del receptor de EGF. El día 20, se administró un tratamiento final y los tumores

se eliminaron de 2 animales 1 hora después de la dosificación, 3 animales 4 horas después de la dosificación y 3 animales 24 horas después de la dosificación. Todos los tratamientos mostraron supresión marcada de EGFR y ErbB2 fosforilado mientras que los niveles basales de IGFR fosforilado eran demasiado bajos para distinguir una diferencia en este estudio (Figura 13). Todos los tratamientos mostraron una reducción en la cantidad de EGFR total indicando que había tenido lugar la degradación del receptor.

Ejemplo 13: Selección y Caracterización de Células MCF7 Resistentes a Inhibidor de IGF1R

Se cultivaron células MCF7 (Colección Americana de Cultivos Tipo, N° de Catálogo HTB-22, Manassas, VA) en medio RPMI que contenía hepes 10 mM y FBS al 10% a 37°C en presencia de CO_2 al 5%. El inhibidor de IGF1R de molécula pequeña BMS-754807 se añadió al medio de cultivo y la concentración se aumentó a incrementos graduales a lo largo de un periodo de 10 meses hasta que las células mostraron proliferación continuada en presencia de BMS-754807 200 mM. Las células resistentes se denominaron MCF7r y la CI50 para BMS-754807 fue 1239 nM en comparación con 120 nM para las células MCF7 parentales cuando se midió en un ensayo de proliferación realizado como se ha descrito previamente (Carboni y col., Cancer Res. 69: 161-170 (2009)). Después,

el fármaco se eliminó del medio de cultivo y las células MCF7r se pasaron en medio completo durante 20 ó 60 días adicionales para eliminar todas las trazas de BMS-754807 residual. El análisis de las células MCF7r por inmunotransferencia puso de manifiesto que el EGFR se sobreexpresó significativamente en las células resistentes en comparación con las células MCF7 (Figura 14). Además, cuando las células MCF7 y MCF7r se privaron de suero y después se estimularon con EGF durante 7 minutos, no se pudo detectar EGFR fosforilado en las células MCF7 parentales (probablemente debido a bajos niveles de EGFR) pero era intensamente visible en células MCF7r. En células privadas de suero estimuladas con ligando IGF, se observó IGFR fosforilado en las células MCF7 parentales pero a pesar de los niveles ligeramente superiores de IGFR total presente en las células MCF7r, prácticamente no se observó pIGFR. Esto muestra que el IGFR en las células MCF7r resistentes ha perdido la capacidad de activar IGFR en respuesta a estimulación de IGF1 (Figura 14). La activación de la ruta de MAP cinasa en respuesta a estimulación por EGF era más fuerte en las células MCF7r cuando se midió por activación de pERK.

Ejemplo 14: Estudios Antitumorales en Xenoinjertos de MCF7 y MCF7r

Las células MCF7r se cambiaron de escala en

matraces T75 y se aislaron por centrifugación. Los números de células viables se midieron por exclusión con azul tripano con un Vi-CELL XR (Beckman Coulter, Fullerton, CA), se resuspendieron en PBS hasta 5 x 10^6 células viales/ml y se implantaron por vía subcutánea en el flanco posterior de ratones atímicos en un volumen de 0.2 ml. Para el crecimiento de tumor de MCF7 y MCF7r, todos los ratones su suplementaron con 0.25 mg de gránulos de liberación durante 90 días de 17-β-estradiol (Innovative Research of America, Sarasota, FL, N° de Cat. NE-121). Los tumores se propagaron hasta que alcanzaron un tamaño mediano de 500-1000 mg cuando se extirparon y se reimplantaron fragmentos de 1 mm^3 en el flanco posterior de nuevos ratones atímicos. Los tumores se adaptaron para crecimiento de tumor sólido por pase de trocar seriado en ratones a lo largo de al menos cuatro rondas de crecimiento durante las cuales se controlaron el tiempo de duplicación de volumen de tumor y la velocidad de dispersión para cada pase. Se observaron las características del crecimiento para determinar si los xenoinjertos mostraron propiedades aceptables para servir como un modelo fiable, reproducible. El tipo de tumor MCF7r demostró una velocidad de dispersión y un tiempo de duplicación aceptables y, por lo tanto, satisfizo los criterios para el uso como un modelo de xenoinjerto. El modelo de tumor parental MCF7 se había establecido previamente usando las mismas técnicas. Para el

xenoinjerto parental MCF7, se implantaron por vía subcutánea fragmentos de tumor de 1 mm^3 en el flanco posterior y se dejó que se establecieran hasta un tamaño de 50-150 mg antes del inicio de tratamiento el Día 13 post-implante de tumor. Se obtuvo cetuximab como fármaco comercializado y se administró i.p. a su dosis óptima de 1 mg/ratón y a una dosis menor de 0.1 mg/ratón con un programa Q3DX5 (dosis administradas el Día 13, 16, 19, 22, 25). Los tamaños medios de tumor calculados de grupos de 8 ratones se muestran en la Figura 15A. En el modelo de xenoinjerto MCF7, ni la dosis de 1 mg/ratón o de 0.1 mg/ratón de cetuximab fue activa en %TGI con valores de -9% y 3.2%, respectivamente y los tamaños del tumor no eran estadísticamente diferentes del grupo de control (Tabla 6).

Para el xenoinjerto resistente de MCF7r, se implantaron por vía subcutánea fragmentos de tumor de 1 mm^3 en el flanco posterior y se dejó que se establecieran hasta un tamaño de 50-150 mg antes del inicio del tratamiento el Día 6 post-implante del tumor. Se obtuvo cetuximab como fármaco comercializado y se administró i.p. a su dosis óptima de 1 mg/ratón y a una dosis menor de 0.1 mg/ratón en un programa Q3DX5 (dosis administradas el Día 6, 9, 12, 15, 18). Los tamaños de tumor medios calculados de grupo de 8 ratones se muestran en la Figura 15B. En el modelo de xenoinjerto MCF7r, las dosis de cetuximab eran activas en

%TGI con valores del 105% y 75%, respectivamente. La alta dosis de cetuximab tenía un valor de TGI superior al 100% que indica que provocó regresión de tumor por debajo del tamaño de partida al inicio del tratamiento. Ambas dosis dieron como resultado una diferencia estadísticamente significativa en el tamaño del tumor en comparación con el grupo de control (Tabla 7).

Tabla 6

Resultados del estudio de xenoinjerto de tumor de carcinoma de mama humano MCF7

Grupo	Compuesto	Programa, Vía	Dosis (mg/ratón)	%TGI	valor p para %TGI	Resultado en %TGI
1	Control (no tratado)	---	---	---	1.0	---
2	cetuximab	q3dx5;13 ip[a]	1 mg/ratón	-9	0.223	I
3	cetuximab	q3dx5;13 ip[a]	0.1 mg/ratón	3.2	0.220	I

a El vehículo era solución salina amortiguada con fosfato. Las abreviaturas usadas son las

siguientes: ip, vía intraperitoneal; %TGI, inhibición relativa de % de crecimiento de tumor calculada como %TGI=[(Ct-Tt)/(Ct-C0)] x 100 donde Ct = peso mediano de tumor de ratones de control en el momento t en días después del implante de tumor, Tt = peso mediano de tumor de ratones tratados en el momento t, C0 = peso mediano de tumor de ratones de control en el momento 0. El valor %TGI se calculó en tres momentos como la inhibición promedio del Día 20, 24 y Día 27. Resultado, un régimen de tratamiento se consideró activo si produjo un valor estadísticamente significativo de %TGI de >50%; q3dx5;13, el compuesto se administró cada tres días durante seis dosis comenzando el decimotercer día después del implante de tumor. Los valores p se calcularon el Día 24 con respecto al grupo de control en un análisis emparejado de dos colas con 8 mediciones por grupo. Resultado en %TGI, A= activo e I= inactivo.

Tabla 7

Resultados del estudio de xenoinjerto de tumor de carcinoma de mama humano MCF7r

Grupo	Compuesto	Programa, Vía	Dosis (mg/ratón)	%TGI	valor p para %TGI	Resultado en %TGI
1	Control (no tratado)	---	---	---	1.0	---
2	cetuximab	q3dx5;6 ip[a]	1 mg/ratón	105	0.001	A
3	cetuximab	q3dx5;6 ip[a]	0.1 mg/ratón	75	0.024	A

Véase las notas a pie de página de la Tabla 6. Los valores p se calcularon el Día 19 con respecto al grupo de control en un análisis emparejado de dos colas con 8 mediciones por grupo.

Ejemplo 15: Estudios Antitumorales en Xenoinjertos de GEO

Se establecieron tumores GEO implantando fragmentos de tumor de 1 mm^3 por vía subcutánea en el

flanco posterior de ratones atímicos y permitiendo que los mismos alcanzaran un tamaño de 50-150 mg antes del inicio del tratamiento el Día 18 post-implante de tumor. Se administró cetuximab ip a 0.25 mg/ratón en un programa Q3DX5 (dosis administradas el Día 18, 21, 24, 27, 30). El inhibidor de IGFR cinasa BMS-754807 se administró a 25 mg/kg en un programa QDX21. Los tamaños medios de tumor calculados de grupos de 8 ratones se muestran en la Figura 16. Cetuximab fue activo a 0.25 mg/ratón con un valor de %TGI del 67%. BMS-754807 fue activo con un %TGI del 80% y la combinación de ambos era considerablemente más activa que cada agente en solitario con un %TGI del 94% (Tabla 8). Todos los grupos de tratamiento eran estadísticamente diferentes del grupo de control el Día 26 (Tabla 8).

Tabla 8

Resultados del estudio de xenoinjerto de tumor de carcinoma de colon humano GEO

	Cetuximab		BMS-754807					
Grupo	Programa, Vía	Dosis (mg/ratón)	Programa, Vía	Dosis (mg/kg)	%TGI	Valor p	Resultado en %TGI	Sinergia
1	Control (no tratado)	---	---	---	---	---	---	---
2	q3dx5;6 ip[a]	0.25 mg/ratón	---		80		A	---
3	---	---	qdx21;18[b]	25	67		A	---
4	q3dx5;6 ip[a]	0.25 mg/ratón	qdx21;18[b]	25	94		A	SÍ

[a] El vehículo para cetuximab era solución salina amortiguada con fosfato. El vehículo para BMS-754807 era polietilenglicol 400 al 50%, agua al 50%. Las abreviaturas usadas son como se describen en la Tabla 6 y la sinergia se define como una actividad estadísticamente significativa que es mejor que cada agente en la combinación demostrada por sí mismo. Resultado en %TGI, A = activo e I = inactivo.

Ejemplo 16: Estudios Antitumorales en Xenoinjertos de H292

Se implantaron por vía subcutánea células H292 en el flanco posterior de ratones atímicos como fragmentos de 1 mm^3 y se dejó que se establecieran hasta un tamaño de 50-150 mg antes del inicio de tratamiento el Día 12 post-implante del tumor. Se administró cetuximab i.p. a 0.1 mg/ratón en un programa Q3DX5. MAB391 es un anticuerpo para IGF1R (R&D Systems, Minneapolis, MN, N° de Cat. MAB391) y se administró a una dosis de 40 mg/kg en un programa BIWX3. Los tamaños medios de tumor calculados de grupos 8 ratones se muestran en la Figura 17. Cetuximab fue activo a 0.1 mg/ratón con un valor de %TGI del 95.1% y MAB391 fue inactivo a 40 mg/kg con un valor de %TGI del 10.5% (Tabla 9). Los ratones dosificados con la combinación de cetuximab y MAB391 mostraron un valor de %TGI del 109.2% indicando regresión de tumor en el grupo de combinación (Tabla 9). Después de que se hubiera suspendido la dosificación, los tumores volvieron a crecer en el grupo tratado con cetuximab más rápidamente que en el grupo tratado con la combinación de cetuximab y MAB391 (Figura 17).

Tabla 9

Resultados del estudio de xenoinjerto de tumor NSCLC humano H292

	Cetuximab		MAB391					
Grupo	Programa, Vía	Dosis (mg/ratón)	Programa, Vía	Dosis (mg/kg)	%TGI	Valor p	Resultado en %TGI	Sinergia
1	Control (no tratado)	---	---	---	---	---	---	---
2	q3dx5;12 ip[a]	0.1 mg/ratón	---		95.1		A	---
3	---	---	BIWx3;12[a]	40	10.5		I	---
4	q3dx5;12 ip[a]	0.1 mg/ratón	BIWx3;12[a]	40	109.2		A	SÍ

[a] El vehículo para cetuximab y MAB391 fue solución salina amortiguada con fosfato. Las abreviaturas usadas son como se describen en las Tablas 6 y 8.

Ejemplo 17: Ensayo de Formación de Colonias

Para determinar los efectos de los compuestos de ensayo sobre la capacidad de inhibir la formación de colonias en células H292, se sembraron 400 células en placas de 24 pocillos (Becton-Dickinson, Franklin Lakes, NJ, N° de Cat.

351143) en medio completo y se dejó que se adhirieran durante una noche. Al siguiente día, el medio se eliminó y se sustituyó con medio que contenía FBS al 2%. El compuesto de ensayo se diluyó en medio que contenía FBS al 2% y se añadió a células en diluciones seriadas. Las células se incubaron a 37°C durante 14 días. Después de 14 días, el medio se desechó y los pocillos se enjuagaron una vez con 2 ml de PBS. Las células se tiñeron con 0.5 ml de Solución de Tinción Coomassie (Bio-Rad, Hercules, CA, N° de Cat. 161-0436) durante 20 min. La tinción se aspiró y los pocillos se lavaron rápidamente con Solución de Decoloración 1X Coomassie R-250 (Bio-Rad, N° de Cat. 161-0438). Se realizó un enjuagado final con 1 ml de agua por pocillo y las placas se invirtieron y se dejaron secar. Las colonias constituidas por (al menos) 50 células o más se contaron visualmente con pocos aumentos (10X-20X). Todas las muestras se ensayaron por triplicado y se calcularon los valores de CI50 a partir de la regresión lineal del porcentaje de inhibición de control. Los resultados representativos del agente de unión a E/I PEGilado se muestran en la Figura 18 y los valores de CI50 para diversos agentes de unión a E/I basados en ^{10}Fn3, agentes de unión a IGF1R monoespecíficos basados en ^{10}Fn3 y anticuerpo contra EGFR se muestran en la Tabla 10.

Tabla 10

Valores de CI50 de diversos agentes de unión a E/I basados en ^{10}Fn3, agentes de unión a IGF1R monoespecíficos basados en ^{10}Fn3 y anticuerpo contra EGFR en el ensayo de formación de colonias

MUESTRA	CI50 (nM)
E4-GS10-I1 (con Peg)	5
I1-GS10-E5 (con Peg)	1
I1-GS10-E4	6
E2-GS10-I1 (con Peg)	560
Monómero de I1 (con Peg)	15.510
panitumumab	140

Ejemplo 18: Ensayo de mapeo de epítopos

Se desarrolló un ensayo de mapeo de epítopos utilizando anticuerpos disponibles en el mercado donde el sitio de unión en el dominio extracelular de EGFR se conoce aproximadamente de acuerdo con diversos informes bibliográficos. Los anticuerpos usados en este ensayo se enumeran en la Tabla 11 y la Figura 19A ilustra cómo se

localizan los anticuerpos para aproximarse a los dominios de unión en EGFR. El ensayo es una variación del ensayo In Cell Western que se ha descrito previamente y evalúa la capacidad de agentes de unión a EGFR basados en ^{10}Fn3 preincubados con A431 u otras células que expresan EGFR de bloquear la unión de los anticuerpos de detección del panel enumerado en la Tabla 11. El ensayo se realizó del siguiente modo: se recogieron células A431 en crecimiento de fase logarítmica por tripsinización y se sembraron en una placa de 96 pocillos a 24.000 células/pocillo en un volumen total de 100 µl/pocillo. Al día siguiente, el medio se vertió y los agentes de unión a EGFR basados en ^{10}Fn3 diluidos en medio de base DMEM frío se añadieron a la placa y se dejó que se unieran durante 1 hora a 4°C para evitar la internalización del EGFR. Después de la unión, las células se lavaron con 0.2 ml de PBS + Tween-20 al 0.1% y se fijaron durante 20 minutos en PBS + formaldehído al 3.7% a temperatura ambiente. Las células se bloquearon en 0.2 ml de amortiguador de bloqueo Odyssey durante 1 hora a temperatura ambiente. A continuación, los anticuerpos primarios se diluyeron en 50 µl de bloqueante Odyssey por pocillo y se incubaron durante 1-2 horas a

temperatura ambiente. Los anticuerpos primarios se vertieron invirtiendo la placa y cada placa se lavó 3X con 200 µl de PBS + Tween-20 al 0.1%. Los anticuerpos secundarios son los mismos usados en el ensayo In Cell Western y eran apropiados para las especies de anticuerpos que se estaban detectando. Estos anticuerpos secundarios se diluyeron (1:800) en bloqueante Odyssey + Tween-20 al 0.2% y se añadieron en un volumen de 50 µl por pocillo junto con TOPRO3 (Invitrogen, Carlsbad, CA, Catálogo N° T3605) (1:3000) para teñir con colorante de contraste las células para la normalización. Las células se incubaron en una mesa de experimentación durante 1 hora a temperatura ambiente. El anticuerpo secundario se eliminó por vertido y cada pocillo se lavó 4X con 200 µl de PBS+ Tween-20 al 0.1% durante 5 minutos a temperatura ambiente. Las placas se visualizaron en un instrumento Licor a una resolución de 160 µm, calidad media, desplazamiento de foco de 3 mm, intensidad de 5. Este ensayo también se realizó con los anticuerpos de fármaco comercializado cetuximab, panitumumab y nimotuzumab para determinar si los agentes de unión a EGFR basados en ^{10}Fn3 estaban interfiriendo con su unión a EGFR en células A431. Los resultados representativos se muestran en

la Figura 19B.

Tabla 11

Anticuerpos disponibles en el mercado para el dominio extracelular de EGFR

	Clon	PROVEEDOR y N° de cat	ESPECIES	UNE	EPÍTOPE	Motivo de Unión
1		Abcam ab38165	Con	h	Péptido AA 42-58	lineal
2	E234	Abcam ab32198	Con	h,mu,rata	Péptido AA 40-80 (Sin ICC)	lineal
3	N-20	Santa Cruz#31155	IgG de cabra	h	AA 110-160	lineal
4	ICR10	Abcam ab231 Santa Cruz #57095	IgG2a de rata	h(HN5)	AA 124-176[b], neutralizante[e]	conf
5	EGFR1	Abcam ab30 Chemicon MAB88910 Labvision MS-311	IgG1 Mu	h(A431)	AA 176-294, neutralizante[b] ab30&MAB88910@(1 mg/ml)	conf
6	199.12	Labvision MS-396-P	IgG2a Mu	h	AA 124-176, no neutralizante[b]	conf
7	LA22	Upstate 05-104	IgG2a Mu	h(A431)	AA 351-364, neutralizante[a]	lineal

	Clon	PROVEEDOR y N° de cat	ESPECIES	UNE	EPÍTOPE	Motivo de Unión
8		Abcam ab15669	Con	Mu,rat	Péptido AA376-394[d]	lineal
9	225	Sigma E2156 Labvision MS-269-P	IgG1 Mu	h(A431)	AA 294-475, neutralizante[b,c]	conf
10	528	Abcam ab3103 Santa Cruz#120 Labvision MS-268-P	IgG2a Mu	h(A431)	AA 294-475, neutralizante[b,c]	conf
11	B1D8	Labvision MS-666-P	IgG2a Mu	h(A431)	AA 294-475[b]	conf
12	LA1	Upstate 05-101	IgG1 Mu	h	neutralizante	
13	H11	Labvision MS-316-P	IgG1 Mu	h	AA 294-475, no neutralizante[b]	lineal
14	111.6	Labvision MS-378-P Imgenex IMG-80179	IgG1 Mu	h	AA 294-475, neutralizante[b]	lineal

	Clon	PROVEEDOR y N° de cat	ESPECIES	UNE	EPÍTOPE	Motivo de Unión
15	29.1	Sigma E2760 Abcam ab10414	IgG1 Mu	h(A431)	Hidrato de carbono externo no neutralizante	

Abreviaturas: conf: epítopo específico conformacionalmente; lineal: epítopo independiente de conformación. [a]JBC 264(1989)17469 Ala351-Asp364, [b]J Immunological Methods 287(2004)147, [c]Mol Biol Med1(1983)511, [d]Generado contra un péptido para EGFR de ratón [FKGDSFTRTPPLDPRELEI], [e]Int J Oncol 4(1994)277. [f][EEKKVCQGTSNKLTQLGTFEDHFLSLQRMFNNCEVVLGNLEITYVQRNYDLSFLKTIQEVAGYVLI ALNTVERIPLENLQIIRGNMYYENSYALAVLSNY], [g]Ile-Gln-Cys-Ala-His-Tyr-Ile-Asp-Gly-Pro-His-Cys (aminoácidos 580-591). [h]Cancer Cell 7(2005)301.

Usando diversas estrategias, se ha confirmado que el monómero de EGFR E3 se une al domino I de EGFR. Ya que otros monómeros de E tienen propiedades similares en diversos experimentos, se piensa que los otros monómeros de E también se unen al dominio I de EGFR.

Ejemplo 19: Propiedades de Monómeros de I

Análisis BIAcore de las proteínas de armazón basados en fibronectina solubles

Se midió la cinética de monómeros de I que se unen a la diana usando biosensores BIAcore 2000 o 3000 (Pharmacia

Biosensor). Se desarrolló un ensayo de captura utilizando una fusión IGF-IR-Fc. Se ha descrito un reactivo similar por Forbes y col. (Forbes y col. 2002, European J. Biochemistry, 269, 961-968). El domino extracelular de IGF-IR humano (aa 1-932) se clonó en un vector de expresión de mamífero que contenía las regiones bisagra y constante de IgG1 humana. La transfección transitoria del plásmido produjo una proteína de fusión, IGF-IR-Fc que se purificó posteriormente por cromatografía de Proteína A y se capturó en Proteína A inmovilizada sobre chips Biasensor CM5 por acoplamiento de amina. El análisis cinético implicó la captura de IGF-IR-Fc sobre Proteína A seguido de inyección de la proteína de armazón basada en fibronectina en solución y regeneración de la superficie de Proteína A por glicina pH 2.0. Se obtuvieron sensogramas a cada concentración y se evaluaron usando un programa Biaevaluation, BIA Evaluation 2.0 (BIAcore), para determinar las constantes de velocidad k_a (k_{on}) y k_d (k_{off}). La constante de disociación K_D se calculó a partir de la proporción de constantes de velocidad k_{off}/k_{on}. Típicamente, una serie de concentraciones (de 2 μM a 0 μM) de proteína de armazón basada en fibronectina purificada se evaluó para la unión a proteína de fusión IGF-IR-Fc humana capturada en proteína A.

Para experimentos de determinación de la unión a receptor de insulina humano, se acopló receptor de insulina

humano recombinante (IR) y VEGF-R2-Fc humano recombinante directamente a un chip CM5 Biasensor por enlace de grupo amina siguiendo procedimientos convencionales recombinados por Biacore (Uppsala, Suecia). En resumen, 60 µg/ml de IR diluido en acetato 4.5 se acopló/inmovilizó a un nivel de 8300 UR y 11.9 µg/ml de VEGF-R2-Fc diluido en acetato 5.0 se inmovilizó a un nivel de 9700 UR en celdas de flujo 2 y 3. Se preparó una superficie de referencia de blanco en FC1. Se calculó la unión específica a IR o VEGF-R2-Fc restando la unión observada a la celda de flujo 1 de referencia de blanco. Se diluyeron proteínas de armazón basadas en fibronectina hasta 10 µM en HBS-EP (Hepes 10 mM, NaCl 150 mM, EDTA 3 mM, Tensioactivo P20 al 0.05%) y se inyectó a 20 µl/min durante 3 minutos sobre las celdas de flujo a 25°C y se observó la disociación durante 10 min.

Ensayo de Bloqueo de Receptor Basado en Células

Se sembró el adenocarcinoma de mama humano MCF-7 (ATCC, Manassas, VA) en placas de 24 pocillos a una concentración de 50.000 células por pocillo en RPMI 1640 (Invitrogen, Carlsbad, CA) que contenía suero fetal bovino al 10% (Hyclone, Logan, UT). Al día siguiente, las células se lavaron en amortiguador de unión constituido por RPMI 1640 que contenía BSA al 0.1% (Sigma, St. Louis, MO) y después se pre-incubó durante 30 minutos en hielo en 200 µl de amortiguador de unión que contenía competidor de IGF-IR.

Después del periodo de pre-incubación, se añadió [^{125}I]-IGF-I 40 pM (Perkin Elmer, Wellesley, MA), equivalente a aproximadamente 60000 recuentos por minuto, a cada pocillo y se dejó incubar durante tres horas adicionales en hielo con agitación suave. Los pocillos después se lavaron con PBS helado que contenía BSA al 0.1%. Las células se lisaron con 500 µl de amortiguador constituido por SDS al 0.1% + NaOH 0.5 N. Se midió la radiactividad de los lisados usando un Contador Gamma Wallac 1470 (Perkin Elmer, Wellesley, MA) y los datos se analizaron usando SigmaPlot (Systat Software, Point Richmond, CA).

Ensayo de pIGFR

Las proteínas de armazón basadas en fibronectina fusionadas a Fc se evaluaron para su capacidad de inhibir la fosforilación de IGF-1R en células de rabdomiosarcoma humano Rh41. Se empleó una Western Blot para evaluar la capacidad del monómero de I de inhibir la fosforilación de IGF-1R en células de rabdomiosarcoma humano Rh41. Las células se estimularon con ligandos IGF-I, IGF-II, insulina (50 ng/ml) o sin estimulación (NS) y después se trataron con diversas concentraciones del monómero de I. Las membranas se sondaron con anticuerpos fosfo-específicos.

Proliferación Celular en Rh41 (Rabdomiosarcoma humano y Mieloma Múltiple humano H929)

La proliferación se evaluó por incorporación de [^{3}H]-timidina en ADN después de una exposición durante 72 horas a reactivos. Las células Rh41 se sembraron a una densidad de 3500 células/pocillo en placas de microtitulación de 96 pocillos y 24 horas después se expusieron a un intervalo de concentraciones de monómero de I. Después de 72 horas de incubación a 37°C, las células se pulsaron con 4 μCi/ml de [^{3}H] timidina (Amersham Pharmacia Biotech, RU) durante 3 horas, se tripsinizaron, se recogieron en placas GF/B UniFilter-96 (PerkinElmer, Boston, MA) y se midió la escintilación en un TopCount NXT (Packard, CT). Los resultados se expresan como una CI50, que es la concentración de fármaco requerida para inhibir la proliferación celular en el 50% a la de células de control no tratadas. Los datos representan el promedio de pocillos por triplicado mostrándose las desviaciones típicas.

Los resultados de la caracterización del monómero de I se muestran a continuación en la Tabla 12.

Tabla 12

Propiedades de monómeros de I

IGFR				
Monómero	BIAcore KD CI50	Neutraliza Unión de IGF CI50	Inhibición de pIGFR CI50	Inhibición de Proliferación de RH41 CI50
I1	0.11 nM	8 nM	0.2 nM	28 nM

Ejemplo 20: Características adicionales de agentes de unión a EGFR e IGF-IR basados en ^{10}Fn3 monoespecíficos y biespecíficos

Se identificaron agentes de unión basados en ^{10}Fn3 que se unen a EGFR o IGF-IR usando la técnica de selección bioquímica de presentación de ARNm en la que una proteína se une covalentemente a sus secuencias de ácido de nucleico codificantes. Las poblaciones de fusión de proteínas basadas en ^{10}Fn3-ARNm que se unen a IGF-IR o EGFR cuando los receptores se presentaron a concentraciones de 1 a 10 nM se clonaron en *E. coli* y se expresaron como proteínas basadas en ^{10}Fn3. Se identificó un subconjunto de agentes de unión diana que bloqueaban la señalización de EGFR o IGF-IR y tenían propiedades biofísicas adecuadas (Tabla 13). Estos clones iniciales se optimizaron para afinidad de unión a diana y potencia celular con selección de ARNm adicional a

concentraciones diana cada vez menores y selección para constantes de velocidad de disociación menores. Los valores de CI_{50} obtenidos durante los procedimientos de selección variaron de 9 a 304 nM, ilustrando la oportunidad de elegir moléculas a partir de un amplio intervalo de valores de potencia para la construcción de agentes de unión basados en ^{10}Fn3 biespecíficos. Se ensayaron agentes de unión a EGFR basados en ^{10}Fn3 por ensayos de exploración In-Cell Western para el bloqueo de fosforilación de EGFR y ERK, una molécula de señalización cadena debajo de activación de EGFR (procedimientos similares al Ejemplo 1). Se realizaron estudios similares en agentes de unión a IGF-IR optimizados. Los clones de unión a EGFR-optimizados (E3, E1 y E2) inhibieron la fosforilación de EGFR en Y1068 y la fosforilación cadena abajo de ERK e Y204 de p42/p44 *in vitro* variando los valores de CI_{50} de 9 a 40 nM, potencias que eran más de 100 veces superiores al clon de EGFR parental (Tabla 13, procedimientos similares al Ejemplo 1).

I1 se unión a IGF-IR con un valor de K_D de 0.11 nM e inhibió la fosforilación de IGF-IR estimulada por IGF-I con una CI_{50} de 0.2 nM (Tabla 13, procedimientos similares al Ejemplo 6). Los agentes de unión a IGF-IR y EGFR basados en ^{10}Fn3 de dominio único optimizados eran > 95% monoméricos basándose en cromatografía de exclusión por tamaño, tenían temperaturas de fusión > 56°C (Tabla 13, procedimientos

similares al Ejemplo 4), y mostraron potencial inmunógeno mínimo como se predijo por EpiMatrix (< 7 para cinco de seis bucles), un algoritmo basado en matriz para mapeo de epítopos de células T (De Groot AS, Moise L (2007) Prediction of immunogenicity for therapeutic proteins: state of the art. Curr Opin Drug Discovery Devel 10: 332-340). Los agentes de unión basados en ^{10}Fn3 E1, E2 y E3 se seleccionaron para desarrollo posterior y tenían constantes de unión de EGFR en el intervalo de 0.7 a 10 nM como se determinó por ensayo Biacore (Tabla 13, procedimientos similares al Ejemplo 5). La unión a EGFR de estos agentes de unión basados en ^{10}Fn3 era competitiva para la unión de EGF a EGFR (Tabla 13) como se midió por un ensayo de desplazamiento usando EGF marcado con Europio (procedimientos similares al Ejemplo 10). De forma similar, la unión de IGF-I a IGF-IR se midió por I1 (Tabla 13, procedimientos similares al Ejemplo 19).

Caracterización Biofísica de Agentes de Unión basados en ^{10}Fn3 Bi-específicos. Los valores de T_m de agentes de unión a E/I basados en ^{10}Fn3 seleccionados variaron de 49-58°C y sus perfiles de SEC indicaron que la proteína era en > 90% monómero (Tabla 14, procedimientos similares al Ejemplo 4). Los agentes de unión basados en ^{10}Fn3 monoespecíficos y agentes de unión a E/I basados en ^{10}Fn3 mostraron afinidades de unión comparables, aunque los valores de T_m

disminuyeron ligeramente cuando los agentes de unión basados en ^{10}Fn3 de dominio único se unieron entre sí (Tablas 13 y 14). Para aumentar la semivida sérica para aplicaciones *in vivo*, los agentes de unión a E/I basados en ^{10}Fn3 se PEGilaron con un PEG ramificado de 40 kDa (procedimientos similares al Ejemplo 3). La PEGilación de agentes de unión a E/I basados en ^{10}Fn3 dio como resultado una reducción de 10 a 20 veces de la afinidad de unión con respecto a las construcciones no PEGiladas debido a constantes de velocidad de asociación disminuidas pero no disminuyó la T_m. Además, la PEGilación no redujo de forma marcada la inhibición de la fosforilación de EGFR/IGF-IR en las células. La orientación E-I PEGilado (en la que el agente de unión a EGFR está en el N-terminal e IGF1R está en el C-terminal) mostró valores de CI_{50} ligeramente menores para la inhibición de la fosforilación de EGFR e IGF-IR por ELISA en comparación con la orientación I-E. Aunque se encontraron diferencias menores en los valores de K_D y actividad biológica entre la orientación E-I PEGilado frente a la orientación I-E, no había ninguna tendencia constante.

Tabla 13

Propiedades de Agentes de Unión Basados en ^{10}Fn3 Monoespecíficos Pertinentes para la Construcción de Agentes de Unión a E/I basados en ^{10}Fn3

Nombre	T_m °C	% en Monómero o SEC	KD de EGFR nM	KD de IGF-IR nM	CI_{50} de pEGFR de A431, nM	CI_{50} de pERK de A431, nM	CI_{50} de pEGFR de H292, nM	CI_{50} de pIGF-IR de H292, nM	CI_{50} de Competición de EGFR/IGF-IR, nM
E-parental	56	ND	42.5		2580	2370	1148 ± 21	ND	29 ± 12.73
E3	60	>80	3.4	NA	15 ± 8	11 ± 7	22 ± 1	>7000	4.75 ± 1.77
E1	64	>95	9.92	NA	24 ± 7	13 ± 3	9 ± 2	>3400	15.9 ± 2.97
E2	72	>95	0.7	NA	38 ± 15	40 ± 9	31 ± 1	>3400	9.4 ± 3.68
I-parental	ND	ND	NA	1.8	ND	ND	ND	ND	13**
I1	61.5	>95	>6210	0.11	NA	NA	NA	0.2	8**

ND, no realizado; NA, no aplicable; SEC, cromatografía de exclusión por tamaño. *Los valores de CI_{50} para niveles de fosforilación de EGFR y ERK en células A431 se determinaron por ensayo In-Cell Western (ICW). Los niveles de

fosforilación de EGFR e IGF-IR en células H292 se determinaron por ensayo inmunoabsorbente ligado a enzimas (ELISA). ** Competición para unión a IGF-IR. Las desviaciones típicas son de 3 - 6 experimentos.

Tabla 14

Propiedades de los agentes de unión a E/I basados en ^{10}Fn3

Nombre	T_m °C	K_D de EGFR nM	K_D de IGF-IR nM	CI_{50} de pEGFR de H292, nM	CI_{50} de pIGF-IR de H292, nM	CI_{50} de pERK de A431, nM	CI_{50} de pEGFR de A431, nM	CI_{50} de Competición de EGF-EGFR, nM
E3-GS10-I1	52	0.7	0.1	7	6	12	14	25 ± 6.5
E3-GS10-I1-PEG	52.5	10.4	0.74	10	6	40	42	80.5 ± 12.02
E1-GS10-I1	48	3.8	0.8	30	1	51	36	51
E1-GS10-I1-PEG	49	57.9	2.4	123	4	295	297	396 ± 223
E2-GS10-I1	56	0.5	0.2	8	0.1	20	19	2.1 ± 0.57
E2-GS10-I1-PEG	57.5	10.1	1.17	32	0.3	78	77	56.5 ± 24.5
I1-GS10-E2-PEG	60	3.6	0.46	47	0.8	118	97	128 ± 4.95

Las mediciones de T_m son de fluorometría de exploración térmica. Los valores de K_D son ensayos de unión

Biacore usando dominios recombinantes de EGFR o IGF-IR adsorbidos sobre el chip. Se realizaron ensayos In-Cell Western (ICW) para determinar la capacidad de Tándems de EI de inhibir la fosforilación de EGFR o ERK en células A431. Se usaron ensayos inmunoabsorbentes ligados a enzimas (ELISA) para determinar la fosforilación de EGFR o IGF-IR en células H292.

Ejemplo 21: Reactividad Cruzada entre Especies de Agentes de Unión a E/I basados en ^{10}Fn3

Se analizaron los agentes de unión a E/I basados en ^{10}Fn3 pegilados con respecto a sus afinidades de unión a EGFR de ratón, rata y mono usando análisis de resonancia de plasmón superficial (BIAcore) (procedimientos idénticos al Ejemplo 5). El EGFR de ratón se adquirió de R&D Systems (Minneapolis, MN), el EGFR de rata se produjo internamente y el EGFR de mono se adquirió en KEMP (Frederick, MD)

Como se muestra en la Tabla 15, todos los agentes de unión a E/I basados en ^{10}Fn3 pegilados se unieron a EGFR de ratón, rata y mono con afinidades nanomolares bajas, indicando que todos los agentes de unión a E/I pegilados presentan reactividad cruzada con EGFR humano, de ratón, de rata y de mono.

Tabla 15

Analito	KD (nM) (EGFR de ratón)	KD (nM) (EGFR de rata)	KD (nM) (EGFR de mono)
I1-GS10-E105 (pegilado)	2.7	2.9	4.4
I1-GS10-E5 (pegilado)	3.4	3.6	5.1
I1-GS10-E4 (pegilado)	5.5	3.7	3.9
E4-GS10-I1 (pegilado)	6.9	5.6	5.7
E2-GS10-I1 (pegilado)	9.6	9.6	18.0
I1-GS10-E85 (pegilado)	13.9	10.7	7.0

Ejemplo 22: Caracterización de Agentes de Unión a E/I basados en ^{10}Fn3-adicionales

La Figura 43 resume diversas características de agentes de unión a E/I basados en ^{10}Fn3 adicionales.

Los agentes de unión a E/I basados en ^{10}Fn3 pegilados se ensayaron para determinar la inhibición de la

fosforilación de EGFR y ERK inducida por EGF en A431, usando procedimientos como se han descrito previamente en el Ejemplo 1. Los resultados demostraron que los agentes de unión a E/I basados en ^{10}Fn3 pegilados inhibieron la fosforilación de EGFR inducida por EGF variando las CI50 entre 12 nM - 297 nM y la fosforilación de ERK variando las CI50 entre 12 nM - 295 nM (Figura 43, columnas a y b).

La capacidad de agentes de unión a E/I basados en ^{10}Fn3 pegilados de inhibir la actividad de IGFR y EGFR también se examinó en células H292 usando procedimientos que se han descrito previamente en los Ejemplos 6 y 7. Los resultados indicaron que los agentes de unión a E/I basados en ^{10}Fn3-pegilados inhibieron la actividad de IGFR variando las CI50 entre 0.2 nM - 6 nM (Figura 43, columna d) e inhibieron la actividad de EGFR variando las CI50 entre 1.3 nM - 123 nM (Figura 43, columnas c).

Los agentes de unión a E/I basados en ^{10}Fn3 pegilados se ensayaron para determinar si podrían inducir la degradación de EGFR e IGFR en células Difi como se muestra en las columnas e y f de la Tabla 16. Las células se trataron con 1 μM de agentes de unión a E/I basados en ^{10}Fn3 pegilados y se recogieron en puntos de tiempo que comenzaban a las 7 h y finalizaban a las 120 h y los niveles de EGFR e IGF1R se determinaron por análisis de Western Blot. La intensidad de la degradación se puntuó como (+) indicando que el tándem

degradaba ese receptor pero la degradación no se mantenía y la expresión del receptor reaparecía durante el curso de tiempo o (++) que indica que el tándem degradaba el receptor y mantenía esa degradación a lo largo del curso del tiempo. Los resultados (Figura 43, columna e y f) demostraron que los agentes de unión a E/I basados en ^{10}Fn3 pegilados presentaban diversos patrones de degradación de EGFR e IGF1R; degradación solamente de IGFR, degradación tanto de EGFR como de IGFR o ninguna degradación de ningún receptor. Ningún tándem ensayado mostró la capacidad de degradar solamente EGFR.

La afinidad de unión de los agentes de unión a E/I basados en ^{10}Fn3 pegilados por EGFR e IGF1R se evaluó por análisis de resonancia de Plasmón superficial (BIAcore) como se ha descrito previamente en el Ejemplo 5. Los resultados demostraron que los agentes de unión a E/I basados en ^{10}Fn3 pegilados se unieron a EGFR con afinidades que variaban entre 3.35 nM- 57.9 nM y se unieron a IGF1R con afinidades que variaban entre 0.37 nM - 2.43 nM (Figura 43, columnas g y h).

Los agentes de unión a E/I basados en ^{10}Fn3 pegilados se ensayaron para determinar su potencia para bloquear la unión de EGF a EGFR sobre la superficie de células A431 usando procedimientos que se han descrito previamente en el Ejemplo 10. Los agentes de unión a E/I basados en ^{10}Fn3 pegilados bloquearon la unión de EGF a células A431 variando las CI50 de 19.5 nM a 238 nM (Figura

43, columna i).

Los agentes de unión a E/I basados en ^{10}Fn3 pegilados se evaluaron con respecto a su capacidad de inhibir la formación de colonias de células H292 usando procedimientos que se han descrito en el Ejemplo 17. Como se muestra en la Figura 43, columna j, los agentes de unión a E/I basados en ^{10}Fn3 pegilados inhibieron la formación de colonias variando los valores de CI50 entre 1 nM - 560 nM y tres de los cuatro agentes de unión a E/I basados en ^{10}Fn3 pegilados ensayados eran 23-140 veces más potentes que el anticuerpo monoclonal anti-EGFR panitumumab. El cuarto agente de unión a E/I basado en ^{10}Fn3 pegilado era 4 veces menos potente que panitumumab. El monómero I1 pegilado era sólo marginalmente activo inhibiendo la formación de colonias en H292 con una CI50 >15 μM y esto se esperaba ya que el crecimiento de células H292 está dirigido principalmente por señalización de EGFR y no por señalización de IGF1R.

Se evaluó la temperatura de fusión para agentes de unión a E/I basados en ^{10}Fn3 pegilados por DSC (como se ha descrito previamente en el Ejemplo 4) o por metodología de fusión térmica de colorante. Para la evaluación de fusión térmica de colorante, los agentes de unión a E/I basados en ^{10}Fn3 pegilados se diluyeron a 0.2 mg/ml en amortiguador NaAc 50 mM pH 4.5. En cada muestra se realizaron adiciones de 1 μl de Naranja Sypro 200x en amortiguador DMSO para una

concentración final de colorante al 0.5%. Cada muestra se cargó en la bandeja de 96 pocillos y se revistió con 5 µl de de aceite de silicona. La bandeja se centrifugó a 1.000 RPM y se cargó en el sistema Bio-Rad CFX96 y se seleccionó al siguiente procedimiento: 25°C durante 10 minutos + Lectura de Placa a una temperatura de 25°C a 95°C a incrementos de 0.5°C durante 15 minutos + Lectura de Placa. El análisis de datos se realizó para el punto de inflexión con el software CFX. Como se muestra en la Figura 43, columna k, todos los agentes de unión a E/I basados en ^{10}Fn3 pegilados tenían mediciones de Tm similares, que variaban entre 49-62.5 grados celsius. Las mediciones de Tm para los agentes de unión a E/I basados en ^{10}Fn3 pegilados eran independientes de la concentración y permanecieron constantes a todas las concentraciones ensayadas. El análisis de un ejemplo de agente de unión, I1-GS10-E5 pegilado, medido con un intervalo de exploración de 15-95°C a concentraciones de proteína de 1 mg/ml en PBS, dio como resultado una medición de Tm de 55.2°C como se muestra en la Figura 20.

Se realizó cromatografía de exclusión por tamaño (SEC) en los agentes de unión a E/I basados en ^{10}Fn3 pegilados como se ha descrito previamente en el Ejemplo 4. El análisis de SEC puso de manifiesto que todos los agentes de unión a E/I basados en ^{10}Fn3 pegilados eran >

95% monoméricos como se muestra en la 43 (columna 1 de Tabla).

Ejemplo 23: Propiedades bioquímicas y biofísicas del agente de unión a E/I basado en ^{10}Fn3 I1-GS10-E5 pegilado con cambios de aminoácidos seleccionados

Se construyó el I1-GS10-E5 pegilado sin el marcador 6HIS y también con diversas alteraciones en la región adaptadora. Además, se realizó un cambio global en todas las construcciones donde la cola C-terminal del primer monómero tenía un único cambio puntual del ácido aspártico a ácido a ácido glutámico (de una D a una E). Se prepararon varios clones con restos de serina seleccionados mutados a cisteínas (de S a C) para proporcionar sitios de PEGilación alternativos. El efecto de estos cambios sobre las propiedades bioquímicas y biofísicas de la molécula se compararon y se resume en la Tabla 17. Los procedimientos para medir la inhibición de pEGFR se describen en el Ejemplo 7, de pIGFR en el Ejemplo 6, de pERK en el Ejemplo 1, Tm en el Ejemplo 4, KD de EGFR e IGFR en el Ejemplo 5. También se realizó un análisis detallado de la cinética de unión en estos clones y se presentan en las Tablas 18 y 19 (usando procedimientos similares a los descritos en el Ejemplo 5).

Tabla 17

NOMBRE DE CLON	CI50 de pEGFR (nM)	CI50 de pIGFR (nM)	CI50 de pERK (nM)	Tm (°C)	KD de EGFR (nM)	KD de IGFR (nM)	% de mono de SEC
I1-GS10-E5 pegilado	28	2.2	12	56	2.7	0.25	96
I1-GS10-E5 pegilado[1]	30	1.2	11	56.8	Adhesivo[9]	0.23	94.1
I1-GSGCGS8-E5[3]	19.8	1.4	8	54.8	4	0.29	95.2
I1-GS10-E5-GSGC[4]	28.7	1.2	19	55	1.4	0.25	92.7
I1 (S62C)-GS10-E5[5]	21	1.9	10	55.5	8.7	0.7	97.45
I1-GS10-E5 (S62C) [6]	68.4	2.2	30	56	1.7	0.26	96.12
I1 (S91C)-GS10-E5[7]	22.7	6.2	15	52	17	7.16	95.98
I1-GS10-E5(S91C)[8]	22.6	2.1	29	50.5	17.9	0.28	93.39

(1) No se usó un marcador de His para esta construcción. (2) se realizó un cambio global en todas las construcciones alternativas de I1-GS10-E5

pegilado, donde la cola C-terminal del primer monómero tenía un único cambio puntual de ácido aspártico a ácido glutámico (de D a una E). (3) Monómero de I1 unido con GSGC más GS8, a E5. (4) I1 unido con GS10 a E5 con GSGC en la cola de E5. (5) I1 unido con GS10 a E5, donde I1 tiene un único cambio puntual de serina a cisteína en la posición 62. (6) I1 unido con GS10 a E5, donde E5 tiene un único cambio puntual de serina a cisteína en la posición 62. (7) I1 unido con GS10 a E5, donde I1 tiene un único cambio puntual de serina a cisteína en la posición 91. (8) I1 unido con GS10 a E5, donde el E5 tiene un único cambio puntual de serina a cisteína en la posición 91. (9) Esta construcción demuestra unión no específica a la celda de flujo de tal forma que no fue posible una determinación precisa de la afinidad en este experimento.

Tabla 18

Unión Biacore de clones pegilados de I1-GS10-E5 alterados a EGFR645-Fc.

Descripción	ka (1/Ms)	kd (1/s)	Kd (nm)	Δka (veces)	Δkd (veces)	ΔKd (veces)
I1-GS10-E5 Pegilado	2.93 ± 0.67 E+04	7.24 ± 3.14 E-05	2.69 ± 1.53	---	---	---
I1-GS10-E5 pegilado	2.27E+04	1.49E-04	6.6	0.8	0.5	0.4
I1-GS10-E5 pegilado[1]	Unión no específica a superficie celular de referencia a mayores concentraciones de analito (600 nM, 200 nM de determinación de valor cinético prohibida)					
CLONES ALTERNATIVOS[2]						
I1-GSGCGS8-E5[3]	2.94E+04	1.18E-04	4.0	1.0	0.6	0.7
I1-GS10-E5-GSGC[4]	3.34E+04	4.52E-05	1.4	1.1	1.6	2.0
I1(S62C)-GS10-E5[5]	2.28E+04	1.99E-04	8.7	0.8	0.4	0.3
I1-GS10-E5(S62C)[6]	1.78E+04	3.04E-05	1.7	0.6	2.4	1.6
I1(S91C)-GS10-E5[7]	1.96E+04	3.34E-04	17.0	0.7	0.2	0.2
I1-GS10-E5(S91C)[8]	1.08E+04	1.93E-04	17.9	0.4	0.4	0.2

(1) No se usó marcador de His para esta construcción. (2) se realizó un cambio global en todas las construcciones alternativas de I1-GS10-E5 pegilado, donde la cola C-terminal del primer

monómero tenía un único cambio puntual de ácido aspártico a ácido glutámico (de D a una E). (3) El monómero de I1 unido con GSGC más GS8, a E5. (4) I1 unido con GS10 a E5 con GSGC en la cola de E5. (5) I1 unido con GS10 a E5, donde el I1 tiene un único cambio puntual de serina a cisteína en la posición 62. (6) I1 unido con GS10 a E5, donde E5 tiene un único cambio puntual de serina a cisteína en la posición 62. (7) I1 unido con GS10 a E5, donde I1 tiene un único cambio puntual de serina a cisteína en la posición 91. (8) I1 unido con GS10 a E5, donde E5 tiene un único cambio puntual de serina a cisteína en la posición 91.

Tabla 19

Unión Biacore de clones pegilados de I1-GS10-E5 alterados a IGF1R-Fc.

Descripción	ka (1/Ms)	kd (1/s)	Kd (nm)	Δka (veces)	Δkd (veces)	ΔKd (veces)
I1-GS10-E5 pegilado	1.04 ± 0.04 E+06	2.62 ± 0.21 E-04	0.25 ± 0.01	---	---	---
I1-GS10-E5 pegilado	1.10E+06	2.78E-04	0.25	1.1	0.9	1.0
I1-GS10-E5 pegilado[1]	1.28E+06, 1.22E+06	2.88E-04, 2.76E-04	0.22, 0.23	1.2	0.9	1.1
CLONES ALTERNATIVOS[2]						
I1-GSGCGS8-E5[3]	8.52E+05	2.45E-04	0.29	0.8	1.1	0.9
I1-GS10-E5-GSGC[4]	1.07E+06	2.65E-04	0.25	1.0	1.0	1.0
I1(S62C)-GS10-E5[5]	3.34E+05	2.34E-04	0.70	0.3	1.1	0.4
I1-GS10-E5(S62C) [6]	1.07E+06	2.79E-04	0.26	1.0	0.9	1.0
I1(S91C)-GS10-E5[7]	8.22E+04	5.89E-04	7.16	0.1	0.4	0.04
I1-GS10-E5(S91C) [8]	9.86E+05	2.81E-04	0.28	0.9	0.9	0.9

(1) No se usó marcador de His para esta construcción. (2) Se realizó un cambio global en todas las construcciones alternativas de I1-GS10-E5 pegilado, donde la cola C-terminal del primer monómero tenía un único cambio puntual de ácido aspártico a ácido glutámico (de D a una E).

(3) El monómero I1 unido con GSGC más GS8, a E5. (4) I1 unido con GS10 a E5 con GSGC en la cola de E5. (5) I1 unido con GS10 a E5, donde I1 tiene un único cambio puntual de serina a cisteína en la posición 62. (6) I1 unido con GS10 a E5, donde E5 tiene un único cambio puntual de serina a cisteína en la posición 62. (7) I1 unido con GS10 a E5, donde I1 tiene un único cambio puntual de serina a cisteína en la posición 91. (8) I1 unido con GS10 a E5, donde E5 tiene un único cambio puntual de serina a cisteína en la posición 91.

Ejemplo 24: inhibición de rutas de señalización aguas abajo compartidas de EGFR e IGFR

La inhibición de las rutas de señalización aguas abajo se analizó con un ELISA pAKT idéntico a los descritos previamente en el Ejemplo 8. Los resultados de este estudio demuestran que I1-GS10-E5 pegilado es más potente que I1 pegilado solo en el bloqueo de la activación de AKT estimulada por IGF1 en células H292. El E5 pegilado, el agente de unión a EGFR monoespecífico solo no impidió eficazmente la activación de AKT por estimulación de IGF1 (Figura 21).

Ejemplo 25: Inhibición de la proliferación celular por agentes de unión basados en ^{10}Fn3 y anticuerpo comparador

Se realizaron experimentos de proliferación de células H292 y RH41 como se describe en el Ejemplo 9. El

agente de unión a EGFR monoespecífico basado en ^{10}Fn3 E5-pegilado inhibió la proliferación de células H292 con un valor de CI50 de 0.016 μM. El agente de unión a IGFR monoespecífico basado en ^{10}Fn3 I1-pegilado tuvo un valor de CI50 > 8.4 μM mientras que el agente de unión a E/I basado en ^{10}Fn3 I1-GS10-E5 pegilado era ligeramente más potente con un valor de CI50 de 0.006 μM (Figura 22). La línea celular H292 procede de cáncer de pulmón y es sensible a la inhibición de IGFR y EGFR ((Akashi Y, y col. (2008) Enhancement of the antitumor activity of ionising radiation by nimotuzumab, a humanised monoclonal antibody to the epidermal growth factor receptor, in non-small cell lung cancer cell lines of differing epidermal growth factor receptor status. Br. J. Cancer 98: 749-755; y Buck E, y col. (2008) Feedback mechanisms promote cooperativity for small molecule inhibitors of epidermal and insulin-like growth factor receptors. Cancer Res. 68: 8322-8332.)) Por el contrario, sólo el agente de unión I1-GS10-E5 pegilado y el agente de unión I1-pegilado inhibían la proliferación de células RH41 (los valores de CI50 fueron de 0.0002 y 0.0004 μM, respectivamente, Figura 23). Esto era esperado, ya que RH41 es una línea celular de rabdomiosarcoma pediátrica que se sabe que se dirige predominantemente por la señalización de IGFR ((Huang F, y col. (2009). The mechanisms of differential sensitivity to an insulin-like growth factor-1

receptor inhibitor (BMS-536924) and rationale for combining with EGFR/HER2 inhibitors. Cancer Res. 69: 161-170)) y por lo tanto no es sensible al bloqueo de EGFR.

Ejemplo 26: Inhibición de activación de receptor y señalización aguas abajo *in vitro* por agentes de unión basados en ^{10}Fn3 pegilados y no pegilados

Para comprender la dinámica de la señalización de EGFR/IGFR y su inhibición por I1-GS10-E5 pegilado, se privaron de suero células DiFi, H292 o BxPC3, se expusieron a E5 pegilado, I1 pegilado o I1-GS10-E5 pegilado, 1 μM o 0.1 μM, o control de vehículo durante 2 horas, y después se estimuló con EGF, IGF-I o EGF + IGF-I durante 10 minutos.

Las células se cultivaron *in vitro*, privadas de suero durante una noche y después se expusieron a agentes de unión basados en ^{10}Fn3 durante 2 horas antes de la estimulación con 100 ng/ml de EGF o IGF. Se prepararon lisados celulares en amortiguador de lisis (Tritón X-100 al 1%, glicerol al 5%, NaCl 0.15 M, Tris-HCl 20 mM pH 7.6, Comprimidos de Cóctel Inhibidor de Proteasa Completo [Roche, Indianapolis, IN] y Cóctel Inhibidor de Fosfatasa 2 [Sigma-Aldrich Corp.]). Los lisados (30 μg) se resolvieron por SDS-PAGE, se transfirieron a membranas y se sometieron a inmunotransferencia con anticuerpos contra fosfo-EGFR y EGFR total (Santa Cruz Biotechnology, Carlsbad, CA), fosfo-AKT (Ser 473), fosfo-p44/42 MAPK (Thr202/Tyr204) (Cell Signaling

Technology, Beverly, MA), o actina total (Chemicon International, Temecula, CA) en Amortiguador de Bloqueo Odyssey con Tween 20 al 0.1% (LI-COR Biosciences, Lincoln, NE). Las membranas se incubaron con los anticuerpos secundarios apropiados. La visualización de las proteínas se realizó usando un sistema de formación de imágenes por infrarrojos LI-COR Biosciences Odyssey.

Como se muestra en la figura 24, los niveles basales de EGFR fosforilado, IGF-IR y AKT fueron casi indetectables después de la privación de suero. En células DiFi, ni I1-GS10-E5 pegilado ni E5 pegilado (agente de unión a EGFR monoespecífico) pueden suprimir completamente la fosforilación de EGFR estimulada por EGF. En células H292 y BxPC3 hay una fuerte inhibición de la fosforilación de EGFR por I1-GS10-E5 pegilado y E5 pegilado. En células DiFi y BxPC3, I1-GS10-E5 pegilado bloquea la fosforilación de IGFR estimulada por IGF más que I1 pegilado (agente de unión a IGFR monoespecífico) por sí mismo. En células H292, la estimulación de IGF activa de forma cruzada al EGFR solo cuando el EGFR está bloqueado. I1-GS10-E5 pegilado inhibía pAKT estimulado por EGF en DiFi; aumentaba pAKT en H292 estimuladas por EGF y en BxPC3 EGF no activaba pAKT. En células DiFi, H292 y BxPC3 I1-GS10-E5 pegilado inhibía pIGFR estimulado por IGF más que el E5 pegilado y el I1 pegilado individuales por sí mismos. I1-GS10-E5 pegilado tenía un

efecto muy pequeño o nulo sobre pERK estimulado por EGF en DiFi, H292 o BxPC3. La estimulación por IGF no inducía pERK en ninguna línea celular examinada.

En otro experimento con agentes de unión basados en ^{10}Fn3 no pegilados, se privaron de suero células H292, se expusieron a agente de unión a EGFR E2 monoespecífico no pegilado 1 μM, agente de unión a IGFR I1 o E2-GS10-I1 o control de vehículo durante 1 hora, y después se estimularon con EGF, IGF-I o EGF + IGF-I durante 10 minutos. Los niveles basales de EGFR, IGFR y AKT fosforilados fueron casi indetectables después de la privación de suero (Figura 25). La estimulación con EGF indujo la fosforilación de EGFR, pero no transactiva IGFR. La fosforilación de EGFR se bloqueó por E2, y E2-GS10-I1, pero no I1. De forma similar, la estimulación con IGF-I inducía una fuerte fosforilación de IGFR que se bloqueaba por I1 y E2-GS10-I1, pero no por E2. La estimulación por EGF sólo aumentó ligeramente la fosforilación de AKT, pero IGF-I o EGF + IGF-I indujeron fuertemente la fosforilación de AKT que se suprimió a niveles basales tanto por I1 como por E2-GS10-I1. La combinación de IGF-I y EGF indujo la fosforilación de AKT más que cualquier factor de crecimiento solo. E2 redujo parcialmente pAKT inducida por la combinación de EGF e IGF-I. Sin embargo, I1 mostró la reducción más dramática en pAKT, lo que sugiere que la estimulación con EGF + IGF-I condujo a una fuerte

fosforilación de AKT a lo largo de la ruta de IGFR. Sorprendentemente, el bloqueo de la ruta de EGFR por E2 seguido de la estimulación con ligando EGF aumentó realmente la fosforilación de AKT, quizás como resultado de la activación de AKT independiente de EGFR ((Dobashi Y, y col. (2009) EGFR-dependent and independent activation of Akt/mTOR cascade in bone and soft tissue tumors. Mod Pathol (Epub Ahead of Print)). Estos resultados ilustran la compleja interacción entre las rutas de EGFR e IGFR y los mecanismos de retroalimentación.

Ejemplo 27: Estudios de unión competitiva con agentes de unión a E/I basados en ^{10}Fn3

Para los experimentos de competición Biacore, se inmovilizó EGFR-Fc (3 µg/ml en Na-acetato pH 5.0) en la superficie del chip Biacore CM5 usando la química de acoplamiento de amida EDC/NHS convencional a una densidad de superficie de 300 RU. Los anticuerpos contra EGFR se obtuvieron como un fármaco comercializado y la competición entre agente de unión a EGFR monoespecífico E2 y anticuerpos por la unión a EGFR-Fc se evaluó por la unión de E2 450 nM (30 µl/min, tiempo de contacto 200 seg), seguido inmediatamente de E2 450 nM solo, o una mezcla de E2 450 nM más cetuximab, panitumumab o nimotuzumab 450 nM (30 µl/min, tiempo de contacto 200 seg). La

superficie se regeneró satisfactoriamente entre ciclos usando dos pulsos de 10 segundos de NaOH 50 mM a un caudal de 30 µl/min. La inyección inicial de E2 muestra la unión a EGFR en la superficie del chip. Una segunda inyección de E2 mezclado con una cantidad igual de cetuximab, panitumumab o nimotuzumab no muestra competición por la unión de anticuerpos a EGFR por E2 (Figura 26A).

Se utilizó un análisis de resonancia de plasmón superficial (BIAcore) para demostrar el encaje simultáneo de EGFR-Fc capturado e IGF1R en fase de solución por agentes de unión a E/I basados en ^{10}Fn3. EGFR-Fc humano recombinante (aa 1-645 del dominio extracelular de EGFR humano fusionado a Fc humana) se adquirió en R&D Systems (Minneapolis, MN). IGF1R recombinante (aa 1-932 del propéptido IGF1R humano, escindido proteolíticamente y unido por enlaces disulfuro) se adquirió en R&D Systems (Minneapolis, MN). Para demostrar el encaje simultáneo, se inmovilizó IgG antihumana en celdas de flujo 1 y 2 de un chip CM5 siguiendo las recomendaciones del fabricante (GE Healthcare, Piscataway, NJ). EGFR-Fc (50 nM) se capturó en una celda de flujo de 2 a 10 µl/min durante 2 minutos. La unión de agentes de unión a E/I basados en ^{10}Fn3 a

EGFR-Fc se consiguió inyectando muestras de proteína basadas en ^{10}Fn3 (100 nM) sobre las dos celdas de flujo a 10 µl/min durante 2 minutos. El encaje simultáneo de EGFR-Fc e IGF1R se sondó por inyección posterior de IGF1R (0, 100 nM) sobre las dos celdas de flujo a 30 µl/min durante 2 minutos. La disociación del complejo se monitorizó durante 300 segundos. Se usaron dos segundas inyecciones de $MgCl_2$ 3 M para la regeneración del complejo unido de la superficie de IgG anti-humana. Para solapar los sensogramas y retirar los picos de aire se utilizó Biacore T100 Evaluation Software, Versión 2.0.1 (GE healthcare/Biacore). Como se muestra en la Figura 26B, los dos dominios del agente de unión a E/I basado en ^{10}Fn3 son funcionales y pueden unirse a EGFR-Fc e IGF1R simultáneamente.

La especificidad de unión de E2-GS10-I1 pegilado a receptores de la familia HER se evaluó por Biacore como se describe en el Ejemplo 5. Se capturaron HER-2-Fc, HER-3-Fc y HER-4-Fc (R&D Systems) en la superficie del chip CM5 con IgG anti-humana. E2-GS10-I1 pegilado no mostró ninguna unión perfectible a otros miembros de la familia HER en condiciones en las que se observó una unión sólida para EGFR-Fc (HER-1) (Tabla 20).

Tabla 20

Afinidad de unión de E2-GS10-I1 pegilado a dominios extracelulares de la familia HER de receptores.

Nombre	EGFR-Fc K_D, nM*	HER-2-Fc K_D, nM	HER-3-Fc K_D, nM	HER-4-Fc K_D, nM
E2-GS10-I1 pegilado	10.1	> 1000	>1 000	> 1000

Ejemplo 28: Medición de biomarcadores en plasma

Se midieron los niveles de biomarcadores TGFα y mIGF1 solubles en plasma de ratón al final de estudios de xenoinjerto o en ratones que no llevaban tumores a diversos tiempos después del tratamiento. Se obtuvo sangre por punción cardiaca terminal en tubos que contenían EDTA como anticoagulante. Se preparó plasma por centrifugación de la sangre a 1300 xg durante 10 minutos a 4 grados C y retirando el sobrenadante clarificado a un tubo separado. Los niveles de TGFα se midieron en 0.1 ml de plasma, los niveles de mIGF1 se midieron en 0.02 ml de plasma con un ensayo ELISA como recomienda el fabricante (R&D Systems, Minneapolis, MN). Los niveles plasmáticos de TGFα estaban elevados en los ratones tratados con I1-GS10-E5 pegilado o el agente de unión a EGFR monoespecífico E5 pegilado pero sin cetuximab (Figura 27A-C).

El TGFα pudo secretarse del tumor humano o puede representar TGFα de ratón endógeno. Debido a la alta homología entre TGFα humano y de ratón (identidad de aminoácidos del 93%) el ELISA puede presentar reacción cruzada con TGFα de ratón. Además, el TGFα humano secretado por el tumor implantado puede unirse al EGFR de ratón. Como tanto I1-GS10-E5 pegilado como E5 pegilado pueden unirse a EGFR humano y de ratón, todos los sitios de unión de EGFR del hospedador y del tumor están bloqueados por estos agentes de unión basados en ^{10}Fn3, mientras que el cetuximab no se une a EGFR de ratón. Para determinar si estos agentes de unión basados en ^{10}Fn3 producen aumentos en el TGFα de ratón endógeno y si el ELISA presenta reacciones cruzadas con TGFα de ratón, a ratones desnudos que no tenían tumores se les dosificó con I1-GS10-E5 pegilado a 100 mg/kg y se tomaron muestras plasmáticas 4, 24, 48 y 72 horas después de la dosificación. De hecho, se observaron aumentos en el TGFα de ratón que persistieron pasadas 72 horas (Figura 28A). También se ensayaron muestras plasmáticas de ratones sin tumores con respecto a mIGF1 con un ELISA específico de ratón y también se observaron aumentos en este ligando (Figura 28B).

Ejemplo 29: Resultados de estudios de xenoinjerto de tumor humano *in vivo* para diversos agentes de unión a E/I basados en ^{10}Fn3

Se evaluaron varios agentes de unión a E/I basados

en ^{10}Fn3 en un estudio comparativo de NSCLC H292 (procedimientos descritos en el Ejemplo 12) a una dosis menor que la usada previamente de forma que pudieron averiguarse las diferencias en la actividad relativa. Se comparó la eficacia de los agentes de unión a E/I basados en ^{10}Fn3 E2-GS10-I1 pegilado, E4-GS10-I1 pegilado, I1-GS10-E5 pegilado, I1-GS10-E85 pegilado, I1-GS10-E4 pegilado, I1-GS10-E105 pegilado a una sola dosis de 0.625 mg/ratón y panitumumab a dos dosis (1 mg/ratón y 0.1 mg/ratón).

Las dos dosis de panitumumab y todos los agentes de unión a E/I basados en ^{10}Fn3 evaluados en este estudio fueron activos por un punto final de inhibición del crecimiento tumoral (TGI). Durante la fase de dosificación, E4-GS10-I1 pegilado, I1-GS10-E5 pegilado, I1-GS10-E4 pegilado y panitumumab produjeron regresión tumoral (Tabla 21, valores de TGI mayores del 100%) mientras que E2-GS10-I1 pegilado, I1-GS10-E85 pegilado e I1-GS10-E105 pegilado produjeron inhibición del crecimiento tumoral (Tabla 21, valores de TGI hasta el 100%). Las diferencias en actividad fueron estadísticamente significativas cuando se compararon con el grupo de control. Todos los tratamientos fueron bien tolerados sin muertes relacionadas con el tratamiento o una pérdida de peso excesiva durante el transcurso del estudio. La comparación de la eficacia de los agentes de unión a E/I basados en ^{10}Fn3 y panitumumab se presentan en la Tabla 21

mostrada a continuación y en la Figura 29. En la Figura 29A, las mediciones hasta el día 43 muestran el patrón de extensión de los tumores después de cesar la dosificación. La Figura 29B muestra las mediciones hasta el día 27 y el eje y se amplía para ilustrar las diferencias relativas en actividad entre los grupos de tratamiento.

Tabla 21

Actividad antitumoral *in vivo* en el estudio de NSCLC H292

Grupo	Compuesto	Programa, Vía	Dosis (mg/kg)	Cambio de peso MEDIO (g)	%TGI	valor de p para %TGI	Resultado por %TGI
1	Control (sin tratar)	---	---	3.36	---	1.0	---
2	panitumumab	q3dx5;6 ip[a]	1 mg/ratón	5.19	107	0.0023	A
3	panitumumab	q3dx5;6 ip[a]	0.1 mg/ratón	5.9	105	0.0029	A
4	E2-GS10-I1 pegilado	TIWX3;6 ip[a]	0.625 mg/ratón	-1.4	93	0.0067	A

Grupo	Compuesto	Programa, Vía	Dosis (mg/kg)	Cambio de peso MEDIO (g)	%TGI	valor de p para %TGI	Resultado por %TGI
5	E4-GS10-I1 pegilado	TIWX3;6 ip[a]	0.625 mg/ratón	-0.23	105	0.0023	A
6	I1-GS10-E5 pegilado	TIWX3;6 ip[a]	0.625 mg/ratón	-2.92	103	0.0033	A
7	I1-GS10-E85 pegilado	TIWX3;6 ip[a]	0.625 mg/ratón	1.08	86	0.0114	A
8	I1-GS10-E4 pegilado	TIWX3;6 ip[a]	0.625 mg/ratón	-1.21	103	0.0034	A
9	I1-GS10-E105 pegilado	TIWX3;6 ip[a]	0.625 mg/ratón	-1.54	95	0.0035	A

[a] El vehículo era solución salina amortiguada con fosfato. Las abreviaturas usadas son las siguientes: ip, vía intraperitoneal; %TGI, % relativo de inhibición del crecimiento tumoral calculado como $\%TGI=[(C_t-T_t)/(C_t-C_0)] \times 100$ donde C_t = peso medio del tumor de ratones de control a

tiempo t en días después del implante del tumor, T_t = peso medio del tumor de ratones tratados a tiempo t, C_0 = peso medio del tumor de ratones de control a tiempo 0. El valor de %TGI se calculó en dos puntos como la inhibición media del Día 20, Día 24 y Día 27. Resultado, un régimen de tratamiento se considera activo si producía un valor de %TGI estadísticamente significativo > 50%; q3dx5;6, el compuesto se administró cada tres días para seis dosis empezando el sexto día después del implante de tumor; 6 on/1 off; 6, el compuesto se administró una vez al día durante 6 días y después no hubo tratamiento durante 1 día y este régimen empezó el sexto día después del implante del tumor. Los valores de p se calcularon el Día 20 con respecto al grupo de control en un análisis de muestras emparejadas de dos colas con 8 mediciones por grupo.

Además se realizaron estudios *in vivo* con los agentes de unión a E/I basados en ^{10}Fn3 seleccionados, en diversos modelos de xenoinjerto usando los métodos descritos en el Ejemplo 12. A continuación se proporciona una descripción de los diversos modelos de xenoinjerto: H292 es un carcinoma pulmonar no microcítico (NSCLC) y se describe con más detalle en el Ejemplo 12; el carcinoma de mama MCF7r se describe en el Ejemplo 14; y el carcinoma de colon GEO se describe en el Ejemplo 15. El carcinoma de colón humano DiFi expresa altos niveles de EGFR activado y también expresa

IGFR; RH41 es una línea celular de rabdomiosarcoma pediátrica que se sabe que se dirige predominante por la señalización de IGFR (Huang F, y col. ((2009)) The mechanisms of differential sensitivity to an insulin-like growth factor-1 receptor inhibitor (BMS-536924) and rationale for combining with EGFR/HER2 inhibitors. Cancer Res. 69: 161-170) y por lo tanto no es sensible al bloqueo de EGFR; Cal27 es un carcinoma de cabeza y cuello humano que expresa altos niveles de EGFR y niveles moderados de IGFR; BxPC3 es un carcinoma pancreático humano; y H441 es un NSCLC.

La comparación de la eficacia de agentes de unión a E/I basados en ^{10}Fn3 se presenta en la Tabla 22. En estos estudios de eficacia, todos los agentes de unión a E/I basados en ^{10}Fn3 mostraron una actividad equivalente al panitumumab y todos los tratamientos pudieron provocar la regresión de tumores H292 por debajo de su tamaño de partida como se indica por valores de %TGI mayores del 100%. En el estudio DiFi, el panitumumab produjo la regresión de tumores a la dosis de 1 mg/ratón y fue activo a la dosis de 0.1 mg/ratón mientras que todos los agentes de unión a E/I basados en ^{10}Fn3 fueron inactivos aunque el I1-GS10-E5 pegilado mostró alguna inhibición del crecimiento tumoral (TGI = 43.8%). En el estudio de RH41, el panitumumab no era activo a ninguna dosis, la construcción de E2-pegilado no era activa mientras que los agentes de unión a E/I basados en

^{10}Fn3 y la construcción de I1-pegilado eran activos. La Figura 32 muestra la eficacia antitumoral en el modelo de RH41 para una construcción representativa E2-GS10-I1 pegilado (datos mostrados también en la Tabla 23). En el estudio de Cal27 del panitumumab produjo la regresión de los tumores a la dosis de 1 mg/ratón y fue activo a la dosis de 0.1 mg/ratón, pero entre los agentes de unión a E/I basados en ^{10}Fn3 sólo fue activa la construcción de unión a E/I basado en ^{10}Fn3 I1-GS10-E5 pegilado.

Los resultados de los estudios de xenoinjerto de tumor humano con I1-GS10-E5 pegilado y los componentes individuales I1 y E5 diseñados para evaluar la sinergia se presentan en la Tabla 23. Estos estudios de combinación (sinergia) se estructuraron de tal forma que se incluyeron las piezas individuales de los agentes de unión a E/I basados en ^{10}Fn3 (es decir, versiones pegiladas monoespecíficas de IGFR y EGFR) de forma que pudieran discernirse los efectos antitumorales más allá de la contribución de los extremos aislados. En el estudio de MCF7r, I1 pegilado no era activo mientras que los clones de E5 pegilado, (E5 pegilado + I1 pegilado) e I1-GS10-E5 pegilado eran activos y presentaban una actividad similar, lo que significa que toda la actividad antitumoral probablemente procede de la inhibición de EGFR y el bloqueo de la ruta de IGFR no proporcionaba ninguna mejora. El cetuximab producía la regresión de los tumores a

la dosis de 1 mg/ratón y no era activo a la dosis de 0.1 mg/ratón. BMS-754807 tampoco era activo, demostrando que el bloqueo de la ruta de IGFR con un inhibidor de pequeña molécula no producía eficacia en este modelo.

En el estudio de BxPC3, I1 pegilado no era activo mientras que los clones de E5 pegilado y (E5 pegilado + I1 pegilado) eran activos (TGI = 61.2% y 68.8%, respectivamente). El clon I1-GS10-E5 pegilado era más activo (TGI = 78%) que las piezas individuales de las que está hecho y la diferencia era estadísticamente significativa mediante un ensayo t de muestras emparejadas de dos colas, lo que demuestra que tiene una actividad sinérgica en este modelo. El cetuximab era activo a todas las dosis estudiadas, pero la adición en la inhibición de IGFR por combinación con el I1-pegilado no produjo sinergia.

En el estudio GEO, I1 pegilado no era activo mientras que el E5 pegilado y los clones (E5 pegilado + I1 pegilado) e I1-GS10-E5 pegilado eran activos (TGI = 83.5%, 92.1 y 92.1%, respectivamente). Aunque puede haber alguna mejora proporcionada por la combinación de la inhibición de EGFR e IGFR conjuntamente en este modelo, la diferencia no fue significativamente mejor que la del E5 pegilado por sí mismo. El cetuximab era activo a las dos dosis estudiadas, pero la adición en la inhibición de IGFR por combinación con el I1-pegilado no produjo sinergia.

En el estudio H441, I1 pegilado y E5 pegilado no eran activos por sí mismos pero (E5 pegilado + I1 pegilado) era activo (TGI = 54.5%). El clon de I1-GS10-E5 pegilado era más activo (TGI = 69.2%) que las piezas individuales de las que está hecho, pero las diferencias no eran estadísticamente significativas, lo que demuestra que proporciona mayor actividad pero no sinergia en este modelo. El cetuximab era activo a la dosis de 1 mg/ratón y no era activo a la dosis de 0.1 mg/ratón. La adición en la inhibición de IGFR por combinación con I1-pegilado no produjo ninguna mejora en este modelo.

Tabla 22

Resultados *in vivo* de agentes de unión a E/I basados en ^{10}Fn3

Grupo	Compuesto	Programa	Dosis (mg/kg)[a]	Cambio de peso MEDIO (g)	%TGI	valor de p para %TGI	Resultado por %TGI
Actividad antitumoral *in vivo* en el estudio de H292							
1	Control (sin tratar)	---	---	5.7	---	[illegible].0	---
2	panitumumab	Q3dx5;6 ip[a]	1 mg/ratón	5.0	104	0.0006	A
3	panitumumab	Q3dx5;6	0.1	1.5	102	0.0005	A

		ip[a]	mg/ratón				
4	E4-GS10-I1 pegilado	TIWX3;6	2 mg/ratón	-4.86	105	0.0004	A
5	I1-GS10-E5 pegilado	TIWX3;6	2 mg/ratón	-10.0	102	0.0006	A
6	I1-GS10-E4 pegilado	TIWX3;6	2 mg/ratón	-1.41	105	0.0005	A
Actividad antitumoral *in vivo* en el estudio de DiFi							
1	Control (sin tratar)	---	---	-0.5	---	1.0	---
2	panitumumab	Q3dx5;6 ip[a]	1 mg/ratón	5.3	109.7	0.006	A
3	panitumumab	Q3dx5;6 ip[a]	0.1 mg/ratón	2.6	99.9	0.005	A
4	E4-GS10-I1 pegilado	TIWX3;6	3 mg/ratón	-10.8	-1.1	0.815	I
5	I1-GS10-E5 pegilado	TIWX3;6	3 mg/ratón	-16.4	43.8	0.310	I
6	I1-GS10-E4 pegilado	TIWX3;6	3 mg/ratón	-8.5	1.4	0.977	I
Actividad antitumoral *in vivo* en el estudio de RH41							
1	Control (sin tratar)	---	---	7.2	---	1.0	---
2	panitumumab	q3dx5;6	1	10.7	16.5	0.721	I

		ip[a]	mg/ratón				
3	panitumumab	q3dx5;6 ip[a]	0.1 mg/ratón	8.6	38.4	0.563	I
4	E4-GS10-I1 pegilado	TIWX3;6	2.5 mg/ratón	-5.3	72.7	0.02	A
5	I1-GS10-E5 pegilado	TIWX3;6	2.5 mg/ratón	-7.8	68	0.019	A
6	I1-GS10-E4 pegilado	TIWX3;6	2.5 mg/ratón	-2.9	64.5	0.018	A
7	Control (sin tratar)	---	---	12.3	---	1.0	---
8	E2-GS10-I1 pegilado	TIWX3;18	2.5 mg/ratón	-1.8	58.6	0.044	A
9	E2-pegilado	TIWX3;18	1.25 mg/ratón	5.9	20.2	0.530	I
10	I1 pegilado	TIWX3;18	1.25 mg/ratón	7.1	58.6	0.025	A
Actividad antitumoral *in vivo* en el estudio de Cal27							
1	Control (sin tratar)	---	---	9.4	---	1.0	---
2	Panitumumab	q3dx5;6 ip[a]	1 mg/ratón	6.1	109.8	0.0005	A
3	panitumumab	q3dx5;6 ip[a]	0.1 mg/ratón	5.8	72.9	0.003	A

4	E4-GS10-E1 pegilado	TIWX3;6	2 mg/ratón	-1.2	-11.4	0.587	I
5	I1-GS10-E5 pegilado	TIWX3;6	2 mg/ratón	-11.6	57.6	0.037	A
6	I1-GS10-E4 pegilado	TIWX3;6	2 mg/ratón	-2.2	-9.2	0.177	I

[a] El vehículo era solución salina amortiguada con fosfato para todos los tratamientos. Las abreviaturas usadas son las siguientes: ip, vía intraperitoneal; po, vía oral; %TGI, % de inhibición del crecimiento tumoral relativo calculado como %TGI=[(Ct-Tt)/(Ct-C0)] x 100 donde Ct = peso medio del tumor de ratones de control a tiempo t en días después del implante del tumor, Tt = peso medio del tumor de ratones tratados a tiempo t, C0 = peso medio del tumor de ratones de control a tiempo 0. El valor de %TGI se calculó a dos puntos como inhibición media el Día 19 y 23 para H292, Día 39 y 41 para DiFi, Día 34 y 37 para RH41 para los grupos 1-6 y Día 35, 36 y 39 para los grupos 7-10, Día 18 y 20 para Cal27. Resultado, un régimen de tratamiento se consideró activo si producía un valor de %TGI estadísticamente significativo >50%; q3dx5;6, el compuesto se administró cada tres días durante seis dosis empezando el sexto día después del implante del tumor; TIWX3;6, el compuesto se administró tres veces por semana durante tres semanas y este régimen empezó el sexto día después del implante del tumor. Los

valores de p se calcularon con respecto al grupo de control en un análisis de muestras emparejadas de dos colas con 8 mediciones por grupo el Día 23 para H292, el Día 39 para DiFi, Día 37 para RH41 para los grupos 1-6, el Día 39 para los grupos 7-10 y el Día 20 para Cal27.

Tabla 23

Resumen de experimentos *in vivo* con agentes de unión basados en ^{10}Fn3 y comparadores

Grupo	Compuesto	Programa	Dosis (mg/kg)[a]	Cambio de peso MEDIO (g)	%TGI	valor de p para %TGI	Resultado por %TGI
Actividad antitumoral *in vivo* en el estudio de MCF7r							
1	Control (sin tratar)	---	---	6.1	---	1.0	---
2	I1 pegilado[a]	TIWX3;7	50 mg/kg, ip	17.1	-40.8	0.195	I
3	E5 pegilado[a]	TIWX3;7	50 mg/kg, ip	5.1	75.8	0.007	A
4	E5 pegilado[a] + I1 pegilado[a]	TIWX3;7	50 mg/kg, ip	-3.0	81.8	<0.0001	A
5	I1-GS10-E5 pegilado[a]	TIWX3;7	100mg/kg, ip	-4.5	78	0.009	A

6	cetuximab[a]	Q3DX5;7	1 mg/ratón, ip	11.7	105.4	0.0009	A
7	cetuximab[a]	Q3DX5;7	0.1 mg/ratón, ip	7.5	34.3	0.031	I
8	BMS-754807[b]	QDX14;7	50 mg/kg, po	-4.0	44.5	0.146	I
Actividad antitumoral in vivo en el estudio de BxPC3							
1	Control (sin tratar)	---	---	3.1	---	1.0	---
2	I1 pegilado	TIWX3;9	50mg/kg, ip	4.3	14.3	0.315	I
3	E5 pegilado	TIWX3;9	50mg/kg, ip	-5.3	61.2	0.0003	A
4	E5 pegilado + I1 pegilado	TIWX3;9	50mg/kg, ip	-4.9	68.8	0.0019	A
5	I1-GS10-E5 pegilado	TIWX3;9	100mg/kg, ip	-14.0	73.0	0.0002	A
6	cetuximab	Q3DX5;9	1 mg/ratón, ip	5.2	62.6	0.0026	A

7	cetuximab	Q3DX5;9	0.25 mg/ratón, ip	2.5	62.8	0.0005	A
8	cetuximab +I1 pegilado	Q3DX5;9 TIWX3;9	1 mg/ratón, ip 50mg/kg, ip	3.6	62.1	0.0005	A
Actividad antitumoral in vivo en el estudio de GEO							
1	Control (sin tratar)	---	---	7.5	---	1.0	---
2	I1 pegilado	TIWX3;9	50 mg/kg, ip	-7.2	26.8	0.594	I
3	E5 pegilado	TIWX3;9	50 mg/kg, ip	9.7	83.5	0.0028	A
4	E5 pegilado + I1 pegilado	TIWX3;9	50 mg/kg, ip	5.4	92.1	0.0005	A
5	I1-GS10-E5 pegilado	TIWX3;9	100 mg/kg, ip	-7.3	92.1	0.0006	A
6	cetuximab	Q3DX5;9	1 mg/ratón, ip	7.7	91.8	0.0008	A

7	cetuximab	Q3DX5;9	0.25 mg/ratón, ip	7.8	92.0	0.0007	A
8	cetuximab + I1 pegilado	Q3DX5;9 TIWX3;9	1 mg/ratón, ip 50 mg/kg, ip	7.1	91.3	0.0006	A
Actividad antitumoral in vivo en el estudio de H441							
1	Control (sin tratar)	---	---	12.4	---	1.0	---
2	I1 pegilado	TIWX3;9	50 mg/kg, ip	11.5	30.8	0.701	I
3	E5 pegilado	TIWX3;9	50 mg/kg, ip	-8.8	43.1	0.292	I
4	E5 pegilado + I1 pegilado	TIWX3;9	50 mg/kg, ip	-0.8	54.5	0.011	A
5	I1-GS10-E5 pegilado	TIWX3;9	100 mg/kg, ip	-3.9	69.2	0.022	A
6	cetuximab	Q3DX5;9	1 mg/ratón, ip	12.6	65.2	0.002	A
7	cetuximab	Q3DX5;9	0.25	13.7	43.9	0.110	-

			mg/ratón, ip				
8	cetuximab +I1 pegilado	Q3DX5;9 TIWX3;9	1 mg/ratón, ip 50 mg/kg, ip	10.2	66.7	0.060	-

[a] El vehículo fue solución salina amortiguada con fosfato para todos los tratamientos. Las abreviaturas usadas son las siguientes: ip, vía intraperitoneal; po, vía oral; %TGI, % de inhibición del crecimiento tumoral relativo calculado como %TGI=[(Ct-Tt)/(Ct-C0)] x 100 donde Ct = peso medio del tumor de ratones de control a tiempo t en días después del implante del tumor, Tt = peso medio del tumor de ratones tratados a tiempo t, C0 = peso medio del tumor de ratones de control a tiempo 0. El valor de %TGI se calculó a dos puntos como inhibición media. el Día 22 y 26 para MCF7r, el Día 23 y 27 para BxPC3, el Día 29 y 31 para GEO y el Día 17 para H441. Resultado, un régimen de tratamiento se consideró activo si producía un valor de %TGI estadísticamente significativo > 50%; q3dx5;6, el compuesto se administró cada tres días durante seis dosis empezando el sexto día después del implante del tumor; TIWX3;6, el compuesto se administró tres veces por semana durante tres semanas y este régimen empezó el sexto día después del

implante del tumor. Los valores de p se calcularon con respecto al grupo de control en un análisis de muestras emparejadas de dos colas con 8 mediciones por grupo el Día 26 para MCF7r, el Día 27 para BxPC3, el Día 29 para GEO y el Día 17 para H441.

Ejemplo 30: Perfil farmacocinético de diversos agente de unión a E/I basados en ^{10}Fn3 en ratones

Los perfiles farmacocinéticos del agente de unión a E/I basado en ^{10}Fn3 pegilado, E2-GS10-I1, se evaluaron en ratones por inyección intraperitoneal. Tres ratones desnudos por grupo de dosificación se dosificaron con E2-GS10-I1, formulado en PBS, a 10 y 100 mg/kg, ip y se recogieron muestras plasmáticas en solución de citrato fosfato y dextrosa antes de la dosificación, y 0.5, 2, 4, 8, 12, 24, 48, 72, 96, 144 y 168 horas después de la dosificación. En las muestras plasmáticas se evaluaron los niveles de agente de unión basado en Fn3 E2-GS10-I1 pegilado usando un ensayo de electroquimioluminiscencia (ECL) cuantitativo desarrollado para detectar y cuantificar el agente de unión a E/I basado en ^{10}Fn3 pegilado en muestras de plasma. En este ensayo, un anticuerpo monoclonal de ratón con especificidad por la región de unión a EGFR se adsorbió en placas Meso Scale Discovery durante una noche a 4°C para permitir la captura del agente de unión a E/I basado en ^{10}Fn3 en las muestras plasmáticas. Las muestras plasmáticas se añadieron a las

placas y se incubaron a 22°C durante 1 hora. El agente de unión a E/I basado en ^{10}Fn3 pegilado capturado se detectó por un anticuerpo policlonal de conejo específico para la región de armazón del agente de unión a E/I basado en ^{10}Fn3, mezclado con un anticuerpo de cabra anti-conejo unido con un marcador SULFO-TAG. Después de un lavado para retirar el reactivo SULFO-TAG no unido, se añadió un amortiguador de lectura y se usó la detección ECL. El nivel de E2-GS10-I1 pegilado en muestras plasmáticas se calculó basándose en la comparación con un ajuste de 4 parámetros de una curva patrón del agente de unión basado en Fn3 E2-GS10-I1 pegilado.

Los ratones que recibieron 10 ó 100 mg/kg por vía intraperitoneal (ip) de E2-GS10-I1 pegilado produjeron niveles máximos de aproximadamente 200 y 1700 µg/ml, respectivamente, indicando una farmacocinética proporcional a la dosis (Figura 30). Los parámetros farmacocinéticos para la Figura 30 se calcularon de una forma similar a los descritos en el párrafo presentado más adelante (obsérvese que "T 1/2" es intercambiable con "HL_lambda_z" y AUC es intercambiable con "AUCINF_obs". La semivida del E2-GS10-I1 pegilado en ratones fue de 15.75 ± 1.52 horas (Figura 30). Basándose en estos parámetros farmacocinéticos, la administración de 100 mg/kg tres veces por semana (TIW) en estudios de xenoinjerto de tumores humanos pudo mantener niveles de fármaco de 10 a 100 veces mayores que el valor de

CI50 *in vitro*.

Se realizaron experimentos farmacocinéticos adicionales sobre varios agentes de unión a E/I basados en ^{10}Fn3 pegilados, donde a ratones se les administraron 10 ó 100 mg/kg por vía intraperitoneal (ip) y, en el caso del I1-GS10-E5 pegilado, 10 ó 64 mg/kg por vía subcutánea (sc), se recogió plasma y se analizó como se ha descrito anteriormente para medir los niveles de agentes de unión a E/I basados en ^{10}Fn3 pegilados. Los parámetros farmacocinéticos de estos diversos agentes de unión a E/I basados en ^{10}Fn3 se obtuvieron por análisis no compartimental de datos de concentración plasmática (suero) frente al tiempo. Se usó un software WinNonlin (versión 5.1, Pharsight Corp. Mountain View CA) para calcular la semivida terminal (HL_lambda_z), la concentración máxima observada (Cmax), el área bajo la curva de este tiempo cero extrapolado al infinito (AUCINF_obs), el aclaramiento (CL_F_obs), el volumen de distribución basado en la fase terminal (Vz_F_obs) y el tiempo de residencia media extrapolado al infinito (MRTINF_obs). Los resultados demostraron que la vida media para los agentes de unión a E/I basados en ^{10}Fn3 pegilados estaba comprendida entre 12.1-20.9 horas, como se muestra en la Figura 44 y en la Figura 31.

Ejemplo 31: Farmacodinámica

Se tomaron muestras a partir de los modelos de xenoinjerto H292 y DiFi descritos en la Tabla 22 al final del

estudio y se procesaron como se indica en la sección de *Medición de Puntos Finales de Farmacodinámica en tumores* en el Ejemplo 12 para el análisis de los niveles totales de proteína EGFR e IGFR y EGFR e IGFR fosforilado. Los efectos diana de I1-GS10-E5 pegilado y panitumumab se evaluaron por inmunotransferencia como se describe en el Ejemplo 11. En la Figura 33A, los niveles de EGFR, pEGFR e IGFR totales fueron menores en los tumores tratados con I1-GS10-E5 pegilado que en los tumores no tratados al final del modelo de xenoinjerto de DiFi. En la Figura 33B, los niveles de pEGFR fueron menores en los tumores tratados con panitumumab e I1-GS10-E5-pegilado. Los niveles de EGFR total fueron menores sólo los tumores tratados con I1-GS10-E5-pegilado, pero no en los tumores tratados con panitumumab. Los niveles de IGFR totales fueron menores en tumores tratados con I1-GS10-E5-pegilado y en un tumor tratado con panitumumab, pero no en el otro. La cantidad de pIGFR en estos modelos fue demasiado baja para detectar diferencias después del tratamiento. Se sondaron inmunotransferencias con GAPDH para demostrar la carga igual de proteína.

Ejemplo 32: Optimización de agentes de unión a EGFR basados en ^{10}Fn3 y Análisis de la Secuencia Consenso

El agente de unión basado en ^{10}Fn3 679F09 (como se describe en el documento PCT WO 2009/102421) (Figura 34) se identificó como un agente de unión a la proteína de fusión

ectodominio de EGFR-Fc (R&D Systems). La actividad de unión se seleccionó usando una perla recubierta con EGFR-Fc y agentes de unión basados en ^{10}Fn3 acoplados a su secuencia codificante de ácido nucleico (véase, por ejemplo, Xu y col., Directed Evolution of High-Affinity Antibody Mimics Using MRNA Display, Chem. Biol. 9: 933-942 (2002)). También se identificaron variantes más potentes del agente de unión a EGFR parental 679F09 que tenían alteraciones en las secuencias de aminoácidos en los bucles BC, DE y FG.

Análisis de Secuencia I: Todos los agentes de unión basados en ^{10}Fn3 seleccionados para la unión de alta afinidad a EGFR

Para revelar los patrones de secuencia que definían una fuerte afinidad por EGFR, todas las secuencias de unión a EGFR únicas (1044) se analizaron usando varios métodos. En primer lugar, las secuencias se analizaron por la frecuencia de aminoácidos en cada posición en los bucles (Figuras 35-38). Sólo se analizaron secuencias únicas para cada bucle.

A partir del análisis de secuencia anterior, se definieron los siguientes motivos de secuencia amplios:

Motivo de Secuencia N° 1

(a) Bucle BC: "YQ" en las posiciones 7-8 (es decir, correspondiente a las posiciones 29 y 30 de la SEC ID N°: 1)

(b) Bucle DE: resto alifático ("V/I/L/M/A") en posición 3 (es decir correspondiente a la posición 54 de la

SEC ID N°: 1)

(c) Bucle FG: "D/N" en posición 1 (es decir correspondiente a la posición 77 de la SEC ID N°: 1)

Las 1044 secuencias analizadas, excepto una, siguen el patrón de secuencia de bucle FG (c). De todas las secuencias únicas analizadas, el 90% sigue en el patrón (a) para el bucle BC, y el 95% sigue en el patrón (b) para el bucle DE. Todas las secuencias analizadas, excepto cuatro, siguen al menos dos de los tres patrones anteriores. Además, el bucle FG de quince aminoácidos de longitud es una característica de secuencia destacable.

Además del Motivo de Secuencia N° 1 amplio definido anteriormente, los datos de las Figuras 35-38 se usaron para definir un segundo motivo de secuencia basado en los restos dominantes en cada posición. En este motivo se incluyeron restos si la suma de los 3 aminoácidos más frecuentes tenía una frecuencia mayor del 50%.

Motivo de Secuencia N° 2

(a) Bucle BC: XXXXXXYQ (igual que el Motivo N° 1), donde X es cualquier aminoácido

(b) Bucle DE: (G/Y/H)(D/M/G)(V/L/I)X, donde X es cualquier aminoácido

(c) Bucle FG, 10 aminoácidos de longitud: (D/N)(Y/M)(Y/A/M)(Y/H/F)(K/Q/V)(E/P/R)(Y/T/K)X(E/Y/Q)(Y/G/H), donde X es cualquier aminoácido

(d) Bucle FG, 15 aminoácidos de longitud: D(Y/F/W)(Y/F/K)(N/D/P)(P/H/L)(A/T/V)(T/D/S)(H/Y/G)(E/P/V)(Y/H)(T/K/I)(Y/F)(H/N/Q)(T/Q/E)(T/S/I)

Los métodos de análisis usados para definir los Motivos de Secuencia N° 1 y N° 2 evalúan cada posición de resto dentro de un bucle por separado. Para revelar cualquier motivo de secuencia que abarcara múltiples restos dentro de un bucle, los agentes de unión basados en ^{10}Fn3 se sometieron a un análisis adicional. En este análisis, las secuencias del bucle se alinearon usando ClustalW (Thompson JD *y col.* CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice. *Nucleic Acids Research* **22**: 4673-4680, 1994). A partir de este alineamiento, se agruparon familias de secuencias usando inspección manual. Para los bucles BC y DE, se observaron patrones de secuencias similares a los Motivos de Secuencia N° 1 y N° 2. Sin embargo, pudieron definirse motivos de secuencia adicionales para los bucles FG de 10 y 15 aminoácidos de longitud.

Motivo de Secuencia N° 3

(a) Bucle FG, 10 aminoácidos de longitud

(1) DY(A/Y)GKPYXEY, donde X es cualquier aminoácido

(2) DY(A/Y)Y(K/R/Q/T)PYXEY, donde X es

cualquier aminoácido

(3) (D/N)Y(A/Y)(Y/F)(K/R/Q/T)EYXE(Y/H), donde X es cualquier aminoácido

(4) DYY(H/Y)X(R/K)X(E/T)YX, donde X es cualquier aminoácido

(5) DYY(H/Y)(K/H/Q)(R/K)T(E/T)Y(G/P)

(6) (D/N)MMHV(E/D)YXEY, donde X es cualquier aminoácido

(7) DYMHXXYXEY (igual que el bucle FG de 679F09), donde X es cualquier aminoácido

(8) D(M/Y)YHX(K/R)X(V/I/L/M)YG, donde X es cualquier aminoácido

(b) Bucle FG, 15 aminoácidos de longitud

(1) D(Y/F)(Y/F)NPXTHEYXYXXX, donde X es cualquier aminoácido

(2) D(Y/F)(Y/F)D(P/L)X(T/S)HXYXYXXX, donde X es cualquier aminoácido

(3) D(Y/F)(K/R)PHXDGPH(T/I)YXE(S/Y), donde X es cualquier aminoácido

Análisis de Secuencia II: Agentes de unión basados en ^{10}Fn3 que muestran una inhibición más potente de la fosforilación de EGFR

Se realizó otro análisis de secuencia total sobre la subserie de agentes de unión basados en ^{10}Fn3 que mostraban la actividad más potente en un ensayo basado en células (en

lugar del Análisis de Secuencia I, que se realizó en todos los agentes de unión seleccionados para la unión de alta afinidad a EGFR por medio por Profusión). Como muchos de los agentes de unión sólo se procesaban a través de ensayos basados en células de un solo punto, en este análisis se incluyeron los agentes de unión que mostraron una inhibición mayor del 75% de la fosforilación de EGFR a una concentración fija de 100 nM. El porcentaje de inhibición a una concentración dada está relacionado con el valor de CI50 por:

% de inhibición = 100 x concentración/(concentración + CI50).

Normalmente, CI50 se calcula ajustando los datos para el % de inhibición a diversas concentraciones. Sin embargo, dado que sólo se dispone de un solo punto de datos para cada agente de unión, no es apropiado usar este solo punto de datos para calcular un valor de CI50. Por lo tanto, el porcentaje de inhibición de la señalización de EGFR en un solo punto de concentración se usó como aproximación de la potencia del agente de unión. Aunque un agente de unión puede mostrar una inhibición del 75% a una concentración de 100 nM, el aumento de la concentración permitirá al clon mostrar una inhibición del 100% a una mayor concentración. El % de inhibición está relacionado inversamente con el valor de CI50; es decir, cuanto mayor es el % de inhibición menor es el valor de CI50 y más potente será el agente de unión. Si un agente de unión mostró una inhibición del 75% a una

concentración de 100 nM, se considera que es un agente de unión "potente" para los fines del Análisis de Secuencia II. Sin embargo, los agentes de unión que mostraron una inhibición menor del 75% a una concentración 100 nM en su mayor parte aún se unen a EGFR y tienen un efecto sobre la señalización de EGFR. Por ejemplo, el anticuerpo monoclonal anti-EGFR Nimotuzumab (Friedlander E *y col.* ErbB-directed immunotherapy: antibodies in current practice and promising new agents. *Immunol Lett* **116**: 126-140, 2008) actualmente se está desarrollando como agente terapéutico, pero muestra un inhibición <5% a una concentración 100 nM en el ensayo de fosforilación de EGFR (datos no mostrados). Las secuencias de todos los agentes de unión "potentes" ensayados y su % de inhibición de la fosforilación de EGFR a una concentración 100 nM se muestran en la Figura 45.

El número total de agentes de unión únicos basados en ^{10}Fn3 que mostró una inhibición >75% a una concentración 100 nM fue 111. Como anteriormente, las secuencias primero se analizaron por la frecuencia de aminoácidos en cada posición en los bucles (Figuras 39-42). Como estos agentes de unión son una subserie de todos los agentes de unión seleccionados por unión de alta afinidad a EGFR durante la Profusión, también siguen el Motivo de Secuencia N° 1 (véase anteriormente). Todas las secuencias "potentes" analizadas siguen el patrón de secuencias del bucle FG ("D/N" en

posición 1). De todas las secuencias "potentes" únicas analizadas, el 93% sigue el patrón para el bucle BC ("YQ" en las posiciones 7-8), y el 98% siguen el patrón para el bucle DE (resto alifático ("V/I/L/M/A") en posición 3). Todas las secuencias "potentes" analizadas siguen al menos dos de los tres patrones del Motivo de Secuencia N° 1.

Debe destacarse que el bucle FG de 15 aminoácidos de longitud también parece estar muy representado en la mayoría de los agentes de unión "potentes". Aunque el bucle FG de 15 aminoácidos de longitud representa sólo el 55% de todos los agentes de unión seleccionados para la unión de alta afinidad a EGFR (Análisis de Secuencia I), el bucle FG de 15 aminoácidos representa un 86% de los agentes de unión con inhibición > 50% de la fosforilación de EGFR a una concentración 100 nM, y el 91% de los agentes de unión con inhibición > 75% (agentes de unión "potentes" en el Análisis de Secuencia II). Por lo tanto, el bucle FG de más 15 aminoácidos de longitud parece ser un patrón de secuencia asociado con una mayor potencia.

De las 111 secuencias "potentes" analizadas, sólo 10 contienen bucles FG de 10 aminoácidos de longitud, y 6 son únicas. Por lo tanto, un solo motivo de secuencia puede incluir todas las secuencias de bucle FG de 10 aminoácidos "potentes". El Motivo de Secuencia N° 4 se definió basándose en estas 6 secuencias.

Motivo de Secuencia N° 4

Bucle FG, 10-aminoácidos de longitud, agentes de unión "potentes"

(D/N)(M/Y)(M/A/W)(H/F/Y)(V/K)EY(A/Q/R/S/T)E(Y/H/D)

El análisis de secuencia de los agentes de unión "potentes" con bucle FG de 15 aminoácidos también esclareció adicionalmente las posiciones de restos que estaban más conservadas, permitiendo que se definiera el Motivo de Secuencia N° 5. Un "X" en este motivo de secuencia denota posiciones en las que no hay tres aminoácidos dominantes.

Motivo de Secuencia N° 5

Bucle FG, 15 aminoácidos de longitud agentes de unión "potentes"

D(Y/F/W)(Y/F/K)(N/P/D)(P/H/L)X(T/D/S)(H/G/Y)(E/P/Y)(Y/H)XYXXX

, donde X es cualquier aminoácido

Todos los agentes de unión a EGFR que se analizaron son descendientes del 679F09 parental y constituyen una "familia" de secuencia, es decir, están relacionados en secuencia de acuerdo con los motivos de secuencia mencionados anteriormente. Diversos miembros de la familia de agentes de unión 679F09 pueden tolerar una mutación de armazón T51I y retienen la actividad de unión. Por lo tanto, una mutación de armazón T51I podría combinarse con cualquiera de los motivos de secuencia mencionados anteriormente para producir también un agente de unión con unión de alta afinidad a EGFR.

Finalmente, debe indicarse que los aminoácidos con propiedades similares a menudo pueden sustituirse en secuencias de proteínas con un efecto pequeño o nulo sobre la estructura o función. De hecho esto ocurre también en los agentes de unión basados en ^{10}Fn3, donde sustituciones de aminoácidos conservativas en el bucle o en regiones del armazón pueden conducir a agentes de unión que se unen a EGFR. Por ejemplo, la sustitución de "H" por "Y" en la segunda posición del bucle FG del agente de unión E98 produce el agente de unión E99, y los dos agentes de unión muestran una potencia similar en la inhibición de la fosforilación de EGFR (Figura 45).

REIVINDICACIONES

1. Un dímero de proteína similar a anticuerpo caracterizado porque comprende a) un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une a IGF-IR con una K_D menor de 500 nM unido covalentemente o no covalentemente con b) un ^{10}Fn3 que se une a EGFR con una K_D menor de 500 nM;

en el que el ^{10}Fn3 de unión a IGF-IR comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 3, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 3 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-83 de la SEC ID N°: 3 y

en el que el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 112, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 112 y un bucle FG que tiene la secuencia de aminoácidos expuesta en los aminoácidos 76-92 de la SEC ID N°: 112.

2. Un dímero de proteína similar a anticuerpo caracterizado porque comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une a IGF-IR con una K_D menor de 500 nM unido covalentemente o no covalentemente con un ^{10}Fn3 que se une a EGFR con una K_D menor de 500 nM;

en el que el ^{10}Fn3 de unión a IGFIR comprende un bucle BC que tiene la secuencia de aminoácidos $X_aSARLKVAX_b$ (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°: 48) y un bucle FG que tiene la secuencia de aminoácidos $X_eRFRDYQX_f$ (SEC ID N°: 50);

en el que el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos $X_gWAPVDRYQX_h$ (SEC ID N°: 137), un bucle DE que tiene la secuencia de aminoácidos X_iRDVYX_j (SEC ID N°: 138), y un bucle FG que tiene la secuencia de aminoácidos $X_kDYKPHADGPHTYHESX_l$ (SEC ID N°: 139); y

donde X es cualquier aminoácido y a, b, c, d, e, f, g, h, i, j, k y l son números enteros seleccionados independientemente de 0 a 5.

3. El dímero de proteína similar a anticuerpo de conformidad con la reivindicación 2,

caracterizado porque ^{10}Fn3 de unión a IGF-IR comprende un bucle BC que tiene la secuencia de aminoácidos SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47), y bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°: 49); y un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos SWWAPVDRYQ (SEC ID N°: 115), un bucle DE que tiene la secuencia de aminoácidos PRDVYT (SEC ID N°: 116) y un bucle FG que tiene la secuencia

de aminoácidos TDYKPHADGPHTYHESP (SEC ID N°: 117).

4. El dímero de proteína similar a anticuerpo de conformidad con cualquiera de las reivindicaciones 1-3, caracterizado porque el ^{10}Fn3 de unión a IGF-IR tiene una secuencia de aminoácidos que es idéntica al menos en el 90% a la SEC ID N°: 3 y el armazón de ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos que es idéntica al menos en el 90% a la SEC ID N°: 112.

5. El dímero de proteína similar a anticuerpo de conformidad con cualquiera de las reivindicaciones 1-4, caracterizado porque el ^{10}Fn3 de unión a IGF-IR está unido covalentemente a ^{10}Fn3 de unión a IGF-IR por un adaptador polipeptídico o un resto de polietilenglicol.

6. El dímero de proteína similar a anticuerpo de conformidad con la reivindicación 5, caracterizado porque comprende una secuencia de aminoácidos que es idéntica al menos en el 90% a una cualquiera de las SEC ID N°: 126-132.

7. Una proteína similar a anticuerpo caracterizada porque comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une a EGFR con una K_D, menor de 500 nM, en el que el ^{10}Fn3 de unión a IGF-IR comprende un bucle BC que tiene la secuencia de aminoácidos expuesta en los aminoácidos 21-30 de la SEC ID N°: 112, un bucle DE que tiene la secuencia de aminoácidos expuesta en los aminoácidos 51-56 de la SEC ID N°: 112 y un bucle FG que tiene la secuencia de

aminoácidos expuesta en los aminoácidos 76-92 de la SEC ID N°: 112.

8. Una proteína similar a anticuerpo caracterizada porque comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une a EGFR con una K_D, menor de 500 nM, en el que el ^{10}Fn3 de unión a IGF-IR comprende un bucle BC que tiene la secuencia de aminoácidos $X_gWAPVDRYQX_h$ (SEC ID N°: 137), un bucle DE que tiene la secuencia de aminoácidos X_iRDVYX_j (SEC ID N°: 138) y un bucle FG que tiene la secuencia de aminoácidos $X_kDYKPHADGPHTYHESX_l$ (SEC ID N°: 139); y donde X es cualquier aminoácido y a, b, c, d, e, f, g, h, i, j, k y l son números enteros seleccionados independientemente de 0 a 5.

9. La proteína similar a anticuerpo de conformidad con la reivindicación 8, caracterizada porque el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos SWWAPVDRYQ (SEC ID N°: 115), un bucle DE que tiene la secuencia de aminoácidos PRDVYT (SEC ID N°: 116) y un bucle FG que tiene la secuencia de aminoácidos TDYKPHADGPHTYHESP (SEC ID N°: 117).

10. La proteína similar a anticuerpo de conformidad con cualquiera de las reivindicaciones 7-9, caracterizada porque comprende además un segundo décimo dominio de fibronectina de tipo III (^{10}Fn3).

11. La proteína similar a anticuerpo de conformidad

con la reivindicación 10, caracterizada porque el segundo ^{10}Fn3 se une a IGF-IR.

12. La proteína similar a anticuerpo de conformidad con las reivindicaciones 10 u 11, caracterizada porque el segundo ^{10}Fn3 está unido covalentemente al ^{10}Fn3 de unión a EGFR por un adaptador polipeptídico o un resto de polietilenglicol.

13. Un dímero de proteína similar a anticuerpo caracterizado porque comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une a IGF-IR con una K_D menor de 500 nM unido covalentemente o no covalentemente con un ^{10}Fn3 que se une a EGFR con una K_D menor de 500 nM;

en el que el ^{10}Fn3 de unión a IGF-IR comprende un bucle BC que tiene la secuencia de aminoácidos X_aSARLKVAX_b (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX$_d$ (SEC ID N°: 48) y un bucle FG que tiene la secuencia de aminoácidos X_eRFRDYQX_f (SEC ID N°: 50);

en el que el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos X_gDSGRGSYQX_h (SEC ID N°: 40), un bucle DE que tiene la secuencia de aminoácidos X_iGPVHX_j (SEC ID N°: 42) y un bucle FG que tiene la secuencia de aminoácidos X_kDHKPHADGPHTYHEX_l (SEC ID N°: 44); y

donde X es cualquier aminoácido y a, b, c, d, e, f, g, h, i, j, k y l son número enteros seleccionados

independientemente de 0 a 5.

14. El dímero de proteína similar a anticuerpo de conformidad con la reivindicación 13,

caracterizado porque el ^{10}Fn3 de unión a IGF-IR comprende un bucle BC que tiene la secuencia de aminoácidos SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47) y un bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°: 49); y un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos SWDSGRGSYQ (SEC ID N°: 39), un bucle DE que tiene la secuencia de aminoácidos PGPVHT (SEC ID N°: 41) y un bucle FG que tiene la secuencia de aminoácidos TDHKPHADGPHTYHESP (SEC ID N°: 43).

15. El dímero de proteína similar a anticuerpo de conformidad con las reivindicaciones 13 ó 14, caracterizado porque el ^{10}Fn3 de unión a IGF-IR tiene una secuencia de aminoácidos idéntica al menos en el 90% a la SEC ID N°: 3 y el armazón de ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica al menos en el 90% a la SEC ID N°: 5.

16. El dímero de proteína similar a anticuerpo de conformidad con cualquiera de las reivindicaciones 13-15, caracterizado porque el ^{10}Fn3 de unión a IGF-IR está unido covalentemente con el ^{10}Fn3 de unión a EGFR a través de un adaptador polipeptídico o un resto de polietilenglicol.

17. El dímero de proteína similar a anticuerpo de

conformidad con la reivindicación 16, caracterizado porque comprende una secuencia de aminoácidos idéntica al menos en el 90% a las SEC ID N°: 20, 21, 23 ó 24.

18. Un dímero de proteína similar a anticuerpo caracterizado porque comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une a IGF-IR con una K_D menor de 500 nM unido covalentemente o no covalentemente con un ^{10}Fn3 que se une a EGFR con una K_D menor de 500 nM;

en el que el ^{10}Fn3 de unión a IGFIR comprende un bucle BC que tiene la secuencia de aminoácidos $X_aSARLKVAX_b$ (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°: 48) y un bucle FG que tiene la secuencia de aminoácidos $X_eRFRDYQX_f$ (SEC ID N°: 50);

en el que el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos $X_mVAGAEDYQX_n$ (SEC ID N°: 34), un bucle DE que tiene la secuencia de aminoácidos X_oHDLVX_p (SEC ID N°: 36) y un bucle FG que tiene la secuencia de aminoácidos $X_qDMMHVEYTEHX_r$ (SEC ID N°: 38); y

donde X es cualquier aminoácido y a, b, c, d, e, f, m, n, o, p, q y r son número enteros seleccionados independientemente de 0 a 5.

19. El dímero de proteína similar a anticuerpo de conformidad con la reivindicación 18,

caracterizado porque el ^{10}Fn3 de unión a IGF-IR comprende un bucle BC que tiene la secuencia de aminoácidos

SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47) y un bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°: 49); unido covalentemente o no covalentemente con un ^{10}Fn3 de unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos SWVAGAEDYQ (SEC ID N°: 33), un bucle DE que tiene la secuencia de aminoácidos PHDLVT (SEC ID N°: 35) y un bucle FG que tiene la secuencia de aminoácidos TDMMHVEYTEHP (SEC ID N°: 37).

20. El dímero de proteína similar a anticuerpo de conformidad con las reivindicaciones 18 ó 19, caracterizado porque el ^{10}Fn3 de unión a IGF-IR tiene una secuencia de aminoácidos idéntica al menos en el 90% a la SEC ID N°: 3 y el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos idéntica al menos en el 90% a la SEC ID N°: 7.

21. El dímero de proteína similar a anticuerpo de conformidad con cualquiera de las reivindicaciones 18-20, caracterizado porque el armazón de ^{10}Fn3 de unión a IGF-IR está unido covalentemente con el armazón de ^{10}Fn3 de unión a EGFR a través de un adaptador polipeptídico o un resto de polietilenglicol.

22. El dímero de proteína similar a anticuerpo de conformidad con la reivindicación 21, caracterizado porque e comprende una secuencia de aminoácidos idéntica al menos en el 90% a las SEC ID N°: 26, 27, 29 ó 30.

23. Un dímero de proteína similar a anticuerpo caracterizado porque comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une a IGF-IR con una K_D menor de 500 nM unido covalentemente o no covalentemente a un ^{10}Fn3 que se une a EGFR con una K_D menor de 500 nM;

en el que el ^{10}Fn3 de unión a IGFIR comprende un bucle BC que tiene la secuencia de aminoácidos $X_aSARLKVAX_b$ (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°: 48) y un bucle FG que tiene la secuencia de aminoácidos $X_eRFRDYQX_f$ (SEC ID N°: 50);

en el que el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos $X_sLPGKLRYQX_t$ (SEC ID N°: 60), un bucle DE que tiene la secuencia de aminoácidos X_uHDLRX_w (SEC ID N°: 62) y un bucle FG que tiene la secuencia de aminoácidos $X_yNMMHVEYSEYX_z$ (SEC ID N°: 64); y

donde X es cualquier aminoácido y a, b, c, d, e, f, s, t, u, w, y y z son números enteros seleccionados independientemente de 0 a 5.

24. El dímero de proteína similar a anticuerpo de conformidad con la reivindicación 23,

caracterizado porque el ^{10}Fn3 de unión a IGF-IR comprende un bucle BC que tiene la secuencia de aminoácidos SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47) y un bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°:

49); unido covalentemente o no covalentemente a un ^{10}Fn3 de un unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos LPGKLRYQ (SEC ID N°: 59), un bucle DE que tiene la secuencia de aminoácidos PHDLR (SEC ID N°: 61) y un bucle FG que tiene la secuencia de aminoácidos TNMMHVEYSEY (SEC ID N°: 63).

25. El dímero de proteína similar a anticuerpo de conformidad con las reivindicaciones 23 ó 24, caracterizado porque el ^{10}Fn3 de unión a IGF-IR tiene una secuencia de aminoácidos que es idéntica al menos en el 90% a la SEC ID N°: 3 y el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos que es idéntica al menos en el 90% a la SEC ID N°: 82.

26. El dímero de proteína similar a anticuerpo de conformidad con cualquiera de las reivindicaciones 23-25, caracterizado porque el armazón de ^{10}Fn3 de unión a IGF-IR está unido covalentemente al armazón de ^{10}Fn3 de unión a EGFR a través de un adaptador polipeptídico o un resto de polietilenglicol.

27. El dímero de proteína similar a anticuerpo de la reivindicación 26, caracterizado porque comprende una secuencia de aminoácidos que es idéntica al menos en el 90% a la SEC ID N°: 53, 54, 87, 88, 98, 99, 104 ó 105.

28. Un dímero de proteína similar a anticuerpo caracterizado porque comprende un décimo dominio de

fibronectina de tipo III (^{10}Fn3) que se une a IGF-IR con una K_D menor de 500 nM unido covalentemente o no covalentemente a un ^{10}Fn3 que se une a EGFR con una K_D menor de 500 nM,

en el que el ^{10}Fn3 de unión a IGFIR comprende un bucle BC que tiene la secuencia de aminoácidos $X_aSARLKVAX_b$ (SEC ID N°: 46), un bucle DE que tiene la secuencia de aminoácidos X_cKNVYX_d (SEC ID N°: 48), y un bucle FG que tiene la secuencia de aminoácidos $X_eRFRDYQX_f$ (SEC ID N°: 50);

en el que el ^{10}Fn3 de unión a EGFR comprende un bucle BC que tiene la secuencia de aminoácidos $X_gHERDGSRQX_h$ (SEC ID N°: 134), un bucle DE que tiene la secuencia de aminoácidos X_iGGVRX_j (SEC ID N°: 135) y un bucle FG que tiene la secuencia de aminoácidos $X_kDYFNPTTHEYIYQTTX_l$ (SEC ID N°: 136); y

donde X es cualquier aminoácido y a, b, c, d, e, f, g, h, i, j, k y l son números enteros seleccionados independientemente de 0 a 5.

29. El dímero de proteína similar a anticuerpo de conformidad con la reivindicación 28,

caracterizado porque ^{10}Fn3 de unión a IGF-IR comprende un bucle BC que tiene la secuencia de aminoácidos SWSARLKVAR (SEC ID N°: 45), un bucle DE que tiene la secuencia de aminoácidos PKNVYT (SEC ID N°: 47) y un bucle FG que tiene la secuencia de aminoácidos TRFRDYQP (SEC ID N°: 49); unido covalentemente o no covalentemente con un ^{10}Fn3 de

unión a EGFR que comprende un bucle BC que tiene la secuencia de aminoácidos SWHERDGSRQ (SEC ID N°: 109), un bucle DE que tiene la secuencia de aminoácidos PGGVRT (SEC ID N°: 110) y un bucle FG que tiene la secuencia de aminoácidos TDYFNPTTHEYIYQTTP (SEC ID N°: 111).

30. El dímero de proteína similar a anticuerpo de conformidad con las reivindicaciones 28 ó 29, caracterizado porque el ^{10}Fn3 de unión a IGF-IR tiene una secuencia de aminoácidos que es idéntica al menos en el 90% a la SEC ID N°: 3 y el ^{10}Fn3 de unión a EGFR tiene una secuencia de aminoácidos que es idéntica al menos en el 90% a la SEC ID N°: 107.

31. El dímero de proteína similar a anticuerpo de conformidad con cualquiera de las reivindicaciones 28-30, caracterizado porque el armazón de ^{10}Fn3 de unión a IGF-IR está unido covalentemente al armazón de ^{10}Fn3 de unión a EGFR por un adaptador polipeptídico o un resto de polietilenglicol.

32. El dímero de proteína similar a anticuerpo de conformidad con la reivindicación 31, caracterizado porque comprende una secuencia de aminoácidos que es idéntica al menos en el 90% a una cualquiera de las SEC ID N°: 118-125.

33. Una composición farmacéuticamente aceptable caracterizada porque comprende el dímero de proteína similar a anticuerpo o proteína similar a anticuerpo de una

cualquiera de las reivindicaciones 1-32, donde la composición está esencialmente libre de pirógenos.

34. Un procedimiento para tratar un trastorno hiperproliferativo en un sujeto caracterizado porque comprende administrar a un sujeto que lo necesite una cantidad terapéuticamente eficaz de la composición de conformidad con la reivindicación 33.

35. Una proteína similar a anticuerpo caracterizada porque comprende un décimo dominio de fibronectina de tipo III (^{10}Fn3) que se une a EGFR con una K_D menor de 500 nM, en la que el ^{10}Fn3 de unión a EGFR comprende un bucle BC que comprende la secuencia de aminoácidos XXXXXXYQ, un bucle DE que comprende la secuencia de aminoácidos XX(V/I/L/M/A)X y un bucle FG que comprende la secuencia de aminoácidos (D/N)X_n, donde X es cualquier aminoácido y n es 9-14 aminoácidos.

36. La proteína similar a anticuerpo de conformidad con la reivindicación 35, caracterizada porque n es 14.

37. La proteína similar a anticuerpo de conformidad con las reivindicaciones 35 ó 36, caracterizada porque comprende además un segundo décimo dominio de fibronectina de tipo III (^{10}Fn3).

38. La proteína similar a anticuerpo de conformidad con la reivindicación 37, caracterizada porque el segundo ^{10}Fn3 se une a IGF-IR.

39. La proteína similar a anticuerpo de conformidad

con la reivindicación 37 ó 38, caracterizada porque el segundo ^{10}Fn3 está unido covalentemente al ^{10}Fn3 de unión a EGFR por un adaptador polipeptídico o un resto de polietilenglicol.

40. Una composición farmacéuticamente aceptable caracterizada porque comprende la proteína similar a anticuerpo de conformidad con cualquiera de las reivindicaciones 35-39, en la que la composición está esencialmente libre de pirógenos.

41. Un procedimiento para tratar un trastorno hiperproliferativo en un sujeto, caracterizado porque comprende administrar a un sujeto. que lo necesite una cantidad terapéuticamente eficaz de la composición de conformidad con la reivindicación 40.

RESUMEN

La presente invención se refiere a moléculas biespecíficas que comprenden un dominio de unión a EGFR y un dominio de unión a IGFIR distinto para el uso en aplicaciones de diagnóstico, investigación y terapéuticas. La invención se refiere además a células que comprenden tales proteínas, a polinucleótidos que codifican tales proteínas o fragmentos de las mismas y a vectores que comprenden los polinucleótidos que codifican las proteínas innovadoras. Ejemplos de moléculas biespecíficas incluyen dímeros de proteína similar a anticuerpo basados en el décimo dominio de fibronectina de tipo III.

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Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

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

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp His Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 22
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<212> PRT
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<220>
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<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 22

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
        115                 120                 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser
    130                 135                 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145                 150                 155                 160

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

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
            180                 185                 190

Asp His Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His
    210                 215                 220
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His His His His
225

<210> 23
<211> 220
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<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 23

Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His Lys Pro
65 70 75 80

His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro
115 120 125

Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser
130 135 140

Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly
145 150 155 160

Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn
165 170 175

Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
180 185 190

Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 24
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<220>
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<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 24
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 25
<211> 228
<212> PRT
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<220>
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<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 25
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His
210 215 220

His His His His
225

<210> 26
<211> 208
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 26
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
130 135 140

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

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
165 170 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
180 185 190

Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

<210> 27
<211> 217
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 27
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Met Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 28
<211> 223
<212> PRT
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<220>
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<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 28
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Met Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His His His
210 215 220

<210> 29
<211> 208
<212> PRT
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<220>
<221> origen

<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 29

Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met Met His
65 70 75 80

Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile
85 90 95

Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val
115 120 125

Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu
130 135 140

Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
145 150 155 160

Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr
165 170 175

Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
180 185 190

Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

<210> 30
<211> 217
<212> PRT

<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 30

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65                  70                  75                  80

Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90                  95

Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu
        115                 120                 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
    130                 135                 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145                 150                 155                 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
                165                 170                 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
            180                 185                 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
        195                 200                 205
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Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 31
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<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 31
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65 70 75 80

Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu
115 120 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
130 135 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145 150 155 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
165 170 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
180 185 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His His His
210 215 220

<210> 32
<211> 146
<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
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<222> (21)..(40)
<223> Cualquier aminoácido

<220>
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<222> (21)..(40)
<223> /nota="Esta región puede abarcar 1-20 restos"

<220>
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<222> (61)..(80)
<223> Cualquier aminoácido

<220>
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<222> (61)..(80)
<223> /nota="Esta región puede abarcar 1-20 restos"

<220>
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<222> (100)..(139)
<223> Cualquier aminoácido

<220>
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<222> (100)..(139)
<223> /nota="Esta región puede abarcar 1-40 restos"

<400> 32
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu
35 40 45

Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
85 90 95

Tyr Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr
130 135 140

Arg Thr
145

<210> 33
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 33
Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
1 5 10

<210> 34
<211> 18
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
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<222> (1)..(5)
<223> Cualquier aminoácido

<220>
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<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Cualquier aminoácido

<220>
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<222> (14)..(18)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 34
Xaa Xaa Xaa Xaa Xaa Val Ala Gly Ala Glu Asp Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 35
<211> 6
<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 35
Pro His Asp Leu Val Thr
1 5

<210> 36
<211> 14
<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
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<223> Cualquier aminoácido

<220>
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<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
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<222> (10)..(14)
<223> Cualquier aminoácido

<220>
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<222> (10)..(14)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 36
Xaa Xaa Xaa Xaa Xaa His Asp Leu Val Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 37
<211> 12
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 37
Thr Asp Met Met His Val Glu Tyr Thr Glu His Pro
1 5 10

<210> 38
<211> 20
<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
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<223> Cualquier aminoácido

<220>
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<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
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<223> Cualquier aminoácido

<220>
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<222> (16)..(20)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 38
Xaa Xaa Xaa Xaa Xaa Asp Met Met His Val Glu Tyr Thr Glu His Xaa
1 5 10 15

Xaa Xaa Xaa Xaa
20

<210> 39
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 39
Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
1 5 10

<210> 40
<211> 18
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
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<222> (1)..(5)
<223> Cualquier aminoácido

<220>
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<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
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<222> (14)..(18)
<223> Cualquier aminoácido

<220>
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<222> (14)..(18)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 40
Xaa Xaa Xaa Xaa Xaa Asp Ser Gly Arg Gly Ser Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 41
<211> 6
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 41
Pro Gly Pro Val His Thr
1 5

<210> 42
<211> 14
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Cualquier aminoácido

<220>
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<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
<221> MOD_RES
<222> (10)..(14)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (10)..(14)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 42
Xaa Xaa Xaa Xaa Xaa Gly Pro Val His Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 43
<211> 17
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 43
Thr Asp His Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser
1 5 10 15

Pro

<210> 44
<211> 24
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Cualquier aminoácido

<220>
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<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
<221> MOD_RES
<222> (20)..(24)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (20)..(24)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 44
Xaa Xaa Xaa Xaa Xaa Asp His Lys Pro His Ala Asp Gly Pro His Thr
1 5 10 15

Tyr His Glu Xaa Xaa Xaa Xaa Xaa
20

<210> 45
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 45
Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
1 5 10

<210> 46
<211> 17
<212> PRT
<213> Secuencia Artificial

<220>
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<220>
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<222> (1)..(5)
<223> Cualquier aminoácido

<220>
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<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
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<223> Cualquier aminoácido

<220>
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<222> (13)..(17)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 46
Xaa Xaa Xaa Xaa Xaa Ser Ala Arg Leu Lys Val Ala Xaa Xaa Xaa Xaa
1 5 10 15

Xaa

<210> 47
<211> 6
<212> PRT
<213> Secuencia Artificial

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<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 47
Pro Lys Asn Val Tyr Thr
1 5

<210> 48
<211> 14
<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
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<222> (1)..(5)
<223> Cualquier aminoácido

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<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
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<222> (10)..(14)
<223> Cualquier aminoácido

<220>
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<222> (10)..(14)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 48
Xaa Xaa Xaa Xaa Xaa Lys Asn Val Tyr Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 49
<211> 8
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 49
Thr Arg Phe Arg Asp Tyr Gln Pro
1 5

<210> 50
<211> 16
<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
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<222> (1)..(5)
<223> Cualquier aminoácido

<220>
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<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
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<222> (12)..(16)
<223> Cualquier aminoácido

<220>
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<222> (12)..(16)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 50
Xaa Xaa Xaa Xaa Xaa Arg Phe Arg Asp Tyr Gln Xaa Xaa Xaa Xaa Xaa
1 5 10 15

<210> 51
<211> 3
<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 51
Gly Pro Gly
1

<210> 52
<211> 109
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 52
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met
65 70 75 80

Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln His His His His His His
100 105

<210> 53
<211> 223
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 53

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met
65                  70                  75                  80

Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
                85                  90                  95

Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu
        115                 120                 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
    130                 135                 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145                 150                 155                 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
                165                 170                 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
            180                 185                 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
        195                 200                 205

Arg Thr Glu Ile Asp Lys Pro Cys Gln His His His His His His
    210                 215                 220
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<210> 54

<211> 223
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 54

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
        115                 120                 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg
    130                 135                 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145                 150                 155                 160

Val Gln Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser
                165                 170                 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
            180                 185                 190
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Asn Met Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Cys Gln His His His His His His
210 215 220

<210> 55
<211> 223
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 55
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65 70 75 80

Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu
115 120 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
130 135 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145 150 155 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
165 170 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
180 185 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Cys Gln His His His His His His
210 215 220

<210> 56
<211> 228
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 56
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 57
<211> 223
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 57
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Met Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Cys Gln His His His His His His
210 215 220

<210> 58
<211> 228
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 58
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

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

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp His Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 59
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 59

Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln
1 5 10

<210> 60
<211> 18
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
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<222> (1)..(5)
<223> Cualquier aminoácido

<220>
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<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
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<222> (14)..(18)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (14)..(18)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 60
Xaa Xaa Xaa Xaa Xaa Leu Pro Gly Lys Leu Arg Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 61
<211> 6
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 61
Pro His Asp Leu Arg Thr
1 5

<210> 62
<211> 14
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
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<222> (1)..(5)
<223> Cualquier aminoácido

<220>
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<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
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<222> (10)..(14)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (10)..(14)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 62
Xaa Xaa Xaa Xaa Xaa His Asp Leu Arg Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 63
<211> 12
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 63
Thr Asn Met Met His Val Glu Tyr Ser Glu Tyr Pro
1 5 10

<210> 64
<211> 20
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen

<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
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<222> (1)..(5)
<223> Cualquier aminoácido

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<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
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<222> (16)..(20)
<223> Cualquier aminoácido

<220>
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<222> (16)..(20)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 64
Xaa Xaa Xaa Xaa Xaa Asn Met Met His Val Glu Tyr Ser Glu Tyr Xaa
1 5 10 15

Xaa Xaa Xaa Xaa
20

<210> 65
<211> 82
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 65
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
1 5 10 15

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
65 70 75 80

Arg Thr

<210> 66
<211> 86
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 66
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Val Ala
1 5 10 15

Gly Ala Glu Asp Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro His Asp Leu Val Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp Met Met His Val Glu Tyr Thr Glu His Pro Ile
65 70 75 80

Ser Ile Asn Tyr Arg Thr
85

<210> 67
<211> 91
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 67
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser
1 5 10 15

Gly Arg Gly Ser Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Pro Val His Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp His Lys Pro His Ala Asp Gly Pro His Thr Tyr
65 70 75 80

His Glu Ser Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 68
<211> 86
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 68
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro
1 5 10 15

Gly Lys Leu Arg Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro His Asp Leu Arg Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asn Met Met His Val Glu Tyr Ser Glu Tyr Pro Ile
65 70 75 80

Ser Ile Asn Tyr Arg Thr
85

<210> 69
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 69
Met Gly Val Ser Asp Val Pro Arg Asp Leu
1 5 10

<210> 70
<211> 9
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 70
Gly Val Ser Asp Val Pro Arg Asp Leu
1 5

<210> 71
<211> 8
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 71
Val Ser Asp Val Pro Arg Asp Leu
1 5

<210> 72
<211> 9
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(2)
<223> Cualquier aminoácido

<220>
<221> característica_misc

<222> (1)..(2)
<223> /nota="Esta región puede abarcar 0-2 restos"

<400> 72
Xaa Xaa Ser Asp Val Pro Arg Asp Leu
1 5

<210> 73
<211> 8
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(2)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (1)..(2)
<223> /nota="Esta región puede abarcar 0-2 restos"

<400> 73
Xaa Xaa Asp Val Pro Arg Asp Leu
1 5

<210> 74
<211> 7
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(2)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (1)..(2)
<223> /nota="Esta región puede abarcar 0-2 restos"

<400> 74
Xaa Xaa Val Pro Arg Asp Leu
1 5

<210> 75
<211> 6
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(2)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (1)..(2)
<223> /nota="Esta región puede abarcar 0-2 restos"

<400> 75
Xaa Xaa Pro Arg Asp Leu
1 5

<210> 76
<211> 5
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(2)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (1)..(2)
<223> /nota="Esta región puede abarcar 0-2 restos"

<400> 76
Xaa Xaa Arg Asp Leu
1 5

<210> 77
<211> 4
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen

<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(2)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (1)..(2)
<223> /nota="Esta región puede abarcar 0-2 restos"

<400> 77
Xaa Xaa Asp Leu
1

<210> 78
<211> 4
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 78
Glu Ile Asp Lys
1

<210> 79
<211> 5
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 79
Glu Ile Asp Lys Pro
1 5

<210> 80
<211> 6
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 80
Glu Ile Asp Lys Pro Ser
1 5

<210> 81
<211> 6
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 81
Glu Ile Asp Lys Pro Cys
1 5

<210> 82
<211> 94
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 82
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met Met His
65 70 75 80

Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 83
<211> 185
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> MOD_RES
<222> (7)..(21)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (7)..(21)
<223> /nota="Esta región puede abarcar 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3 o 1-2 restos"

<220>
<221> MOD_RES
<222> (26)..(35)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (26)..(35)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (46)..(55)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (46)..(55)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (64)..(83)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (64)..(83)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES
<222> (89)..(98)
<223> Cualquier aminoácido

<220>
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<222> (89)..(98)
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<220>
<221> MOD_RES
<222> (105)..(114)
<223> Cualquier aminoácido

<220>
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<222> (105)..(114)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (118)..(137)
<223> Cualquier aminoácido

<220>
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<222> (118)..(137)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
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<222> (147)..(156)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (147)..(156)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (169)..(178)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (169)..(178)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<400> 83

Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro His Asp Leu Val Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Met Met
145 150 155 160

His Val Glu Tyr Thr Glu His Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
165 170 175

Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185

<210> 84
<211> 190
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
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<222> (7)..(21)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (7)..(21)

<223> /nota="Esta región puede abarcar 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3 o 1-2 restos"

<220>
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<222> (26)..(35)
<223> Cualquier aminoácido

<220>
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<222> (26)..(35)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (46)..(55)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (46)..(55)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (64)..(83)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (64)..(83)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES
<222> (89)..(98)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (89)..(98)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (105)..(114)
<223> Cualquier aminoácido

<220>
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<222> (105)..(114)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (118)..(137)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (118)..(137)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES
<222> (147)..(156)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (147)..(156)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (174)..(183)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (174)..(183)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<400> 84

Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Gly Pro Val His Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp His Lys
145 150 155 160

Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Xaa Xaa Xaa
165 170 175

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185 190

<210> 85
<211> 185
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> MOD_RES
<222> (7)..(21)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (7)..(21)
<223> /nota="Esta región puede abarcar 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3 o 1-2 restos"

<220>
<221> MOD_RES
<222> (26)..(35)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (26)..(35)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (46)..(55)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (46)..(55)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (64)..(83)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (64)..(83)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES
<222> (89)..(98)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (89)..(98)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (105)..(114)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (105)..(114)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (118)..(137)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (118)..(137)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES

<222> (147)..(156)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (147)..(156)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (169)..(178)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (169)..(178)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<400> 85

Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro His Asp Leu Arg Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asn Met Met
145 150 155 160

His Val Glu Tyr Ser Glu Tyr Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
165 170 175

Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185

<210> 86
<211> 181
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> MOD_RES
<222> (7)..(21)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (7)..(21)
<223> /nota="Esta región puede abarcar 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3 o 1-2 restos"

<220>
<221> MOD_RES
<222> (26)..(35)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (26)..(35)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (46)..(55)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (46)..(55)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (64)..(83)
<223> Cualquier aminoácido

<220>

<221> característica_misc
<222> (64)..(83)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES
<222> (89)..(98)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (89)..(98)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (105)..(114)
<223> Cualquier aminoácido

<220>
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<222> (105)..(114)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (118)..(137)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (118)..(137)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES
<222> (147)..(156)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (147)..(156)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (165)..(174)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (165)..(174)

<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<400> 86

Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Lys Asn Val Tyr Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Arg Phe Arg
145 150 155 160

Asp Tyr Gln Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser
165 170 175

Ile Asn Tyr Arg Thr
180

<210> 87
<211> 215
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen

<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 87

Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met Met His
65 70 75 80

Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile
85 90 95

Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val
115 120 125

Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu
130 135 140

Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
145 150 155 160

Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr
165 170 175

Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
180 185 190

Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Cys Gln
210 215

<210> 88
<211> 215
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 88

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Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                  10                  15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65                  70                  75                  80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
        115                 120                 125

Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln
    130                 135                 140

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

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
                165                 170                 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met
            180                 185                 190
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Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Cys Gln
210 215

<210> 89
<211> 215
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 89
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met Met His
65 70 75 80

Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile
85 90 95

Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val
115 120 125

Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu
130 135 140

Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
145 150 155 160

Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr
165 170 175

Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
180 185 190

Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Cys Gln
210 215

<210> 90
<211> 220
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 90
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His Lys Pro
65 70 75 80

His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro
115 120 125

Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser
130 135 140

Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly
145 150 155 160

Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn
165 170 175

Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
180 185 190

Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln
210 215 220

<210> 91
<211> 215
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 91
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
130 135 140

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

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
165 170 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
180 185 190

Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Cys Gln
210 215

<210> 92
<211> 220
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 92
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
130 135 140

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

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

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
180 185 190

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln
210 215 220

<210> 93
<211> 6
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 93
Pro Ala Pro Ala Pro Ala
1 5

<210> 94
<211> 12
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 94
Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
1 5 10

<210> 95
<211> 18
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 95
Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
1 5 10 15

Pro Ala

<210> 96
<211> 5
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 96
Glu Gly Ser Gly Ser
1 5

<210> 97
<211> 5
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 97
Glu Gly Ser Gly Cys
1 5

<210> 98
<211> 208
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> característica_misc
<222> (96)..(113)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (208)..(208)
<223> /reemplazar="Cys"

<220>
<221> característica_misc
<222> (208)..(208)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquél en la anotación para dicha posición"

<400> 98

Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr	Pro	Thr
1				5				10					15		

Ser	Leu	Leu	Ile	Ser	Trp	Leu	Pro	Gly	Lys	Leu	Arg	Tyr	Gln	Tyr	Tyr
		20					25					30			

Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln	Glu	Phe
		35					40					45			

Thr	Val	Pro	His	Asp	Leu	Arg	Thr	Ala	Thr	Ile	Ser	Gly	Leu	Lys	Pro
	50					55					60				

Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Asn	Met	Met	His
65					70					75					80

Val	Glu	Tyr	Ser	Glu	Tyr	Pro	Ile	Ser	Ile	Asn	Tyr	Arg	Thr	Glu	Pro
				85					90					95	

Ala	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Pro
		100					105					110			

Ala	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr	Pro
		115					120					125			

Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr
130 135 140

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

Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys
165 170 175

Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg
180 185 190

Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Gly Ser Gly Ser
195 200 205

<210> 99
<211> 208
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> característica_misc
<222> (92)..(109)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (208)..(208)
<223> /reemplazar="Cys"

<220>
<221> característica_misc
<222> (208)..(208)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquél en la anotación para dicha posición"

<400> 99
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp
100 105 110

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
115 120 125

Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln Tyr Tyr Arg Ile Thr
130 135 140

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
145 150 155 160

His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
165 170 175

Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met Met His Val Glu Tyr
180 185 190

Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr Glu Gly Ser Gly Ser
195 200 205

<210> 100
<211> 208
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> característica_misc
<222> (96)..(113)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (208)..(208)

<223> /reemplazar="Cys"

<220>
<221> característica_misc
<222> (208)..(208)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquél en la anotación para dicha posición"

<400> 100

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Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                  10                  15

Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met Met His
65                  70                  75                  80

Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr Glu Pro
                85                  90                  95

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro
            100                 105                 110

Ala Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro
        115                 120                 125

Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr
    130                 135                 140

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

Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys
                165                 170                 175

Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg
            180                 185                 190

Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Gly Ser Gly Ser
        195                 200                 205
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<210> 101
<211> 213
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> característica_misc
<222> (101)..(118)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (213)..(213)
<223> /reemplazar="Cys"

<220>
<221> característica_misc
<222> (213)..(213)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquél en la anotación para dicha posición"

<400> 101

Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr	Pro	Thr
1				5				10						15	

Ser	Leu	Leu	Ile	Ser	Trp	Asp	Ser	Gly	Arg	Gly	Ser	Tyr	Gln	Tyr	Tyr
		20					25						30		

Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln	Glu	Phe
		35					40						45		

Thr	Val	Pro	Gly	Pro	Val	His	Thr	Ala	Thr	Ile	Ser	Gly	Leu	Lys	Pro
	50					55					60				

Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Asp	His	Lys	Pro
65					70					75					80

His	Ala	Asp	Gly	Pro	His	Thr	Tyr	His	Glu	Ser	Pro	Ile	Ser	Ile	Asn
				85					90					95	

Tyr	Arg	Thr	Glu	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala
		100					105						110		

Pro	Ala	Pro	Ala	Pro	Ala	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val
		115					120						125		

Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu
130 135 140

Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
145 150 155 160

Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr
165 170 175

Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
180 185 190

Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Gly Ser Gly Ser
210

<210> 102
<211> 208
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> característica_misc
<222> (92)..(109)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (208)..(208)
<223> /reemplazar="Cys"

<220>
<221> característica_misc
<222> (208)..(208)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquél en la anotación para dicha posición"

<400> 102
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp
100 105 110

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
115 120 125

Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln Tyr Tyr Arg Ile Thr
130 135 140

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
145 150 155 160

His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
165 170 175

Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met Met His Val Glu Tyr
180 185 190

Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr Glu Gly Ser Gly Ser
195 200 205

<210> 103
<211> 213
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> característica_misc
<222> (92)..(109)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (213)..(213)
<223> /reemplazar="Cys"

<220>
<221> característica_misc
<222> (213)..(213)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquél en la anotación para dicha posición"

<400> 103

Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr	Pro	Thr
1				5				10						15	
Ser	Leu	Leu	Ile	Ser	Trp	Ser	Ala	Arg	Leu	Lys	Val	Ala	Arg	Tyr	Tyr
			20					25					30		
Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln	Glu	Phe
		35					40					45			
Thr	Val	Pro	Lys	Asn	Val	Tyr	Thr	Ala	Thr	Ile	Ser	Gly	Leu	Lys	Pro
	50					55					60				
Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Arg	Phe	Arg	Asp
65					70					75					80
Tyr	Gln	Pro	Ile	Ser	Ile	Asn	Tyr	Arg	Thr	Glu	Pro	Ala	Pro	Ala	Pro
				85					90					95	
Ala	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Val	Ser	Asp
			100					105					110		
Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr	Pro	Thr	Ser	Leu	Leu
		115					120					125			
Ile	Ser	Trp	Asp	Ser	Gly	Arg	Gly	Ser	Tyr	Gln	Tyr	Tyr	Arg	Ile	Thr
	130					135					140				
Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln	Glu	Phe	Thr	Val	Pro
145					150					155					160
Gly	Pro	Val	His	Thr	Ala	Thr	Ile	Ser	Gly	Leu	Lys	Pro	Gly	Val	Asp
				165					170					175	
Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Asp	His	Lys	Pro	His	Ala	Asp
			180					185					190		

Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Gly Ser Gly Ser
210

<210> 104
<211> 215
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 104
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met Met His
65 70 75 80

Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile
85 90 95

Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val
115 120 125

Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu
130 135 140

Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
145 150 155 160

Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr
165 170 175

Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
180 185 190

Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 105
<211> 215
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 105
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln
130 135 140

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

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
165 170 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met
180 185 190

Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 106
<211> 99
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 106
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Phe Asn
65 70 75 80

Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr

<210> 107
<211> 114
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 107

Met	Gly	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr
1				5				10						15	

Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	His	Glu	Arg	Asp	Gly	Ser	Arg	Gln
			20					25					30		

Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln
		35					40					45			

Glu	Phe	Thr	Val	Pro	Gly	Gly	Val	Arg	Thr	Ala	Thr	Ile	Ser	Gly	Leu
	50					55					60				

Lys	Pro	Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Asp	Tyr
65					70					75					80

Phe	Asn	Pro	Thr	Thr	His	Glu	Tyr	Ile	Tyr	Gln	Thr	Thr	Pro	Ile	Ser
				85					90					95	

Ile	Asn	Tyr	Arg	Thr	Glu	Ile	Asp	Lys	Pro	Ser	Gln	His	His	His	His
			100					105					110		

His His

<210> 108
<211> 91
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 108

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp His Glu
1 5 10 15

Arg Asp Gly Ser Arg Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Gly Val Arg Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp Tyr Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr
65 70 75 80

Gln Thr Thr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 109
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 109
Ser Trp His Glu Arg Asp Gly Ser Arg Gln
1 5 10

<210> 110
<211> 6
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 110
Pro Gly Gly Val Arg Thr
1 5

<210> 111
<211> 17
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 111
Thr Asp Tyr Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr
1 5 10 15

Pro

<210> 112
<211> 99
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 112
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Lys Pro
65 70 75 80

His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr

<210> 113
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>

<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> VARIANTE
<222> (107)..(107)
<223> /reemplazar="Cys"

<220>
<221> característica_misc
<222> (107)..(107)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquél en la anotación para dicha posición"

<400> 113

Met	Gly	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr
1				5					10					15	

Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Trp	Ala	Pro	Val	Asp	Arg	Tyr	Gln
			20					25					30		

Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln
		35					40					45			

Glu	Phe	Thr	Val	Pro	Arg	Asp	Val	Tyr	Thr	Ala	Thr	Ile	Ser	Gly	Leu
	50					55					60				

Lys	Pro	Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Asp	Tyr
65					70					75					80

Lys	Pro	His	Ala	Asp	Gly	Pro	His	Thr	Tyr	His	Glu	Ser	Pro	Ile	Ser
				85					90					95	

Ile	Asn	Tyr	Arg	Thr	Glu	Ile	Asp	Lys	Pro	Ser	Gln				
			100					105							

<210> 114
<211> 91
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 114

Glu	Val	Val	Ala	Ala	Thr	Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Trp	Ala
1				5					10					15	

Pro Val Asp Arg Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr
65 70 75 80

His Glu Ser Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 115
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 115
Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln
1 5 10

<210> 116
<211> 6
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 116
Pro Arg Asp Val Tyr Thr
1 5

<210> 117
<211> 17
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 117
Thr Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser
1 5 10 15

Pro

<210> 118
<211> 213
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 118
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Phe Asn
65 70 75 80

Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro
115 120 125

Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser
130 135 140

Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly
145 150 155 160

Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn
165 170 175

Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
180 185 190

Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr
210

<210> 119
<211> 220
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> VARIANTE
<222> (219)..(219)
<223> /reemplazar="Cys"

<220>
<221> característica_misc
<222> (219)..(219)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquél en la anotación para dicha posición"

<400> 119
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Phe Asn
65 70 75 80

Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro
115 120 125

Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser
130 135 140

Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly
145 150 155 160

Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn
165 170 175

Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
180 185 190

Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 120
<211> 228
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 120
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 121
<211> 221
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> característica_misc
<222> (101)..(118)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<400> 121

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Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                  10                  15

Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Phe Asn
65                  70                  75                  80

Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser Ile Asn
                85                  90                  95

Tyr Arg Thr Glu Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
            100                 105                 110

Pro Ala Pro Ala Pro Ala Val Ser Asp Val Pro Arg Asp Leu Glu Val
        115                 120                 125

Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu
    130                 135                 140

Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
145                 150                 155                 160

Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr
                165                 170                 175

Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
            180                 185                 190

Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
        195                 200                 205
```

Glu Ile Asp Lys Pro Cys Gln His His His His His His
210 215 220

<210> 122
<211> 213
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 122
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln
130 135 140

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

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
165 170 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
180 185 190

Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr
210

<210> 123
<211> 220
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> VARIANTE
<222> (219)..(219)
<223> /reemplazar="Cys"

<220>
<221> característica_misc
<222> (219)..(219)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquél en la anotación para dicha posición"

<400> 123
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln
130 135 140

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

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
165 170 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
180 185 190

Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 124
<211> 228
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 124
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp His Glu Arg Asp Gly Ser
130 135 140

Arg Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 125
<211> 215
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> característica_misc
<222> (92)..(109)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (214)..(214)
<223> /reemplazar="Cys"

<220>
<221> característica_misc
<222> (214)..(214)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquél en la anotación para dicha posición"

<400> 125
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp
100 105 110

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
115 120 125

Ile Ser Trp His Glu Arg Asp Gly Ser Arg Gln Tyr Tyr Arg Ile Thr
130 135 140

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
145 150 155 160

Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
165 170 175

Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Phe Asn Pro Thr Thr
180 185 190

His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 126
<211> 213
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 126
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Lys Pro
65 70 75 80

His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro
115 120 125

Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser
130 135 140

Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly
145 150 155 160

Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn
165 170 175

Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
180 185 190

Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr
210

<210> 127
<211> 220
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> VARIANTE
<222> (219)..(219)
<223> /reemplazar="Cys"

<220>
<221> característica_misc
<222> (219)..(219)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquél en la anotación para dicha posición"

<400> 127
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Lys Pro
65 70 75 80

His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn
85 90 95

Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp Val Pro
115 120 125

Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser
130 135 140

Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly
145 150 155 160

Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn
165 170 175

Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
180 185 190

Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 128
<211> 228
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 128
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

```
Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
 50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65                  70                  75                  80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
                85                  90                  95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
            100                 105                 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
        115                 120                 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
 130                 135                 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145                 150                 155                 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
                165                 170                 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
            180                 185                 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
 210                 215                 220

His His His His
225
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<210> 129
<211> 215
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> característica_misc
<222> (101)..(118)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (214)..(214)
<223> /reemplazar="Cys"

<220>
<221> característica_misc
<222> (214)..(214)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquél en la anotación para dicha posición"

<400> 129

```
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1               5                  10                  15

Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln Tyr Tyr
            20                  25                  30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
        35                  40                  45

Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
    50                  55                  60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Lys Pro
65                  70                  75                  80

His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn
                85                  90                  95

Tyr Arg Thr Glu Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
            100                 105                 110

Pro Ala Pro Ala Pro Ala Val Ser Asp Val Pro Arg Asp Leu Glu Val
        115                 120                 125

Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu
    130                 135                 140

Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn
145                 150                 155                 160

Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr
                165                 170                 175
```

Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala
180 185 190

Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr
195 200 205

Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 130
<211> 213
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 130
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln
130 135 140

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

Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
165 170 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
180 185 190

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr
210

<210> 131
<211> 220
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> VARIANTE
<222> (219)..(219)
<223> /reemplazar="Cys"

<220>
<221> característica_misc
<222> (219)..(219)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquél en la anotación para dicha posición"

<400> 131
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp
65 70 75 80

Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
115 120 125

Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln
130 135 140

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

Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
165 170 175

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
180 185 190

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
195 200 205

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 132
<211> 228
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 132
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 133
<211> 217
<212> PRT
<213> Secuencia Artificial

<220>

<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> característica_misc
<222> (94)..(111)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (216)..(216)
<223> /reemplazar="Cys"

<220>
<221> característica_misc
<222> (216)..(216)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquél en la anotación para dicha posición"

<400> 133

```
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

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

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val
            100                 105                 110

Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser
        115                 120                 125

Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln Tyr Tyr Arg
    130                 135                 140
```

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

Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly
165 170 175

Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Lys Pro His
180 185 190

Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 134
<211> 18
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<223> /nota="Esta región puede abarcar 0-5 restos"

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<400> 134
Xaa Xaa Xaa Xaa Xaa His Glu Arg Asp Gly Ser Arg Gln Xaa Xaa Xaa
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Xaa Xaa

<210> 135
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<400> 135
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1 5 10

<210> 136
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<223> Cualquier aminoácido

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<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 136
Xaa Xaa Xaa Xaa Xaa Asp Tyr Phe Asn Pro Thr Thr His Glu Tyr Ile
1 5 10 15

Tyr Gln Thr Thr Xaa Xaa Xaa Xaa Xaa
20 25

<210> 137
<211> 18
<212> PRT
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<222> (14)..(18)
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<400> 137
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1 5 10 15

Xaa Xaa

<210> 138
<211> 14

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<400> 138
Xaa Xaa Xaa Xaa Xaa Arg Asp Val Tyr Xaa Xaa Xaa Xaa Xaa
1 5 10

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<211> 25
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<220>
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<400> 139
Xaa Xaa Xaa Xaa Xaa Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr
1 5 10 15

Tyr His Glu Ser Xaa Xaa Xaa Xaa Xaa
20 25

<210> 140
<211> 114
<212> PRT
<213> Secuencia Artificial

<220>
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<400> 140
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His
100 105 110

His His

<210> 141
<211> 91

<212> PRT
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<220>
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<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 141
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln
1 5 10 15

Gly Ser Thr His Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Met Val Tyr Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp Tyr Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr
65 70 75 80

Arg Thr Thr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 142
<211> 108
<212> PRT
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<220>
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<223> /reemplazar="SEQ ID NO: 70" o "SEQ ID NO: 71" o "SEQ ID NO: 72" o "SEQ ID NO: 73" o "SEQ ID NO: 74" o "SEQ ID NO: 75" o "SEQ ID NO: 76" o "SEQ ID NO: 77"

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<220>
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<222> (102)..(108)
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<220>
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<222> (102)..(108)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 142
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 143
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<213> Secuencia Artificial

<220>
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<400> 143
Ser Trp Thr Gln Gly Ser Thr His Tyr Gln
1 5 10

<210> 144
<211> 6
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<400> 144
Pro Gly Met Val Tyr Thr
1 5

<210> 145
<211> 17
<212> PRT
<213> Secuencia Artificial

<220>
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<400> 145
Thr Asp Tyr Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr
1 5 10 15

Pro

<210> 146
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<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Esta región puede abarcar 0-5 restos"

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<222> (14)..(18)
<223> Cualquier aminoácido

<220>
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<222> (14)..(18)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 146
Xaa Xaa Xaa Xaa Xaa Thr Gln Gly Ser Thr His Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 147
<211> 14
<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

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<223> Cualquier aminoácido

<220>
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<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
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<222> (10)..(14)
<223> Cualquier aminoácido

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<222> (10)..(14)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 147
Xaa Xaa Xaa Xaa Xaa Gly Met Val Tyr Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 148
<211> 25
<212> PRT
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<220>
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<220>
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<222> (21)..(25)
<223> Cualquier aminoácido

<220>
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<222> (21)..(25)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 148
Xaa Xaa Xaa Xaa Xaa Asp Tyr Phe Asp Arg Ser Thr His Glu Tyr Lys
1 5 10 15

Tyr Arg Thr Thr Xaa Xaa Xaa Xaa Xaa
20 25

<210> 149
<211> 228
<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 149
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 150
<211> 222
<212> PRT
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<220>
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<220>
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<220>
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<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
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<222> (216)..(222)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
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<222> (216)..(222)
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<400> 150

Met	Gly	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr
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Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Thr	Gln	Gly	Ser	Thr	His	Tyr	Gln
			20					25					30		
Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln
		35					40					45			
Glu	Phe	Thr	Val	Pro	Gly	Met	Val	Tyr	Thr	Ala	Thr	Ile	Ser	Gly	Leu
	50					55					60				
Lys	Pro	Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Asp	Tyr
65					70					75					80
Phe	Asp	Arg	Ser	Thr	His	Glu	Tyr	Lys	Tyr	Arg	Thr	Thr	Pro	Ile	Ser
				85					90					95	
Ile	Asn	Tyr	Arg	Thr	Glu	Ile	Asp	Lys	Gly	Ser	Gly	Ser	Gly	Ser	Gly
			100					105					110		
Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Val	Ser	Asp
		115					120					125			
Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr	Pro	Thr	Ser	Leu	Leu
	130					135					140				
Ile	Ser	Trp	Ser	Ala	Arg	Leu	Lys	Val	Ala	Arg	Tyr	Tyr	Arg	Ile	Thr
145					150					155					160
Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln	Glu	Phe	Thr	Val	Pro
				165					170					175	
Lys	Asn	Val	Tyr	Thr	Ala	Thr	Ile	Ser	Gly	Leu	Lys	Pro	Gly	Val	Asp
			180					185					190		

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 151
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<220>
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<220>
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<222> (103)..(120)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
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<222> (211)..(217)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
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<222> (211)..(217)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 151
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
100 105 110

Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp Val Pro Arg Asp Leu
115 120 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
130 135 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145 150 155 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
165 170 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
180 185 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 152
<211> 228
<212> PRT
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<400> 152

Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 153
<211> 222
<212> PRT
<213> Secuencia Artificial

<220>
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<220>
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<222> (1)..(10)
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<220>
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<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 153

Met	Gly	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr
1				5					10					15	

Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Ser	Ala	Arg	Leu	Lys	Val	Ala	Arg
			20					25					30		

Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln
		35					40					45			

Glu	Phe	Thr	Val	Pro	Lys	Asn	Val	Tyr	Thr	Ala	Thr	Ile	Ser	Gly	Leu
	50					55					60				

Lys	Pro	Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Arg	Phe
65					70					75					80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 154
<211> 217
<212> PRT
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<220>
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<222> (94)..(111)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
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<222> (211)..(217)
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<400> 154

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

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

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val
            100                 105                 110

Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser
        115                 120                 125

Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His Tyr Gln Tyr Tyr Arg
    130                 135                 140

Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr
145                 150                 155                 160
```

Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly
165 170 175

Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Phe Asp Arg
180 185 190

Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 155
<211> 114
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 155
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65 70 75 80

Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His
100 105 110

His His

<210> 156
<211> 91
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 156
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp
1 5 10 15

Glu Gly Leu Pro Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Arg Asp Val Asn Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp Trp Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr
65 70 75 80

His Thr Ile Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 157
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
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<222> (1)..(10)
<223> /reemplazar="SEQ ID NO: 70" o "SEQ ID NO: 71" o "SEQ ID NO: 72" o "SEQ ID NO: 73" o "SEQ ID NO: 74" o "SEQ ID NO: 75" o "SEQ ID NO: 76" o "SEQ ID NO: 77"

<220>
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<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
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<222> (102)..(108)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81"

<220>
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<222> (102)..(108)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 157
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65 70 75 80

Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 158
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 158
Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln
1 5 10

<210> 159
<211> 6
<212> PRT

<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 159
Pro Arg Asp Val Asn Thr
1 5

<210> 160
<211> 17
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 160
Thr Asp Trp Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile
1 5 10 15

Pro

<210> 161
<211> 18
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Cualquier aminoácido

<220>
<221> característica_misc

<222> (14)..(18)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 161
Xaa Xaa Xaa Xaa Xaa Tyr Trp Glu Gly Leu Pro Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 162
<211> 14
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Cualquier aminoácido

<220>
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<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
<221> MOD_RES
<222> (10)..(14)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (10)..(14)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 162
Xaa Xaa Xaa Xaa Xaa Arg Asp Val Asn Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 163
<211> 25
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Cualquier aminoácido

<220>
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<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
<221> MOD_RES
<222> (21)..(25)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (21)..(25)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 163
Xaa Xaa Xaa Xaa Xaa Asp Trp Tyr Asn Pro Asp Thr His Glu Tyr Ile
1 5 10 15

Tyr His Thr Ile Xaa Xaa Xaa Xaa Xaa
20 25

<210> 164
<211> 228
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 164
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65 70 75 80

Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 165
<211> 222
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
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<222> (1)..(10)
<223> /reemplazar="SEQ ID NO: 70" o "SEQ ID NO: 71" o "SEQ ID NO: 72" o "SEQ ID NO: 73" o "SEQ ID NO: 74" o "SEQ ID NO: 75" o "SEQ ID NO: 76" o "SEQ ID NO: 77" o " "

<220>

<221> característica_misc
<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> VARIANTE
<222> (216)..(222)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
<221> característica_misc
<222> (216)..(222)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 165

Met	Gly	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr
1				5					10					15	

Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Tyr	Trp	Glu	Gly	Leu	Pro	Tyr	Gln
			20					25					30		

Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln
		35					40					45			

Glu	Phe	Thr	Val	Pro	Arg	Asp	Val	Asn	Thr	Ala	Thr	Ile	Ser	Gly	Leu
	50					55					60				

Lys	Pro	Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Asp	Trp
65					70				75					80	

Tyr	Asn	Pro	Asp	Thr	His	Glu	Tyr	Ile	Tyr	His	Thr	Ile	Pro	Ile	Ser
			85					90					95		

Ile	Asn	Tyr	Arg	Thr	Glu	Ile	Asp	Lys	Gly	Ser	Gly	Ser	Gly	Ser	Gly
			100					105					110		

Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Val	Ser	Asp
		115					120					125			

Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr	Pro	Thr	Ser	Leu	Leu
	130					135					140				

Ile	Ser	Trp	Ser	Ala	Arg	Leu	Lys	Val	Ala	Arg	Tyr	Tyr	Arg	Ile	Thr
145					150					155					160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 166
<211> 217
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
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<223> /reemplazar="SEQ ID NO: 70" o "SEQ ID NO: 71" o "SEQ ID NO: 72" o "SEQ ID NO: 73" o "SEQ ID NO: 74" o "SEQ ID NO: 75" o "SEQ ID NO: 76" o "SEQ ID NO: 77" o " "

<220>
<221> característica_misc
<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> característica_misc
<222> (103)..(120)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (211)..(217)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
<221> característica_misc
<222> (211)..(217)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 166

Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65 70 75 80

Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
100 105 110

Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp Val Pro Arg Asp Leu
115 120 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
130 135 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145 150 155 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
165 170 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
180 185 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 167
<211> 228
<212> PRT

<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 167

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
        115                 120                 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro
    130                 135                 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145                 150                 155                 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser
                165                 170                 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
            180                 185                 190

Asp Trp Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro
        195                 200                 205
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Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 168
<211> 222
<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
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<223> /reemplazar="SEQ ID NO: 70" o "SEQ ID NO: 71" o "SEQ ID NO: 72" o "SEQ ID NO: 73" o "SEQ ID NO: 74" o "SEQ ID NO: 75" o "SEQ ID NO: 76" o "SEQ ID NO: 77" o " "

<220>
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<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> VARIANTE
<222> (216)..(222)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
<221> característica_misc
<222> (216)..(222)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 168
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Trp Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 169
<211> 217
<212> PRT
<213> Secuencia Artificial

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<220>
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<223> /reemplazar="SEQ ID NO: 70" o "SEQ ID NO: 71" o "SEQ ID NO: 72" o "SEQ ID NO: 73" o "SEQ ID NO: 74" o "SEQ ID NO: 75" o "SEQ ID NO: 76" o "SEQ ID NO: 77" o " "

<220>
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<222> (1)..(10)
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<220>
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<222> (94)..(111)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (211)..(217)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
<221> característica_misc
<222> (211)..(217)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 169

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

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

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val
            100                 105                 110

Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser
        115                 120                 125

Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln Tyr Tyr Arg
    130                 135                 140
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Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr
145 150 155 160

Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly
165 170 175

Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp Tyr Asn Pro
180 185 190

Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 170
<211> 114
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 170
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ala
65 70 75 80

Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His
100 105 110

His His

<210> 171
<211> 91
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 171

Glu	Val	Val	Ala	Ala	Thr	Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Ala	Ser
1				5				10						15	

Asn	Arg	Gly	Thr	Tyr	Gln	Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly
			20					25					30		

Gly	Asn	Ser	Pro	Val	Gln	Glu	Phe	Thr	Val	Pro	Gly	Gly	Val	Ser	Thr
		35					40					45			

Ala	Thr	Ile	Ser	Gly	Leu	Lys	Pro	Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val
	50					55					60				

Tyr	Ala	Val	Thr	Asp	Ala	Phe	Asn	Pro	Thr	Thr	His	Glu	Tyr	Asn	Tyr
65					70					75					80

Phe	Thr	Thr	Pro	Ile	Ser	Ile	Asn	Tyr	Arg	Thr					
				85					90						

<210> 172
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
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<220>
<221> característica_misc

<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> VARIANTE
<222> (102)..(108)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81"

<220>
<221> característica_misc
<222> (102)..(108)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 172

Met	Gly	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr
1				5					10					15	

Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Ala	Ser	Asn	Arg	Gly	Thr	Tyr	Gln
			20					25					30		

Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln
		35					40					45			

Glu	Phe	Thr	Val	Pro	Gly	Gly	Val	Ser	Thr	Ala	Thr	Ile	Ser	Gly	Leu
	50					55					60				

Lys	Pro	Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Asp	Ala
65					70					75					80

Phe	Asn	Pro	Thr	Thr	His	Glu	Tyr	Asn	Tyr	Phe	Thr	Thr	Pro	Ile	Ser
				85					90					95	

Ile	Asn	Tyr	Arg	Thr	Glu	Ile	Asp	Lys	Pro	Ser	Gln				
			100					105							

<210> 173
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 173

Ser	Trp	Ala	Ser	Asn	Arg	Gly	Thr	Tyr	Gln
1				5				10	

<210> 174
<211> 6
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 174
Pro Gly Gly Val Ser Thr
1 5

<210> 175
<211> 17
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 175
Thr Asp Ala Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr
1 5 10 15

Pro

<210> 176
<211> 18
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (14)..(18)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 176
Xaa Xaa Xaa Xaa Xaa Ala Ser Asn Arg Gly Thr Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 177
<211> 14
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
<221> MOD_RES
<222> (10)..(14)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (10)..(14)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 177
Xaa Xaa Xaa Xaa Xaa Gly Gly Val Ser Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 178
<211> 25
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
<221> MOD_RES
<222> (21)..(25)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (21)..(25)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 178
Xaa Xaa Xaa Xaa Xaa Asp Ala Phe Asn Pro Thr Thr His Glu Tyr Asn
1 5 10 15

Tyr Phe Thr Thr Xaa Xaa Xaa Xaa Xaa
20 25

<210> 179
<211> 228
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 179
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ala
65 70 75 80

Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 180
<211> 222
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> VARIANTE
<222> (1)..(10)
<223> /reemplazar="SEQ ID NO: 70" o "SEQ ID NO: 71" o "SEQ ID NO: 72" o "SEQ ID NO: 73" o "SEQ ID NO: 74" o "SEQ ID NO: 75" o "SEQ ID NO: 76" o "SEQ ID NO: 77" o " "

<220>

<221> característica_misc
<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> VARIANTE
<222> (216)..(222)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
<221> característica_misc
<222> (216)..(222)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 180

Met	Gly	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr
1				5					10						15
Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Ala	Ser	Asn	Arg	Gly	Thr	Tyr	Gln
				20					25					30	
Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln
		35					40					45			
Glu	Phe	Thr	Val	Pro	Gly	Gly	Val	Ser	Thr	Ala	Thr	Ile	Ser	Gly	Leu
	50					55					60				
Lys	Pro	Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Asp	Ala
65					70					75					80
Phe	Asn	Pro	Thr	Thr	His	Glu	Tyr	Asn	Tyr	Phe	Thr	Thr	Pro	Ile	Ser
				85					90					95	
Ile	Asn	Tyr	Arg	Thr	Glu	Ile	Asp	Lys	Gly	Ser	Gly	Ser	Gly	Ser	Gly
			100					105					110		
Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Val	Ser	Asp
		115					120					125			
Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr	Pro	Thr	Ser	Leu	Leu
	130					135					140				
Ile	Ser	Trp	Ser	Ala	Arg	Leu	Lys	Val	Ala	Arg	Tyr	Tyr	Arg	Ile	Thr
145					150					155					160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 181
<211> 217
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> VARIANTE
<222> (1)..(10)
<223> /reemplazar="SEQ ID NO: 70" o "SEQ ID NO: 71" o "SEQ ID NO: 72" o "SEQ ID NO: 73" o "SEQ ID NO: 74" o "SEQ ID NO: 75" o "SEQ ID NO: 76" o "SEQ ID NO: 77" o " "

<220>
<221> característica_misc
<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> característica_misc
<222> (103)..(120)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (211)..(217)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
<221> característica_misc
<222> (211)..(217)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 181

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ala
65                  70                  75                  80

Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro Ile Ser
                85                  90                  95

Ile Asn Tyr Arg Thr Glu Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
            100                 105                 110

Pro Ala Pro Ala Pro Ala Pro Ala Val Ser Asp Val Pro Arg Asp Leu
        115                 120                 125

Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala
    130                 135                 140

Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
145                 150                 155                 160

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Lys Asn Val Tyr Thr
                165                 170                 175

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
            180                 185                 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
        195                 200                 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
    210                 215
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<210> 182
<211> 228

<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 182

Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Ala Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 183
<211> 222
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> VARIANTE
<222> (1)..(10)
<223> /reemplazar="SEQ ID NO: 70" o "SEQ ID NO: 71" o "SEQ ID NO: 72" o "SEQ ID NO: 73" o "SEQ ID NO: 74" o "SEQ ID NO: 75" o "SEQ ID NO: 76" o "SEQ ID NO: 77" o " "

<220>
<221> característica_misc
<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> VARIANTE
<222> (216)..(222)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
<221> característica_misc
<222> (216)..(222)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 183
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Ala Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 184
<211> 217
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> VARIANTE
<222> (1)..(10)
<223> /reemplazar="SEQ ID NO: 70" o "SEQ ID NO: 71" o "SEQ ID NO: 72" o "SEQ ID NO: 73" o "SEQ ID NO: 74" o "SEQ ID NO: 75" o "SEQ ID NO: 76" o "SEQ ID NO: 77" o " "

<220>
<221> característica_misc
<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> característica_misc
<222> (94)..(111)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (211)..(217)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
<221> característica_misc
<222> (211)..(217)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 184

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

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

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val
            100                 105                 110

Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser
        115                 120                 125

Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln Tyr Tyr Arg
    130                 135                 140
```

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

Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly
165 170 175

Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ala Phe Asn Pro
180 185 190

Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 185
<211> 114
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 185
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His
100 105 110

His His

<210> 186
<211> 91
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 186
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala
1 5 10 15

Pro Thr Ser Arg Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Gly Leu Ser Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr
65 70 75 80

His Glu Ser Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 187
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> VARIANTE
<222> (1)..(10)
<223> /reemplazar="SEQ ID NO: 70" o "SEQ ID NO: 71" o "SEQ ID NO: 72" o "SEQ ID NO: 73" o "SEQ ID NO: 74" o "SEQ ID NO: 75" o "SEQ ID NO: 76" o "SEQ ID NO: 77"

<220>
<221> característica_misc

<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> VARIANTE
<222> (102)..(108)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81"

<220>
<221> característica_misc
<222> (102)..(108)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 187

Met	Gly	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr
1				5				10						15	

Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Asp	Ala	Pro	Thr	Ser	Arg	Tyr	Gln
			20					25					30		

Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln
		35					40					45			

Glu	Phe	Thr	Val	Pro	Gly	Gly	Leu	Ser	Thr	Ala	Thr	Ile	Ser	Gly	Leu
	50					55					60				

Lys	Pro	Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Asp	Tyr
65					70				75					80	

Lys	Pro	His	Ala	Asp	Gly	Pro	His	Thr	Tyr	His	Glu	Ser	Pro	Ile	Ser
			85					90					95		

Ile	Asn	Tyr	Arg	Thr	Glu	Ile	Asp	Lys	Pro	Ser	Gln
		100					105				

<210> 188
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 188

Ser	Trp	Asp	Ala	Pro	Thr	Ser	Arg	Tyr	Gln
1				5					10

<210> 189
<211> 6
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 189
Pro Gly Gly Leu Ser Thr
1 5

<210> 190
<211> 18
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
<221> MOD_RES
<222> (14)..(18)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (14)..(18)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 190
Xaa Xaa Xaa Xaa Xaa Asp Ala Pro Thr Ser Arg Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 191
<211> 14
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
<221> MOD_RES
<222> (10)..(14)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (10)..(14)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 191
Xaa Xaa Xaa Xaa Xaa Gly Gly Leu Ser Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 192
<211> 228
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 192
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 193
<211> 222
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
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<220>
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<223> /reemplazar="SEQ ID NO: 70" o "SEQ ID NO: 71" o "SEQ ID NO: 72" o "SEQ ID NO: 73" o "SEQ ID NO: 74" o "SEQ ID NO: 75" o "SEQ ID NO: 76" o "SEQ ID NO: 77" o " "

<220>
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<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
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<222> (216)..(222)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
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<222> (216)..(222)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 193

Met	Gly	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr
1				5					10					15	

Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Asp	Ala	Pro	Thr	Ser	Arg	Tyr	Gln
			20					25					30		

Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln
		35					40					45			

Glu	Phe	Thr	Val	Pro	Gly	Gly	Leu	Ser	Thr	Ala	Thr	Ile	Ser	Gly	Leu
	50					55					60				

Lys	Pro	Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Asp	Tyr
65					70				75					80	

Lys	Pro	His	Ala	Asp	Gly	Pro	His	Thr	Tyr	His	Glu	Ser	Pro	Ile	Ser
			85					90					95		

Ile	Asn	Tyr	Arg	Thr	Glu	Ile	Asp	Lys	Gly	Ser	Gly	Ser	Gly	Ser	Gly
			100					105					110		

Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Val	Ser	Asp
		115					120					125			

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 194
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<212> PRT
<213> Secuencia Artificial

<220>
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<220>
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<220>
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<222> (103)..(120)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
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<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
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<222> (211)..(217)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 194

Met	Gly	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr
1				5				10						15	
Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Asp	Ala	Pro	Thr	Ser	Arg	Tyr	Gln
			20					25					30		
Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln
		35					40					45			
Glu	Phe	Thr	Val	Pro	Gly	Gly	Leu	Ser	Thr	Ala	Thr	Ile	Ser	Gly	Leu
	50					55					60				
Lys	Pro	Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Asp	Tyr
65					70					75					80
Lys	Pro	His	Ala	Asp	Gly	Pro	His	Thr	Tyr	His	Glu	Ser	Pro	Ile	Ser
				85					90					95	
Ile	Asn	Tyr	Arg	Thr	Glu	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala
			100					105					110		
Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu
		115					120					125			
Glu	Val	Val	Ala	Ala	Thr	Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Ser	Ala
	130					135					140				
Arg	Leu	Lys	Val	Ala	Arg	Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly
145					150					155					160
Gly	Asn	Ser	Pro	Val	Gln	Glu	Phe	Thr	Val	Pro	Lys	Asn	Val	Tyr	Thr
				165					170					175	
Ala	Thr	Ile	Ser	Gly	Leu	Lys	Pro	Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val
			180					185					190		
Tyr	Ala	Val	Thr	Arg	Phe	Arg	Asp	Tyr	Gln	Pro	Ile	Ser	Ile	Asn	Tyr
		195					200					205			

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 195
<211> 228
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 195
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

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

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 196
<211> 222
<212> PRT
<213> Secuencia Artificial

<220>
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<220>
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<220>
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<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> VARIANTE
<222> (216)..(222)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
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<222> (216)..(222)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 196
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

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

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 197
<211> 217
<212> PRT
<213> Secuencia Artificial

<220>
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<220>
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<220>
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<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> característica_misc
<222> (94)..(111)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (211)..(217)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
<221> característica_misc
<222> (211)..(217)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 197

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

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

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val
            100                 105                 110
```

Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser
115 120 125

Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln Tyr Tyr Arg
130 135 140

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

Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly
165 170 175

Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Lys Pro His
180 185 190

Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 198
<211> 114
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 198
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln His His His His
100 105 110

His His

<210> 199
<211> 91
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 199
Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala
1 5 10 15

Gly Ala Val Thr Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
20 25 30

Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro Gly Gly Val Arg Thr
35 40 45

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
50 55 60

Tyr Ala Val Thr Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr
65 70 75 80

His Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 200
<211> 108
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<220>
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<220>
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<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
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<222> (102)..(108)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81"

<220>
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<222> (102)..(108)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 200

Met	Gly	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr
1				5					10					15	

Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Asp	Ala	Gly	Ala	Val	Thr	Tyr	Gln
			20					25					30		

Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln
		35					40					45			

Glu	Phe	Thr	Val	Pro	Gly	Gly	Val	Arg	Thr	Ala	Thr	Ile	Ser	Gly	Leu
	50					55					60				

Lys	Pro	Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Asp	Tyr
65					70				75					80	

Lys	Pro	His	Ala	Asp	Gly	Pro	His	Thr	Tyr	His	Glu	Tyr	Pro	Ile	Ser
				85					90					95	

Ile	Asn	Tyr	Arg	Thr	Glu	Ile	Asp	Lys	Pro	Ser	Gln				
			100					105							

<210> 201
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 201
Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
1 5 10

<210> 202
<211> 17
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 202
Thr Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr
1 5 10 15

Pro

<210> 203
<211> 18
<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
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<222> (1)..(5)
<223> Cualquier aminoácido

<220>
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<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
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<222> (14)..(18)
<223> Cualquier aminoácido

<220>
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<222> (14)..(18)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 203
Xaa Xaa Xaa Xaa Xaa Asp Ala Gly Ala Val Thr Tyr Gln Xaa Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 204
<211> 25
<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (1)..(5)
<223> Cualquier aminoácido

<220>
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<222> (1)..(5)
<223> /nota="Esta región puede abarcar 0-5 restos"

<220>
<221> MOD_RES
<222> (21)..(25)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (21)..(25)
<223> /nota="Esta región puede abarcar 0-5 restos"

<400> 204
Xaa Xaa Xaa Xaa Xaa Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr
1 5 10 15

Tyr His Glu Tyr Xaa Xaa Xaa Xaa Xaa
20 25

<210> 205
<211> 228
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 205

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65                  70                  75                  80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
                85                  90                  95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
            100                 105                 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
        115                 120                 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
    130                 135                 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145                 150                 155                 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
                165                 170                 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
            180                 185                 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
    210                 215                 220

His His His His
225
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<210> 206
<211> 222
<212> PRT
<213> Secuencia Artificial

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<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

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<220>
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<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> VARIANTE
<222> (216)..(222)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
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<222> (216)..(222)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 206

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65                  70                  75                  80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
                85                  90                  95
```

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Gly Ser Gly Ser Gly Ser Gly
100 105 110

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Val Ser Asp
115 120 125

Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser Leu Leu
130 135 140

Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg Tyr Tyr Arg Ile Thr
145 150 155 160

Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Pro
165 170 175

Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp
180 185 190

Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215 220

<210> 207
<211> 217
<212> PRT
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<220>
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<220>
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<220>
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<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> característica_misc
<222> (103)..(120)

<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (211)..(217)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
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<222> (211)..(217)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 207

Met	Gly	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu	Glu	Val	Val	Ala	Ala	Thr
1				5				10					15		

Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Asp	Ala	Gly	Ala	Val	Thr	Tyr	Gln
		20					25					30			

Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly	Gly	Asn	Ser	Pro	Val	Gln
		35					40					45			

Glu	Phe	Thr	Val	Pro	Gly	Gly	Val	Arg	Thr	Ala	Thr	Ile	Ser	Gly	Leu
	50					55					60				

Lys	Pro	Gly	Val	Asp	Tyr	Thr	Ile	Thr	Val	Tyr	Ala	Val	Thr	Asp	Tyr
65					70					75					80

Lys	Pro	His	Ala	Asp	Gly	Pro	His	Thr	Tyr	His	Glu	Tyr	Pro	Ile	Ser
			85					90					95		

Ile	Asn	Tyr	Arg	Thr	Glu	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala
		100					105					110			

Pro	Ala	Pro	Ala	Pro	Ala	Pro	Ala	Val	Ser	Asp	Val	Pro	Arg	Asp	Leu
		115					120					125			

Glu	Val	Val	Ala	Ala	Thr	Pro	Thr	Ser	Leu	Leu	Ile	Ser	Trp	Ser	Ala
	130					135					140				

Arg	Leu	Lys	Val	Ala	Arg	Tyr	Tyr	Arg	Ile	Thr	Tyr	Gly	Glu	Thr	Gly
145					150					155					160

Gly	Asn	Ser	Pro	Val	Gln	Glu	Phe	Thr	Val	Pro	Lys	Asn	Val	Tyr	Thr
			165					170					175		

Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
180 185 190

Tyr Ala Val Thr Arg Phe Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 208
<211> 228
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 208
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Cys Gln His His
210 215 220

His His His His
225

<210> 209
<211> 222
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> VARIANTE
<222> (1)..(10)
<223> /reemplazar="SEQ ID NO: 70" o "SEQ ID NO: 71" o "SEQ ID NO: 72" o "SEQ ID NO: 73" o "SEQ ID NO: 74" o "SEQ ID NO: 75" o "SEQ ID NO: 76" o "SEQ ID NO: 77" o " "

<220>
<221> característica_misc
<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> VARIANTE
<222> (216)..(222)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
<221> característica_misc
<222> (216)..(222)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 209

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys
                85                  90                  95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
        115                 120                 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr
    130                 135                 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145                 150                 155                 160

Val Gln Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser
                165                 170                 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
            180                 185                 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro
        195                 200                 205

Ile Ser Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
    210                 215                 220
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<210> 210

<211> 217
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> VARIANTE
<222> (1)..(10)
<223> /reemplazar="SEQ ID NO: 70" o "SEQ ID NO: 71" o "SEQ ID NO: 72" o "SEQ ID NO: 73" o "SEQ ID NO: 74" o "SEQ ID NO: 75" o "SEQ ID NO: 76" o "SEQ ID NO: 77" o " "

<220>
<221> característica_misc
<222> (1)..(10)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> característica_misc
<222> (94)..(111)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 repeticiones "Pro-Ala""

<220>
<221> VARIANTE
<222> (211)..(217)
<223> /reemplazar="SEQ ID NO: 10" o "SEQ ID NO: 78" o "SEQ ID NO: 79" o "SEQ ID NO: 80" o "SEQ ID NO: 81" o " "

<220>
<221> característica_misc
<222> (211)..(217)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<400> 210

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Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1               5                  10                  15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
            20                  25                  30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
        35                  40                  45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
    50                  55                  60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65                  70                  75                  80
```

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

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Val
100 105 110

Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr Ser
115 120 125

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

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

Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly
165 170 175

Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Lys Pro His
180 185 190

Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser Ile Asn Tyr
195 200 205

Arg Thr Glu Ile Asp Lys Pro Ser Gln
210 215

<210> 211
<211> 222
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 211
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Glu Lys
85 90 95

Gly Ser Gly Cys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu His His His His His His
210 215 220

<210> 212
<211> 226
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 212
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Glu Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu Gly Ser Gly Cys His His His His
210 215 220

His His
225

<210> 213
<211> 222
<212> PRT

<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 213

Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Cys Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Glu Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu His His His His His His
210 215 220

<210> 214
<211> 222
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 214
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Glu Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Cys
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu His His His His His His
210 215 220

<210> 215
<211> 222
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 215
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

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

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Ser Ile Asn Tyr Arg Thr Glu His His His His His His
210 215 220

<210> 216
<211> 222
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 216
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Arg Leu Lys Val Ala Arg
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Lys Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Arg Phe
65 70 75 80

Arg Asp Tyr Gln Pro Ile Ser Ile Asn Tyr Arg Thr Glu Ile Glu Lys
85 90 95

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
100 105 110

Gly Ser Gly Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala
115 120 125

Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Trp Ala Pro Val Asp Arg
130 135 140

Tyr Gln Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro
145 150 155 160

Val Gln Glu Phe Thr Val Pro Arg Asp Val Tyr Thr Ala Thr Ile Ser
165 170 175

Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr
180 185 190

Asp Tyr Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro
195 200 205

Ile Cys Ile Asn Tyr Arg Thr Glu His His His His His His
210 215 220

<210> 217
<211> 4
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 217
Glu Ile Glu Lys
1

<210> 218
<211> 20
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 218
Gly Ser Gly Cys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
1 5 10 15

Gly Ser Gly Ser
20

<210> 219
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 219
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 220
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 220
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 221
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 221
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Leu Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 222
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 222
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Glu Ala Asn Pro Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 223
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 223
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Pro Gly Ser Arg Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr His Pro Ala Thr Tyr Glu His Glu Tyr His Ala His Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 224
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 224
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Pro Ala Asn Lys Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Gly Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 225
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 225
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 226
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 226
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gln Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 227
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 227
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 228
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 228
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 229
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 229
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 230
<211> 104
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 230
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met
65 70 75 80

Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln His
100

<210> 231
<211> 103
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 231
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Ala Gly Ala Glu Asp Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65 70 75 80

Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 232
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 232
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 233
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 233
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Phe Val Thr His Val Ala Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 234
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 234
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Glu Thr Glu Ser Asn Ala Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gln Ile Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 235
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 235
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Met Thr Ser Pro Ser Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Pro Val Gln Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Glu His Gln His Ala Pro His Gln Tyr Thr Ala His Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 236
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 236
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Pro Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 237
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 237
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Thr Gly Arg Thr Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Asp Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 238
<211> 103
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 238
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Ile Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65 70 75 80

Met His Val Glu Tyr Ala Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 239
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 239
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gln Val Pro Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ser
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 240
<211> 103
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 240
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gly Tyr Gln Ser Gly Gly Tyr Thr
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Ala Tyr Lys Glu Tyr Gln Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 241
<211> 103
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 241
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Trp Ile Gly Ile Pro Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Gly Lys Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65 70 75 80

Met His Val Glu Tyr Ala Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 242
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 242
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Lys Gly Ser Lys Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

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

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr Tyr Glu Tyr Ile Tyr Leu Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 243
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 243
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asn Pro Gly Ser Lys Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Asp Thr His Glu Tyr Leu Tyr Asn Gln Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 244
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 244
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Pro Gly Thr Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Leu Met Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Asn Thr Tyr Glu Tyr Ile Tyr Leu Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 245
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 245
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ile Gly Thr Ile Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Ala Gly Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asp Trp Ala Thr His Glu Tyr Asn Tyr His Thr Ala Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 246
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 246
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Tyr Asn Asp Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Ala Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Ala Thr Tyr Glu Tyr Ile Tyr His Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 247
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 247
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Ser Leu Val Gly Phe Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 248
<211> 103
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 248
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Arg Lys Glu Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Trp Leu Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Met His Val Glu Tyr Ala Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 249
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 249
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Leu Ala Pro Phe Trp Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 250
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 250
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Pro Pro Gly His Gln His Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gln Val Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Tyr Tyr Thr Tyr Tyr Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 251
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 251
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Glu Ser Gly Ser Arg Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Thr Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 252
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 252
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Glu Arg Thr Ser Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

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

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 253
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificïal: Polipéptido sintético"

<400> 253
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asn Ala Arg Thr Asp Ala Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Leu Glu Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr Gln Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 254
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 254
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Ser Ala Phe Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr Ser Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 255
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 255
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Leu Gly Arg Arg Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Ala Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Ala Thr His Glu Tyr Gln Tyr Glu Leu Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 256
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 256
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Pro Pro Asn Ser Gly His Asn
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Asn Thr Tyr Glu Tyr Thr Tyr Gln Phe Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 257
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 257
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Val Pro Asn Trp Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Leu Glu Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Thr Thr Tyr Glu Tyr Thr Tyr Phe Thr Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 258
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 258
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Gly Gly Phe Met Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gln Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 259
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 259
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Glu Gly Pro Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Ala Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Arg Thr His Glu Leu Phe Phe Gln Gln Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 260
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 260
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Lys Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asp Pro Thr Ser Asn Leu Tyr Asn Tyr Asn Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 261
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 261
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Gly Ser Val Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Val Leu Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro Lys Pro Asp Gly Pro His Ile Tyr Gln Ala Val Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 262
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 262
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asn Pro Ala Ser Lys Asp Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gln Val Pro Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr Asp Ser Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 263
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 263
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Arg Ser Ser Ala Thr Ala Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

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

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Trp Ala Thr His Glu Tyr Ile Tyr His Ser Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 264
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 264
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp His Ser Gly Pro Arg Glu Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gln Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Pro Ile Thr His Tyr Tyr Tyr Tyr Glu Leu Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 265
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 265
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Val Gly Leu Ser Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Ser Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 266
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 266
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gly Gly His Arg Ala Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Ala Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Asp Thr His Glu Tyr Lys Tyr His Gln Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 267
<211> 103
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 267
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ser Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Trp Phe Lys Glu Tyr Arg Glu Asp Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 268
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 268
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Val Gly Gly Met Ile Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 269
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 269
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Lys Ala Ser Tyr Thr Gly Tyr Asn
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Val Met Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Asp Thr His Gln Tyr Thr Tyr Arg Arg Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 270
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 270
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Val Gly Gln Val Phe Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 271
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 271
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Ser Gly Asp Tyr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Glu Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Tyr Tyr Lys Tyr Glu Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 272
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 272
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ile Val Gln Gly Gly Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ser Thr His Glu Tyr Lys Tyr His Gln Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 273
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 273
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Val Arg Trp Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Arg Thr His Val Tyr Ile Tyr Asp Gln Phe Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 274
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 274
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Arg Ala Arg Arg Leu Gln Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Ala Thr Met Glu Tyr Thr Tyr Gln Arg Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 275
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 275
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Leu Gln Pro Leu Trp Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Leu Asp Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Val Asp Gly Pro His Ala Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 276
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 276
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Ser Gln Gly Asn Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Ala Val Lys Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Pro Ala Thr His Glu Tyr Ile Tyr His Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 277
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 277
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Cys Leu Asp Gly Gln Leu Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Ser Ile Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65 70 75 80

Tyr Asn Leu Ala Thr His Glu Tyr Asn Tyr Arg Val Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 278
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 278
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Thr Ser Gly Ala Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Ser Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asp Pro Asp Ser His Tyr Tyr Asn Tyr Asn Met Val Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 279
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 279
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Asn Gly Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

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

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Thr Tyr Glu Leu Arg Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 280
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 280
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Thr Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Arg Pro Thr Ser Gln Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asn Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Tyr Ala Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 281
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 281
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Lys Ser Tyr Gly Ser Ala Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Asp Leu Gln Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Ile Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Asp Thr His Glu Tyr Lys Tyr His Val Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 282
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 282
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ser Val Met Gly Leu Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ser Thr Tyr Glu Tyr Lys Tyr Asn Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 283
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 283
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Lys Thr Glu Pro Gly Arg His Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65 70 75 80

Tyr Asn Leu Val Ser His Glu Tyr Val Tyr His Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 284
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 284
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp His Ala Gly Met Ala Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Asp Val Leu Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Pro Val Thr His Glu Tyr Met Tyr His Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 285
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 285
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Ser Ala Arg Gly Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Leu Glu Thr Tyr Glu Tyr His Tyr Tyr Arg Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 286
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 286
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Trp Phe Gly Thr Ser Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Asp Leu Lys Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Val Thr His Glu Tyr Glu Tyr His Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 287
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 287
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Thr Arg Thr Leu Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val His Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Met Val Thr Tyr Glu Tyr Asn Tyr His Leu Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 288
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 288
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Val Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Lys Leu Leu Gly Gly Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Pro Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Pro Arg Thr His Glu Tyr Gln Tyr His Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 289
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 289
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Arg Ala Ser Gly Gly Leu Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Ser Val Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Ala Thr Tyr Glu Tyr Ile Tyr His Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 290
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 290
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ala Gly Arg Ala Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Thr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Tyr Tyr Glu Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 291
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 291
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Ser Gln Pro Leu Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Val Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Tyr Asn Pro Glu Thr His Glu Tyr Thr Tyr His Leu Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 292
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 292
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ser Ala Thr Arg Pro Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Pro Thr Thr His Glu Tyr Tyr Tyr His Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 293
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 293
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Val Glu Arg Ser Val Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ser Thr His Glu Tyr Asn Tyr Leu Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 294
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 294
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Asp Thr Ser Ser Tyr His Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Ser Thr His Glu Tyr Ile Tyr Arg Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 295
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 295
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ser Ser His Arg Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Ser Val Ala Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Asp Thr His Glu Tyr Leu Tyr His Ala Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 296
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 296
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Asn Asn Ser Asn Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Thr Glu Gly Glu His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 297
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 297
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Arg Val Leu Val Asp Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Leu Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Val Asp Gly Pro His Thr Tyr Tyr Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 298
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 298
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Met Phe Val Gly Met Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

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

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Ala Thr His Glu Tyr Ile Tyr His Val Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 299
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 299
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Leu His Arg Lys Asn Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Glu Tyr Asp Tyr Arg Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 300
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 300
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Gln Gly Ser Thr His Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Met Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 301
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 301
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Glu Asn Asn Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Lys Thr His Glu Tyr Asn Tyr Leu Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 302
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 302
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gly Ser Pro Leu Ile Glu Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Ala Thr His Glu Tyr Thr Tyr His Val Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 303
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 303
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Thr Asn Lys Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 304
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 304
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Asp Pro Ala Ala Asn Arg Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Tyr Asn Pro Ala Thr His Gln Tyr Lys Tyr Ser Gln Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 305
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 305
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Arg Asp Val Asn Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Trp
65 70 75 80

Tyr Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 306
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 306
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ser Ala Pro Trp Arg Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Leu Asn Pro Asn Thr Leu Glu Tyr Thr Tyr Gln Arg Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 307
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 307
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Ala Ala Asn His Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Phe
65 70 75 80

Phe Asn Pro Val Thr His Glu Tyr Lys Tyr Arg Thr Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 308
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 308
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 309
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 309
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asn Asn Gly Gly Arg Asn Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 310
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 310
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Val Val Pro Gln Gly Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Phe Asn Pro Ala Thr His Glu Tyr Asn Tyr His Ser Ile Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 311
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 311
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Ala
65 70 75 80

Phe Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 312
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 312
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Leu Pro Gly Lys Leu Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 313
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 313
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 314
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 314
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 315
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 315
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Pro Ala Asn Lys Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 316
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 316
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 317
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 317
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Pro Ala Asn Lys Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 318
<211> 103
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 318
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Thr Pro Ala Asn Lys Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met
65 70 75 80

Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 319
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 319
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp His
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 320
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 320
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Leu Ser Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 321
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 321
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 322
<211> 104
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 322
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ser Gly Arg Gly Ser Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Tyr Asp Val Tyr Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Met
65 70 75 80

Met His Val Glu Tyr Thr Glu His Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln His
100

<210> 323
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 323
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 324
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 324
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 325
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 325
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 326
<211> 103
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 326
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro His Asp Leu Val Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asn Met
65 70 75 80

Met His Val Glu Tyr Ser Glu Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln
100

<210> 327
<211> 108
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 327
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Lys Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Ile Ser
85 90 95

Ile Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln
100 105

<210> 328
<211> 315
<212> ADN
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polinucleótido sintético"

<400> 328
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ctgatcagct ggtctgcgcg tctgaaagtt gcgcgatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgccta aaaacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactaggttc 240

cgcgactacc agccaatttc cattaattac cgcacagaaa ttgacaaacc atgccagcac 300

caccaccacc accac 315

<210> 329
<211> 342
<212> ADN
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polinucleótido sintético"

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ctgatcagct ggcaggttcc gcgtccgatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 330
<211> 342
<212> ADN
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polinucleótido sintético"

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ctgatcagct ggcaggttcc gcgtccgatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacgttca tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

tacaacccgg ctactcatga atacaaatac catcagactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 331
<211> 342

<212> ADN
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<220>
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<223> /nota="Descripción de Secuencia Artificial: Polinucleótido sintético"

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ctgatcagct ggcaggttcc gcgtccgatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacctgac tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 332
<211> 342
<212> ADN
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<220>
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<223> /nota="Descripción de Secuencia Artificial: Polinucleótido sintético"

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ctgatcagct gggaagctaa cccttctcgt tatcaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctgaa cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 333
<211> 342
<212> ADN
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Polinucleótido sintético"

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ctgatcagct ggtacccagg atctcgcacc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactac 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 334
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<220>
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ctgatcagct ggacccctgc taataaatct taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacggtac tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgaccat 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 335
<211> 342
<212> ADN
<213> Secuencia Artificial

<220>
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<223> /nota="Descripción de Secuencia Artificial: Polinucleótido sintético"

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ctgatcagct ggcaggttcc gcgtccgatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 336
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<212> ADN
<213> Secuencia Artificial

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ctgatcagct ggcaggttcc gcgtccgatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtcaggttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 337
<211> 342
<212> ADN
<213> Secuencia Artificial

<220>
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ctgatcagct ggcaggttcc gcgtccgatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacgttac tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 338
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<212> ADN
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<220>
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<400> 338

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acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctgcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

tacaacccgg ctactcatga atacaaatac catcagactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 339
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<220>
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ctgatcagct ggcaggttcc gcgtccgatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacctggt tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgaccat 240

aaaccgcatg ctgacggtcc gcatacttac catgaatctc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

<210> 340
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ctgatcagct ggttgccggg caagctgagg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctgcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactaacatg 240

atgcatgttg aatactctga atacccaatt tccattaatt accgcacaga aattgacaaa 300

ccatcccagc accatcacca ccaccac 327

<210> 341
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ctgatcagct gggtggccgg ggcggaggac taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctggt tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacatg 240

atgcatgttg aatacactga acatccaatt tccattaatt accgcacaga aattgacaaa 300

ccatcccagc accatcacca ccaccac 327

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ctgatcagct ggcaggttcc gcgtccgatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtatggttca cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgaccat 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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ctgatcagct ggttcgtgac gcacgtcgcc taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtctgtc cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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ctgatcagct gggagacgga gagcaacgcg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtcagatcta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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ctgatcagct ggatgacgtc gccctcggtg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtccggttca gacagctacc 180

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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ctgatcagct ggcaggttcc gcgtccgatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacgttat cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacatg 240

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ctgatcagct ggcaggttcc gcgtccgatg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtcaggttcc aacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactct 240

tacaacccgg ctactcatga atacaaatac catcagactc caatttccat taattaccgc 300

acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctgcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactac 240

gcttacaaag aataccagga acatccaatt tccattaatt accgcacaga aattgacaaa 300

ccatcccagc accatcacca ccaccac 327

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ctgatcagct ggtggatcgg catcccggtg taccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctt acgacggtaa aacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgacatg 240

atgcatgttg aatacgctga atacccaatt tccattaatt accgcacaga aattgacaaa 300

ccatcccagc accatcacca ccaccac 327

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acaggaggca atagccctgt ccaggagttc actgtgcctt accatgttta cacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

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acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

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atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

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acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctgcg tacagctacc 180

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acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactat 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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acaggaggca atagccctgt ccaggagttc actgtgcctc atgacctggt tacagctacc 180

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ccatcccagc accatcacca ccaccac 327

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atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactac 240

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ccatcccagc accatcacca ccaccac 327

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acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgaccat 240

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acagaaattg acaaaccatc ccagcaccat caccaccacc ac 342

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<212> ADN
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attagcggtc tgaaaccggg tgttgattac accattaccg tttatgcagt tacccgtttt 240

cgtgattatc agccgattag cattaactat cgcaccgaaa ttgataaagg tagcggtagc 300

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cctcgtgatt tagaagtggt ggcagccaca ccgacctcac tgctgatttc ttgggatgcc 420

ggtgcagtta cctatcagta ttatcgcatc acatacggcg aaacaggcgg aaatagccct 480

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attagcggcc tgaaaccggg tgtggattat accatcacgg tgtacgcggt tacccgtttc 240

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ggcgttgact acacgattac cgtttacgcg gttaccgatt ataaaccgca tgccgatggt 600

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atttctggcc tgaaaccggg tgtggattat accatcacgg tgtacgcggt tacccgtttc 240

cgcgattacc agccgattag catcaactat cgtacggaaa ttgaaaaagg cagtggtagc 300

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ccggtggatc gttaccagta ttaccgcatc acctatggcg aaaccggtgg caattctccg 480

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atttgcggcc tgaaaccggg tgtggattat accatcacgg tgtacgcggt tacccgtttc 240

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ggctctggta gtggcagcgg ttctggcagt ggtagcggct ctggtagtgt aagcgacgtc 360

ccgcgcgacc tggaagttgt tgcagcgacg ccgacgagcc tgctgatctc ttggtgggcc 420

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attagcggcc tgaaaccggg tgtggattat accatcacgg tgtacgcggt tacccgtttc 240

cgcgattacc agccgattag catcaactat cgtacggaaa ttgaaaaagg cagtggtagc 300

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ccgcgcgacc tggaagttgt tgcagcgacg ccgacgagcc tgctgatctc ttggtgggcc 420

ccggtggatc gttaccagta ttaccgcatc acctatggcg aaaccggtgg taacagcccg 480

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ggcgttgact acacgattac cgtttacgcg gttaccgatt ataaaccgca tgccgatggt 600

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acgggcggta acagtccggt tcaggaattt accgtgccga aaaatgttta taccgcaacg 180

attagcggcc tgaaaccggg tgtggattat accatcacgg tgtacgcggt tacccgtttc 240

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20 25 30

Xaa Xaa Xaa Ser Trp His Glu Arg Asp Gly Ser Arg Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Gly Gly Val Arg Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Tyr Phe
145 150 155 160

Asn Pro Thr Thr His Glu Tyr Ile Tyr Gln Thr Thr Pro Xaa Xaa Xaa
165 170 175

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185 190

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<400> 467

Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Trp Ala Pro Val Asp Arg Tyr Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Arg Asp Val Tyr Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Tyr Lys
145 150 155 160

Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Xaa Xaa Xaa
165 170 175

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185 190

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<400> 468

Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Thr Gln Gly Ser Thr His Tyr Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Gly Met Val Tyr Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Tyr Phe
145 150 155 160

Asp Arg Ser Thr His Glu Tyr Lys Tyr Arg Thr Thr Pro Xaa Xaa Xaa
165 170 175

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
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<220>
<221> MOD_RES
<222> (64)..(83)
<223> Cualquier aminoácido

<220>

<221> característica_misc
<222> (64)..(83)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES
<222> (89)..(98)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (89)..(98)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (105)..(114)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (105)..(114)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (118)..(137)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (118)..(137)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES
<222> (147)..(156)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (147)..(156)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (174)..(183)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (174)..(183)

<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<400> 469

Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Tyr Trp Glu Gly Leu Pro Tyr Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Arg Asp Val Asn Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Trp Tyr
145 150 155 160

Asn Pro Asp Thr His Glu Tyr Ile Tyr His Thr Ile Pro Xaa Xaa Xaa
165 170 175

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185 190

<210> 470
<211> 190
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen

<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> MOD_RES
<222> (7)..(21)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (7)..(21)
<223> /nota="Esta región puede abarcar 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3 o 1-2 restos"

<220>
<221> MOD_RES
<222> (26)..(35)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (26)..(35)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (46)..(55)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (46)..(55)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (64)..(83)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (64)..(83)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES
<222> (89)..(98)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (89)..(98)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (105)..(114)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (105)..(114)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (118)..(137)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (118)..(137)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES
<222> (147)..(156)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (147)..(156)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (174)..(183)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (174)..(183)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<400> 470
Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Ala Ser Asn Arg Gly Thr Tyr Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Gly Gly Val Ser Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Ala Phe
145 150 155 160

Asn Pro Thr Thr His Glu Tyr Asn Tyr Phe Thr Thr Pro Xaa Xaa Xaa
165 170 175

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185 190

<210> 471
<211> 190
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> MOD_RES
<222> (7)..(21)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (7)..(21)

<223> /nota="Esta región puede abarcar 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3 o 1-2 restos"

<220>
<221> MOD_RES
<222> (26)..(35)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (26)..(35)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (46)..(55)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (46)..(55)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (64)..(83)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (64)..(83)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES
<222> (89)..(98)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (89)..(98)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (105)..(114)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (105)..(114)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (118)..(137)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (118)..(137)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES
<222> (147)..(156)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (147)..(156)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (174)..(183)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (174)..(183)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<400> 471
Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Asp Ala Pro Thr Ser Arg Tyr Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Gly Gly Leu Ser Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Tyr Lys
145 150 155 160

Pro His Ala Asp Gly Pro His Thr Tyr His Glu Ser Pro Xaa Xaa Xaa
165 170 175

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185 190

<210> 472
<211> 190
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<220>
<221> MOD_RES
<222> (7)..(21)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (7)..(21)
<223> /nota="Esta región puede abarcar 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3 o 1-2 restos"

<220>
<221> MOD_RES
<222> (26)..(35)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (26)..(35)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>

<221> MOD_RES
<222> (46)..(55)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (46)..(55)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (64)..(83)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (64)..(83)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES
<222> (89)..(98)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (89)..(98)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (105)..(114)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (105)..(114)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (118)..(137)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (118)..(137)
<223> /nota="Esta región puede abarcar 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7 o 6-7 restos"

<220>
<221> MOD_RES
<222> (147)..(156)

<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (147)..(156)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<220>
<221> MOD_RES
<222> (174)..(183)
<223> Cualquier aminoácido

<220>
<221> característica_misc
<222> (174)..(183)
<223> /nota="Esta región puede abarcar 0-10, 0-5, 1-10, 1-5 o 2-5 restos"

<400> 472

Glu Val Val Ala Ala Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Ser Leu Leu Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Ser Trp Asp Ala Gly Ala Val Thr Tyr Gln Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Tyr Tyr Arg Ile Thr Tyr Gly Glu Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80

Xaa Xaa Xaa Gln Glu Phe Thr Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
85 90 95

Xaa Xaa Pro Gly Gly Val Arg Thr Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
100 105 110

Xaa Xaa Ala Thr Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
115 120 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Tyr Thr Ile Thr Val Tyr
130 135 140

Ala Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr Asp Tyr Lys
145 150 155 160

Pro His Ala Asp Gly Pro His Thr Tyr His Glu Tyr Pro Xaa Xaa Xaa
165 170 175

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ile Ser Ile Asn Tyr Arg Thr
180 185 190

<210> 473
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> VARIANTE
<222> (3)..(3)
<223> /reemplazar="Tyr"

<220>
<221> característica_misc
<222> (3)..(3)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Cualquier aminoácido

<400> 473
Asp Tyr Ala Gly Lys Pro Tyr Xaa Glu Tyr
1 5 10

<210> 474
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> VARIANTE
<222> (3)..(3)
<223> /reemplazar="Tyr"

<220>
<221> característica_misc
<222> (3)..(3)

<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> MOD_RES
<222> (5)..(5)
<223> /reemplazar="Arg" o "Gln" o "Thr"

<220>
<221> característica_misc
<222> (5)..(5)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquellos en la anotación para dicha posición"

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Cualquier aminoácido

<400> 474
Asp Tyr Ala Tyr Lys Pro Tyr Xaa Glu Tyr
1 5 10

<210> 475
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> VARIANTE
<222> (1)..(1)
<223> /reemplazar="Asn"

<220>
<221> característica_misc
<222> (1)..(1)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> VARIANTE
<222> (3)..(3)
<223> /reemplazar="Tyr"

<220>
<221> característica_misc
<222> (3)..(3)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> VARIANTE

<222> (4)..(4)
<223> /reemplazar="Phe"

<220>
<221> VARIANTE
<222> (4)..(4)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> VARIANTE
<222> (5)..(5)
<223> /reemplazar="Arg" o "Gln" o "Thr"

<220>
<221> característica_misc
<222> (5)..(5)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquellos en la anotación para dicha posición"

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Cualquier aminoácido

<220>
<221> VARIANTE
<222> (10)..(10)
<223> /reemplazar="His"

<220>
<221> característica_misc
<222> (10)..(10)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<400> 475
Asp Tyr Ala Tyr Lys Glu Tyr Xaa Glu Tyr
1 5 10

<210> 476
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> VARIANTE
<222> (4)..(4)
<223> /reemplazar="Tyr"

<220>
<221> característica_misc

<222> (4)..(4)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> MOD_RES
<222> (5)..(5)
<223> Cualquier aminoácido

<220>
<221> VARIANTE
<222> (6)..(6)
<223> /reemplazar="Lys"

<220>
<221> característica_misc
<222> (6)..(6)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Cualquier aminoácido

<220>
<221> VARIANTE
<222> (8)..(8)
<223> /reemplazar="Thr"

<220>
<221> característica_misc
<222> (8)..(8)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> MOD_RES
<222> (10)..(10)
<223> Cualquier aminoácido

<400> 476
Asp Tyr Tyr His Xaa Arg Xaa Glu Tyr Xaa
1 5 10

<210> 477
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> VARIANTE

<222> (4)..(4)
<223> /reemplazar="Tyr"

<220>
<221> VARIANTE
<222> (5)..(5)
<223> /reemplazar="His" o "Gln"

<220>
<221> VARIANTE
<222> (6)..(6)
<223> /reemplazar="Lys"

<220>
<221> característica_misc
<222> (4)..(6)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> VARIANTE
<222> (8)..(8)
<223> /reemplazar="Thr"

<220>
<221> característica_misc
<222> (8)..(8)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> VARIANTE
<222> (10)..(10)
<223> /reemplazar="Pro"

<220>
<221> característica_misc
<222> (10)..(10)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<400> 477
Asp Tyr Tyr His Lys Arg Thr Glu Tyr Gly
1 5 10

<210> 478
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> VARIANTE

<222> (1)..(1)
<223> /reemplazar="Asn"

<220>
<221> característica_misc
<222> (1)..(1)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> VARIANTE
<222> (6)..(6)
<223> /reemplazar="Asp"

<220>
<221> característica_misc
<222> (6)..(6)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Cualquier aminoácido

<400> 478
Asp Met Met His Val Glu Tyr Xaa Glu Tyr
1 5 10

<210> 479
<211> 10
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> MOD_RES
<222> (5)..(6)
<223> Cualquier aminoácido

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Cualquier aminoácido

<400> 479
Asp Tyr Met His Xaa Xaa Tyr Xaa Glu Tyr
1 5 10

<210> 480
<211> 10
<212> PRT

<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> VARIANTE
<222> (2)..(2)
<223> /reemplazar="Tyr"

<220>
<221> característica_misc
<222> (2)..(2)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> MOD_RES
<222> (5)..(5)
<223> Cualquier aminoácido

<220>
<221> VARIANTE
<222> (6)..(6)
<223> /reemplazar="Arg"

<220>
<221> característica_misc
<222> (6)..(6)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Cualquier aminoácido

<220>
<221> VARIANTE
<222> (8)..(8)
<223> /reemplazar="Ile" o "Leu" o "Met"

<220>
<221> característica_misc
<222> (8)..(8)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto a aquellos en la anotación para dicha posición"

<400> 480
Asp Met Tyr His Xaa Lys Xaa Val Tyr Gly
1 5 10

<210> 481
<211> 15
<212> PRT

<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> VARIANTE
<222> (2)..(3)
<223> /reemplazar="Phe"

<220>
<221> característica_misc
<222> (2)..(3)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Cualquier aminoácido

<220>
<221> MOD_RES
<222> (11)..(11)
<223> Cualquier aminoácido

<220>
<221> MOD_RES
<222> (13)..(15)
<223> Cualquier aminoácido

<400> 481
Asp Tyr Tyr Asn Pro Xaa Thr His Glu Tyr Xaa Tyr Xaa Xaa Xaa
1 5 10 15

<210> 482
<211> 15
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> VARIANTE
<222> (2)..(3)
<223> /reemplazar="Phe"

<220>
<221> característica_misc
<222> (2)..(3)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia

con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> VARIANTE
<222> (5)..(5)
<223> /reemplazar="Leu"

<220>
<221> característica_misc
<222> (5)..(5)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Cualquier aminoácido

<220>
<221> VARIANTE
<222> (7)..(7)
<223> /reemplazar="Ser"

<220>
<221> característica_misc
<222> (7)..(7)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Cualquier aminoácido

<220>
<221> MOD_RES
<222> (11)..(11)
<223> Cualquier aminoácido

<220>
<221> MOD_RES
<222> (13)..(15)
<223> Cualquier aminoácido

<400> 482
Asp Tyr Tyr Asp Pro Xaa Thr His Xaa Tyr Xaa Tyr Xaa Xaa Xaa
1 5 10 15

<210> 483
<211> 15
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
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<222> (2)..(2)
<223> /reemplazar="Phe"

<220>
<221> VARIANTE
<222> (3)..(3)
<223> /reemplazar="Arg"

<220>
<221> característica_misc
<222> (2)..(3)
<223> /nota="Los restos indicados en la secuencia no tienen preferencia con respecto a aquellos en la anotación para dichas posiciones"

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Cualquier aminoácido

<220>
<221> VARIANTE
<222> (11)..(11)
<223> /reemplazar="Ile"

<220>
<221> característica_misc
<222> (11)..(11)
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<220>
<221> MOD_RES
<222> (13)..(13)
<223> Cualquier aminoácido

<220>
<221> VARIANTE
<222> (15)..(15)
<223> /reemplazar="Tyr"

<220>
<221> característica_misc
<222> (15)..(15)
<223> /nota="El resto indicado en la secuencia no tiene preferencia con respecto al resto en la anotación para dicha posición"

<400> 483
Asp Tyr Lys Pro His Xaa Asp Gly Pro His Thr Tyr Xaa Glu Ser
1 5 10 15

<210> 484
<211> 95
<212> PRT
<213> Secuencia Artificial

<220>

<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 484
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln Arg Tyr
20 25 30

Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu
35 40 45

Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys
50 55 60

Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Met
65 70 75 80

His Ser Glu Tyr Arg Gln Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

<210> 485
<211> 94
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 485
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Met His
65 70 75 80

Ser Glu Tyr Arg Gln Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 486
<211> 102
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 486
Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln Arg Tyr
20 25 30

Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu
35 40 45

Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu Lys
50 55 60

Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr Met
65 70 75 80

His Ser Glu Tyr Arg Gln Tyr Pro Ile Ser Ile Asn Tyr Arg Thr Glu
85 90 95

Ile Asp Lys Pro Cys Gln
100

<210> 487
<211> 6
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Marcador 6xHis sintético"

<400> 487
His His His His His His
1 5

<210> 488
<211> 18
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<220>
<221> característica_misc
<222> (96)..(113)
<223> /nota="Esta región puede abarcar 3, 6, ó 9 "repeticiones Pro-Ala"

<400> 488
Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala
1 5 10 15

Pro Ala

<210> 489
<211> 4
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 489
Gly Ser Gly Cys
1

<210> 490
<211> 109
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 490
Met Gly Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr
1 5 10 15

Pro Thr Ser Leu Leu Ile Ser Trp Gln Val Pro Arg Pro Met Tyr Gln
20 25 30

Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln
35 40 45

Glu Phe Thr Val Pro Gly Gly Val Arg Thr Ala Thr Ile Ser Gly Leu
50 55 60

Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Asp Tyr
65 70 75 80

Met His Ser Glu Tyr Arg Gln Tyr Pro Ile Ser Ile Asn Tyr Arg Thr
85 90 95

Glu Ile Asp Lys Pro Ser Gln His His His His His His
100 105

<210> 491
<211> 19
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 491
Phe Lys Gly Asp Ser Phe Thr Arg Thr Pro Pro Leu Asp Pro Arg Glu
1 5 10 15

Leu Glu Ile

<210> 492
<211> 100
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polipéptido sintético"

<400> 492
Glu Glu Lys Lys Val Cys Gln Gly Thr Ser Asn Lys Leu Thr Gln Leu
1 5 10 15

Gly Thr Phe Glu Asp His Phe Leu Ser Leu Gln Arg Met Phe Asn Asn
20 25 30

Cys Glu Val Val Leu Gly Asn Leu Glu Ile Thr Tyr Val Gln Arg Asn
35 40 45

Tyr Asp Leu Ser Phe Leu Lys Thr Ile Gln Glu Val Ala Gly Tyr Val
50 55 60

Leu Ile Ala Leu Asn Thr Val Glu Arg Ile Pro Leu Glu Asn Leu Gln
65 70 75 80

Ile Ile Arg Gly Asn Met Tyr Tyr Glu Asn Ser Tyr Ala Leu Ala Val
85 90 95

Leu Ser Asn Tyr
100

<210> 493
<211> 12
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 493
Ile Gln Cys Ala His Tyr Ile Asp Gly Pro His Cys
1 5 10

<210> 494
<211> 16
<212> PRT
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Péptido sintético"

<400> 494
Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
1 5 10 15

<210> 495
<211> 342
<212> ADN
<213> Secuencia Artificial

<220>
<221> origen
<223> /nota="Descripción de Secuencia Artificial: Polinucleótido sintético"

<400> 495
atgggagttt ctgatgtgcc gcgcgacctg gaagtggttg ctgccacccc caccagcctg 60

ctgatcagct ggaaaacaga accaggccgc caccaatatt accgcatcac ttacggcgaa 120

acaggaggca atagccctgt ccaggagttc actgtgcctg gtggtgttcg tacagctacc 180

atcagcggcc ttaaacctgg cgttgattat accatcactg tgtatgctgt cactgactgg 240

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Figura 1

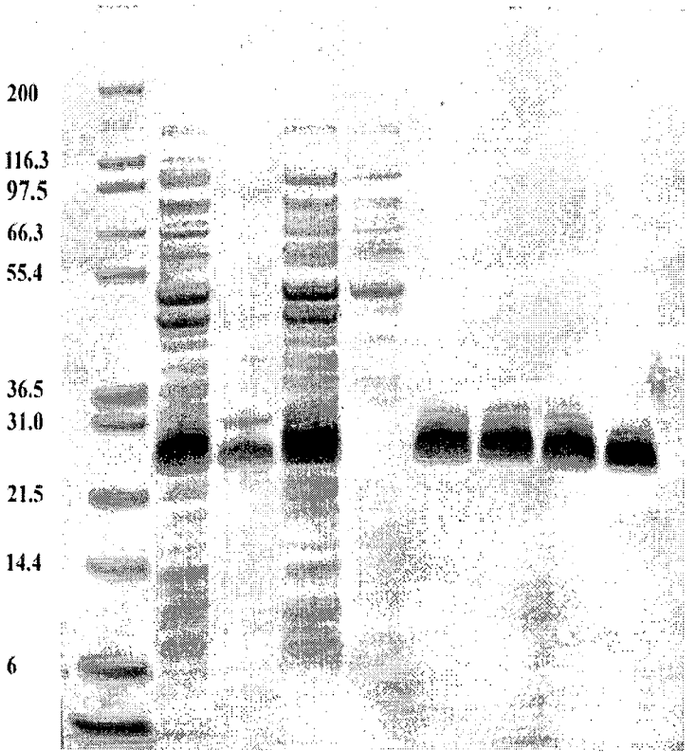


Figura 2

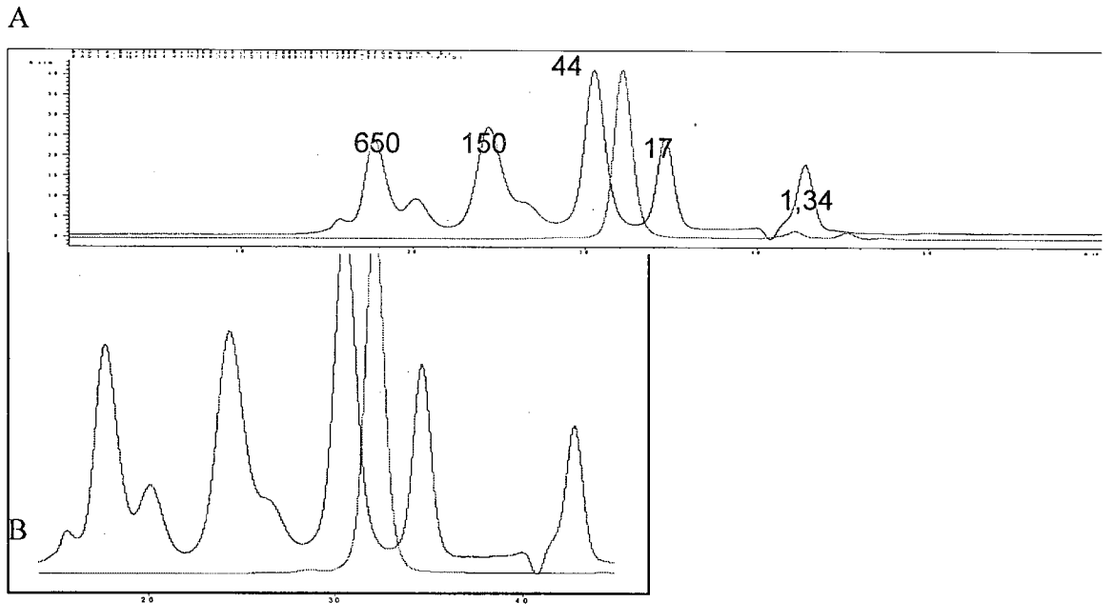
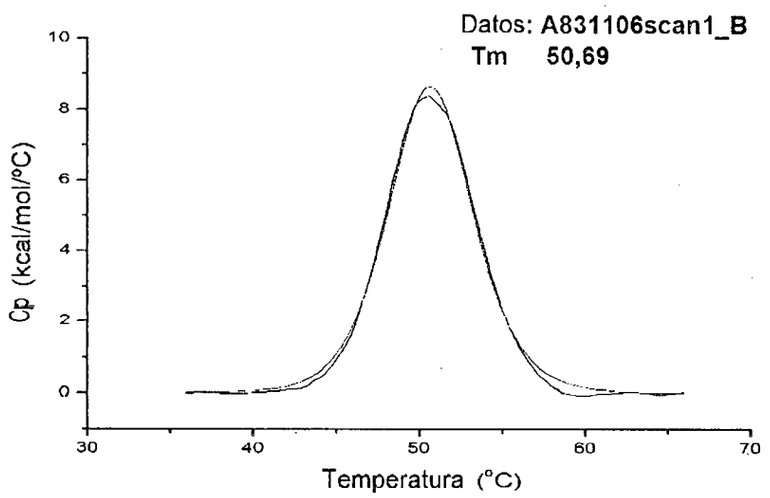


Figura 3

A


Datos: A831106scan1_B
Tm 50,69
Cp (kcal/mol/°C)
Temperatura (°C)

B

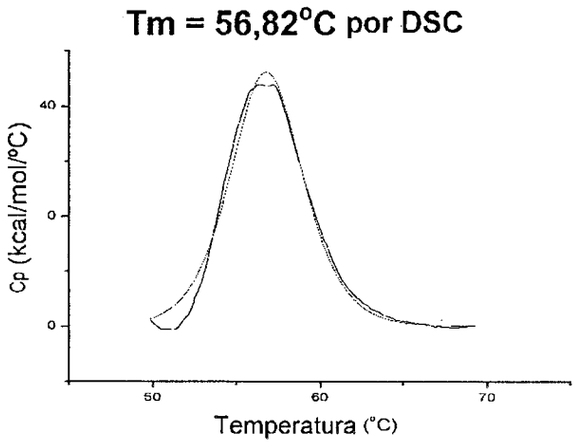

Tm = 56,82°C por DSC
Cp (kcal/mol/°C)
Temperatura (°C)

Figura 4

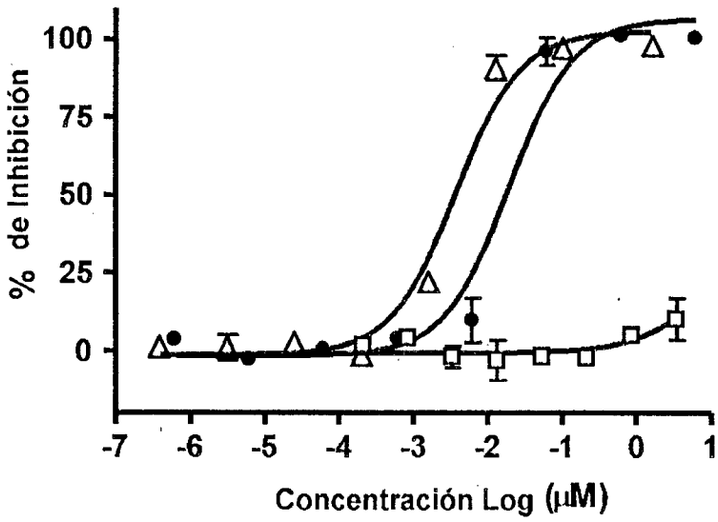


Figura 5

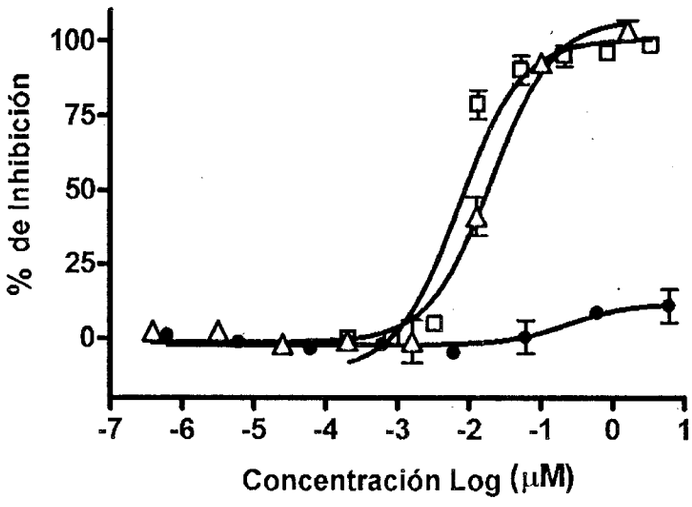


Figura 6

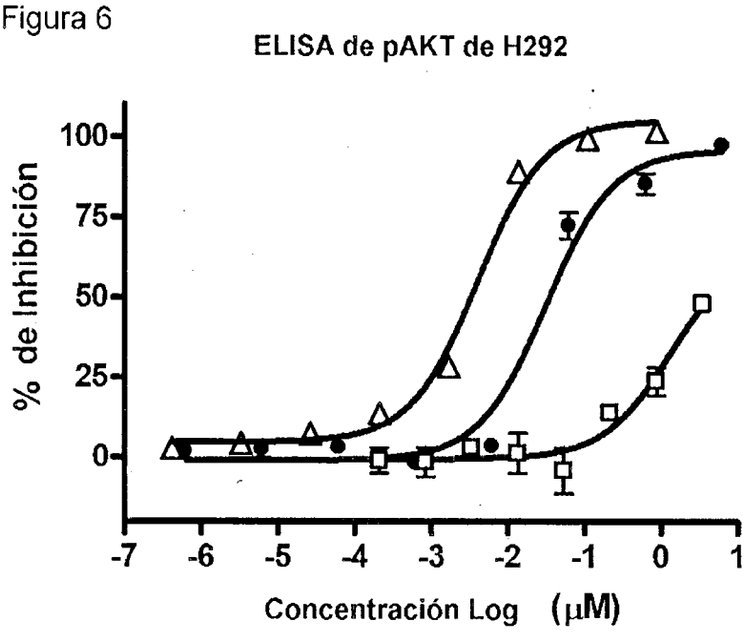


Figura 7

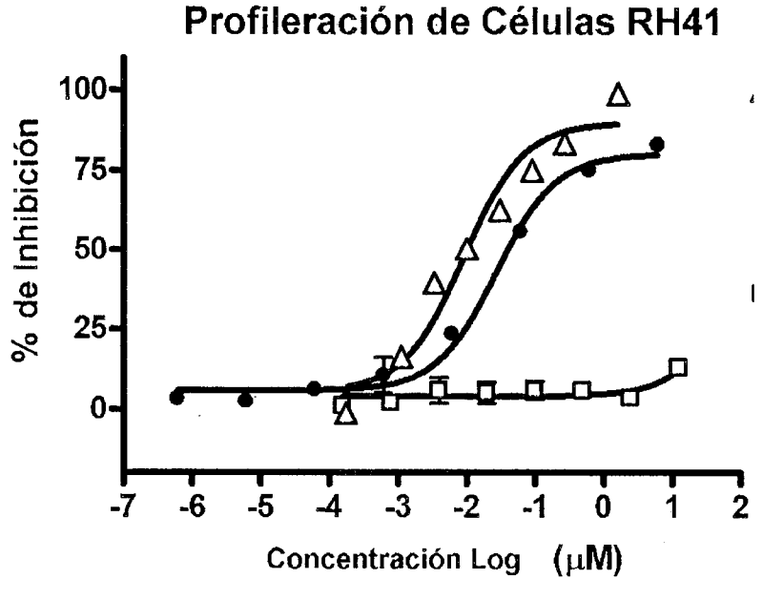


Figura 8

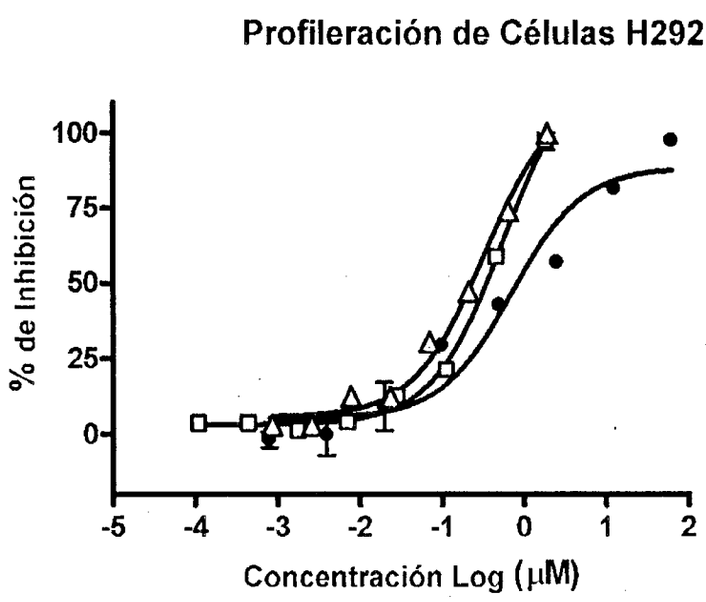


Figura 9

RESUMEN DE ACTIVIDAD EN ENSAYOS BASADOS EN CÉLULAS

Nombre	ELISA de pEGFR de H292 (nM)	ELISA de pIGFR de H292 (nM)	ELISA de pAKT de H292	ICW de pEGFR de A431 (nM)	ICW de pERK de A431 (nM)
E1	8	---		24	13
E1-GS10-I1 (Pegilado)	123	4	5	297	295
E1-GS10-I1	30	1	1	36	51
I1-GS10-E1 (Pegilado)	127	0,9	0,8	302	300
I1-GS10-E1	42	1	1	93	99
E2	31	---		38	40
E2-GS10-I1 (Pegilado)	32	0,3	0,6	77	78
E2-GS10-I1	8	0,1	0,1	19	20
I1-GS10-E2 (Pegilado)	47	0,8	0,6	97	118
I1-GS10-E2	8	0,1	0,1	11	15
E3	21	---		14	11
E3-GS10-I1 (Pegilado)	10	6	4	42	40
E3-GS10-I1	7	6	3	14	12
I1GS10-E3 (Pegilado)	46	2	2	47	50
I1-GS10-E3	25	19	26	47	42

Figura 10

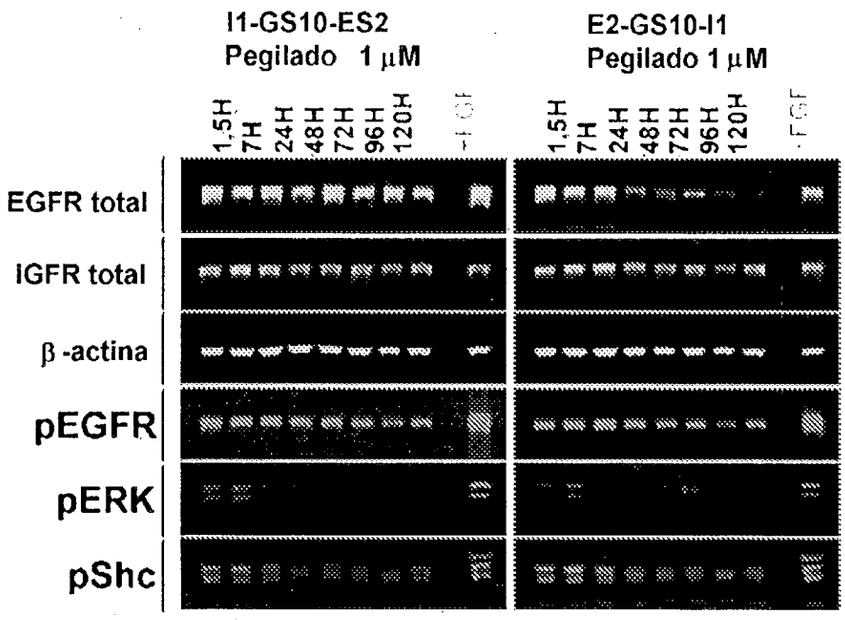


Figura 11

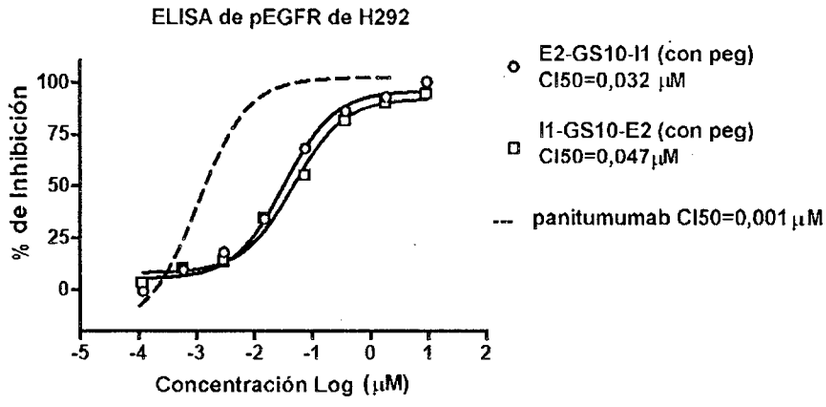


Figura 12A

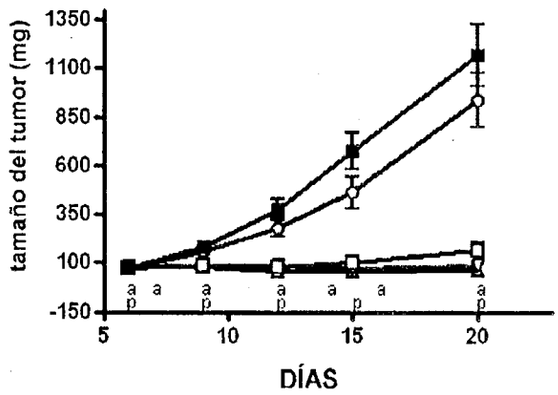


Figura 12B

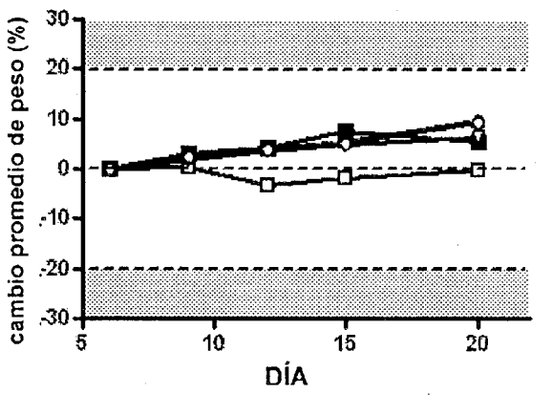


Figura 13

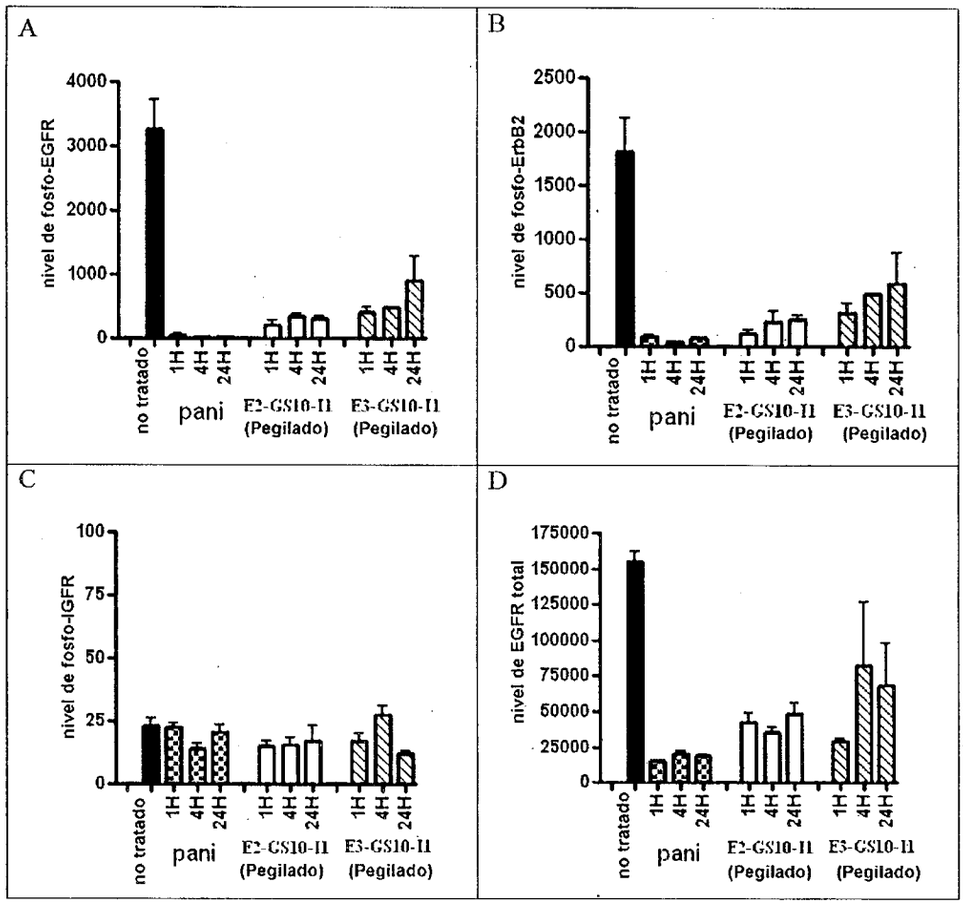

A
nivel de fosfo-EGFR
4000
3000
2000
1000
0
no tratado
1H
4H
24H
pani
E2-GS10-I1 (Pegilado)
E3-GS10-I1 (Pegilado)
B
nivel de fosfo-ErbB2
2500
2000
1500
1000
500
0
C
nivel de fosfo-IGFR
100
75
50
25
D
nivel de EGFR total
175000
150000
125000
100000
75000
50000
25000

Figura 14

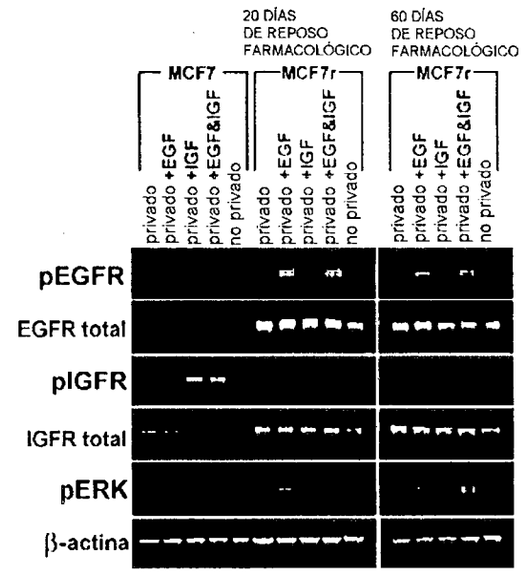


Figura 15

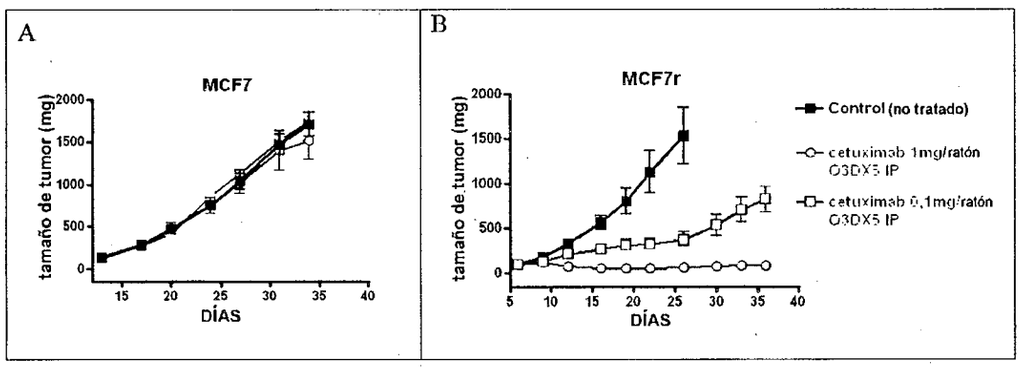
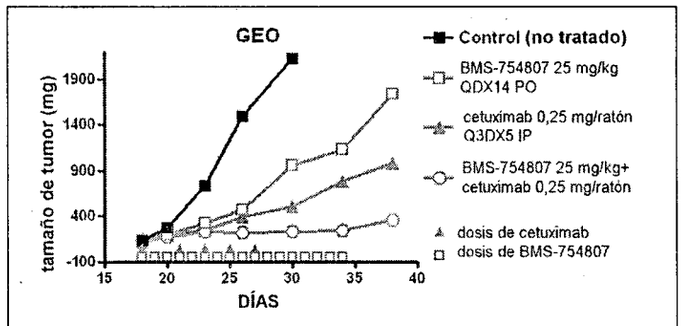
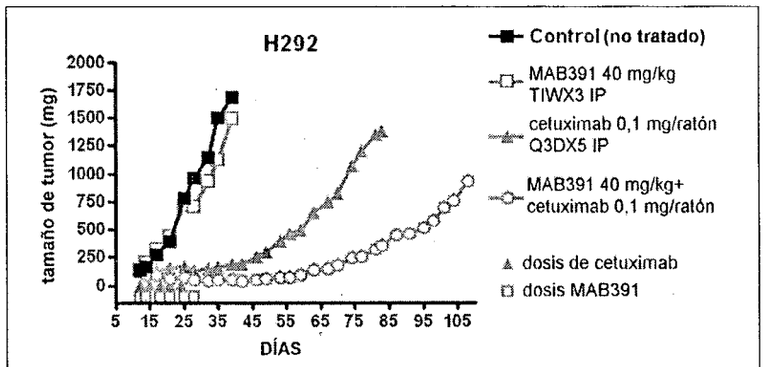


Figura 16



Las dosis de BMS-754807 y cetuximab se indican por casillas pequeñas y triángulos rellenos pequeños en el eje x

Figura 17



Las dosis de BMS-754807 y cetuximab se indican por casillas pequeñas y triángulos pequeños rellenos en el eje x

Figura 18

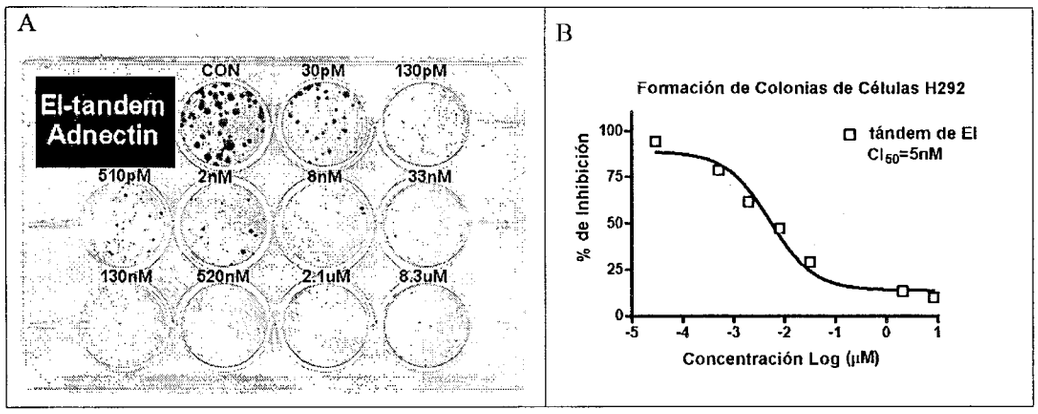


Figura 19

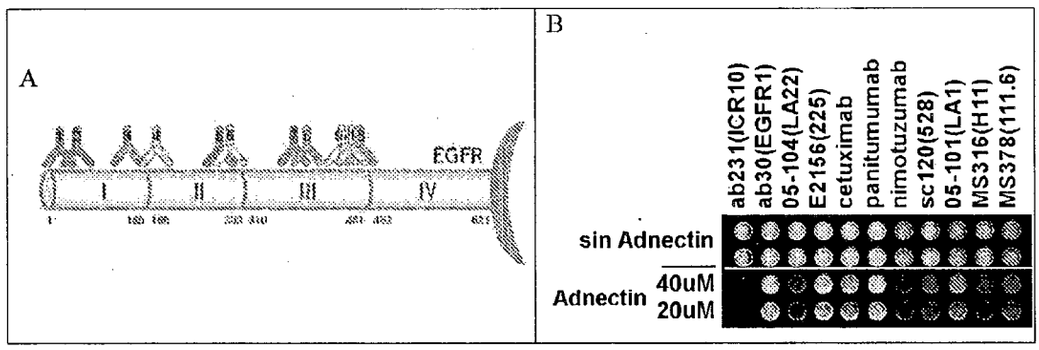


Figura 20

Tm = 55,2°C

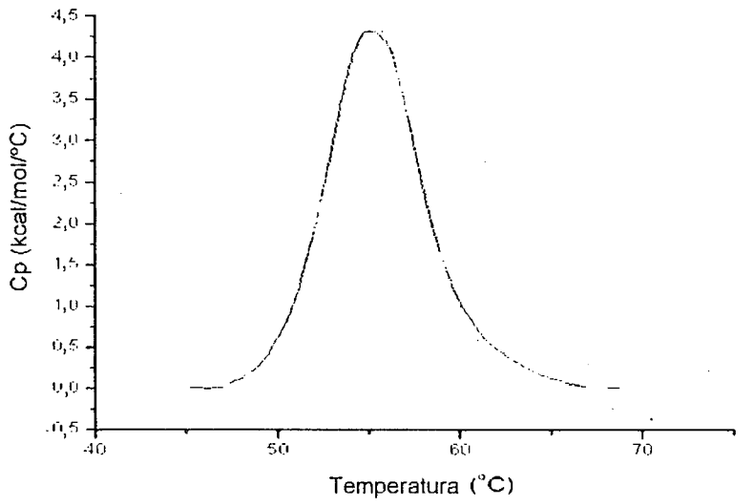


Figura 21

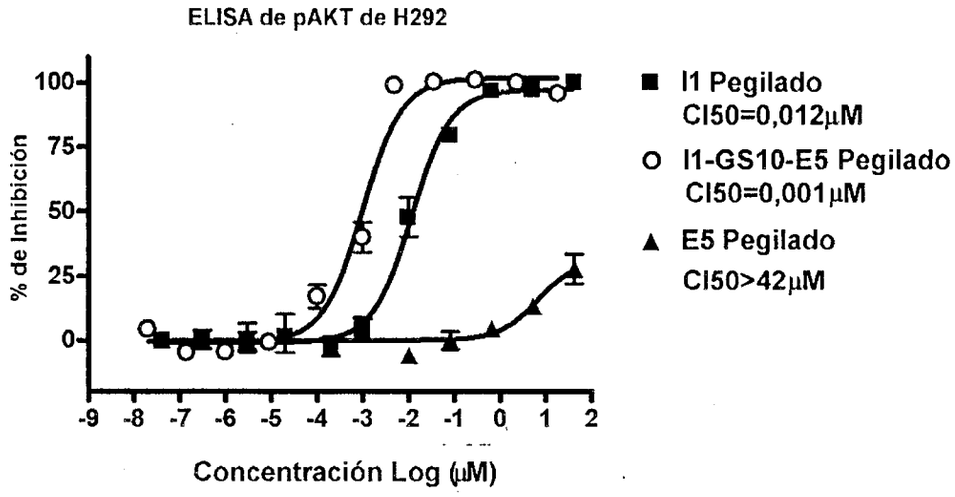


Figura 22

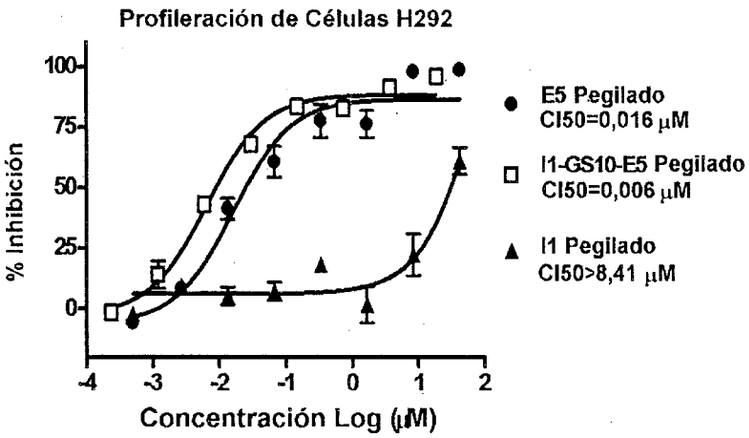


Figura 23

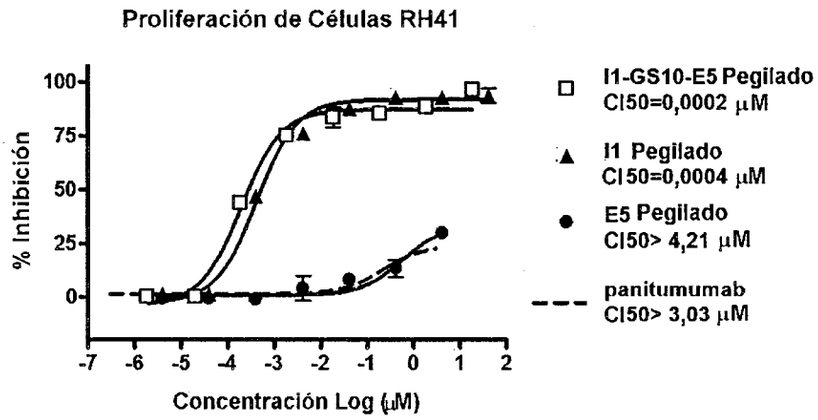
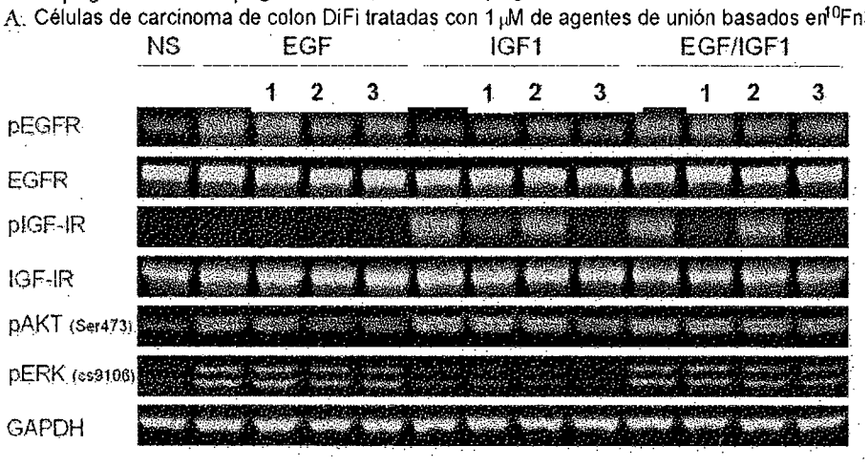


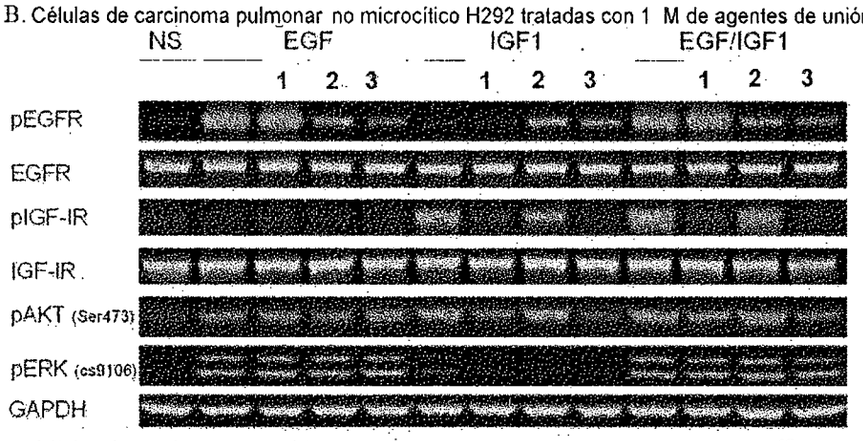
Figura 24

1=I1 pegilado; 2= E5 pegilado; 3=I1-GS10-E5 pegilado

A. Células de carcinoma de colon DiFi tratadas con 1 μM de agentes de unión basados en ^{10}Fn3.



B. Células de carcinoma pulmonar no microcítico H292 tratadas con 1 M de agentes de unión ^{10}Fn3



C. Células de carcinoma pancrático BxPC3 tratadas con 1,1 μM de agentes de unión ^{10}Fn3.

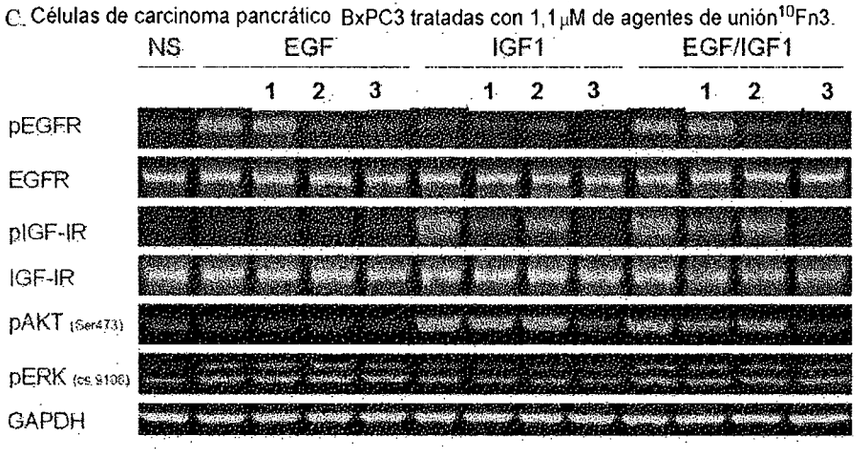
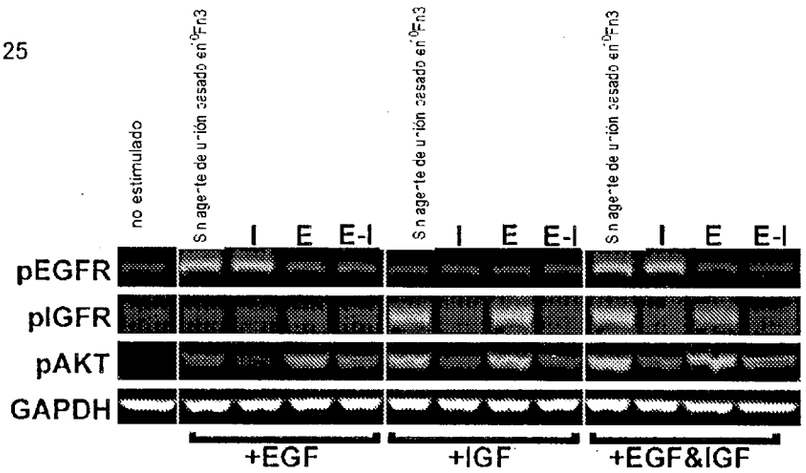


Figura 25



Las abreviaturas son las siguientes: I=I1 (no pegilado); E=E2 (no pegilado); EI=E2-GS10-I1 (no pegilado)

Figura 26

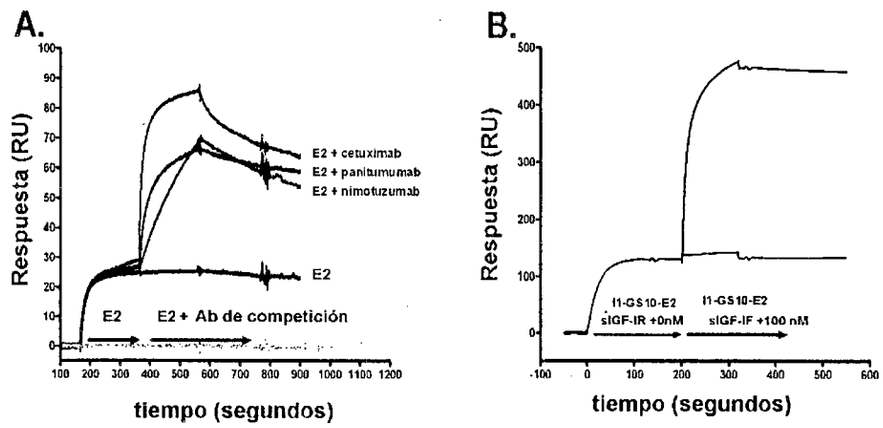


Figura 27

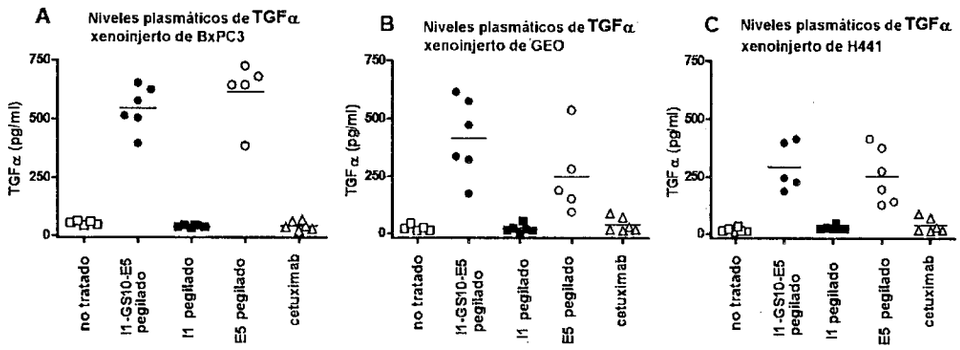


Figura 28

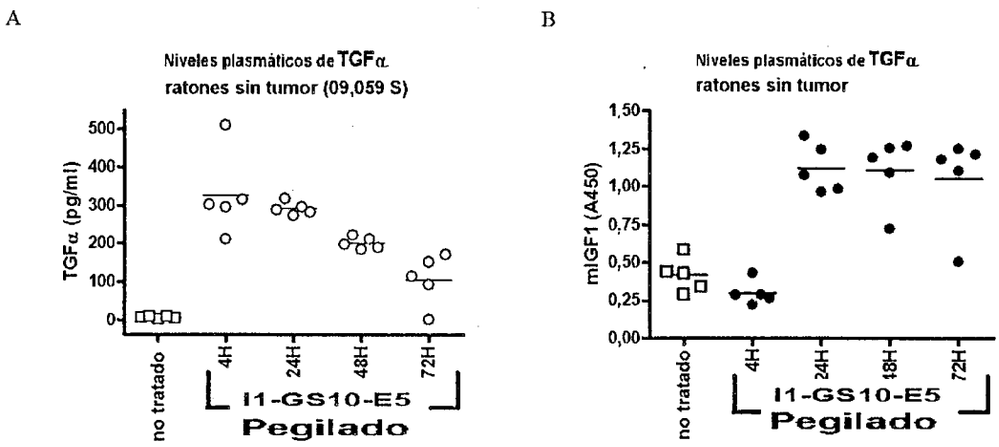
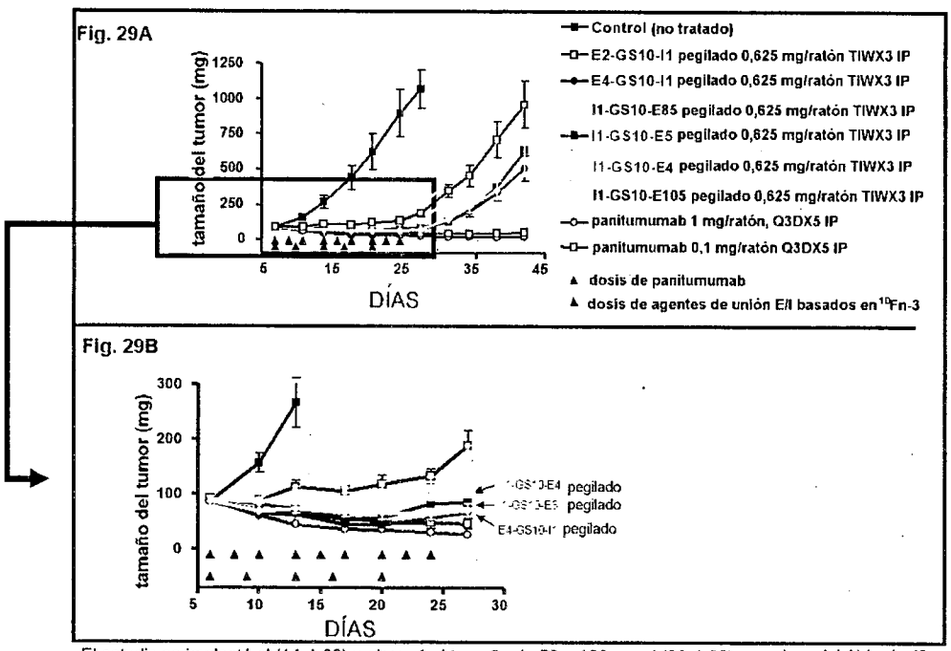
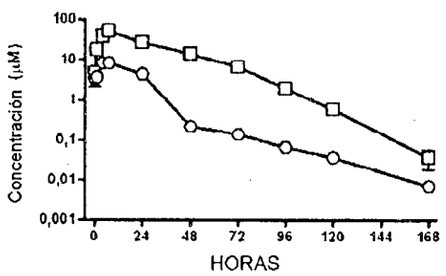


Figura 29



El estudio se implantó el (14-4-09) y alcanzó el tamaño de 50 a 150 mg el (20-4-09) cuando se inició la dosificación

Figura 30. Perfil farmacocinético de E2-GS10-I1 pegilado en ratones



Dosis (mg/kg)	$t_{1/2}$ (h)	C_{max} (µg/ml)	AUC (h*µg/ml)	Vz_F-obs (ml /kg)	Cl_F-obs (ml /h/kg)
10	15,8	205,7	5159	45,8	2,0
100	16,9	1209,6	34481,9	77,9	3,2

Niveles plasmáticos de E2-GS10-I1 pegilado después de dosificar esta construcción a 100 mg/kg (□) y 10 mg/kg (o) por la vía ip

Figura 31

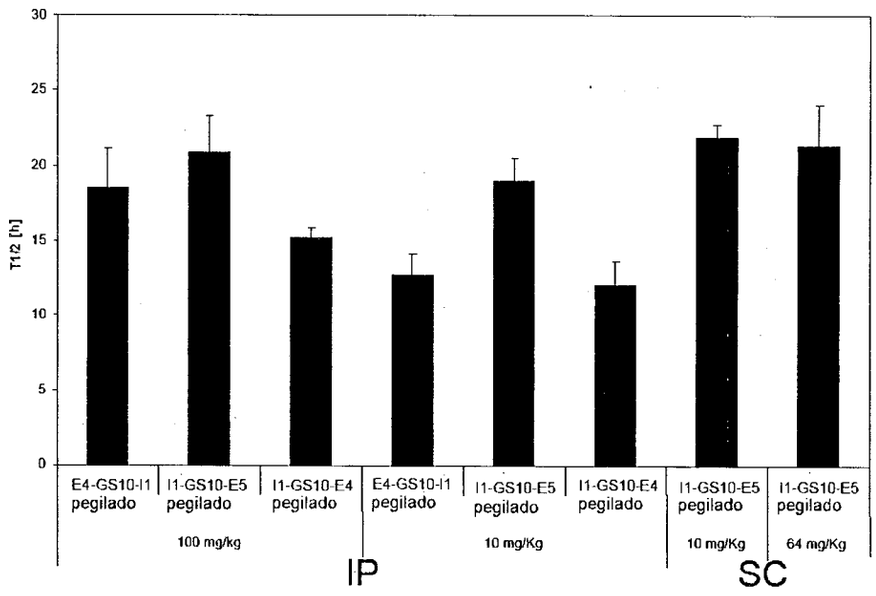


Figura 32

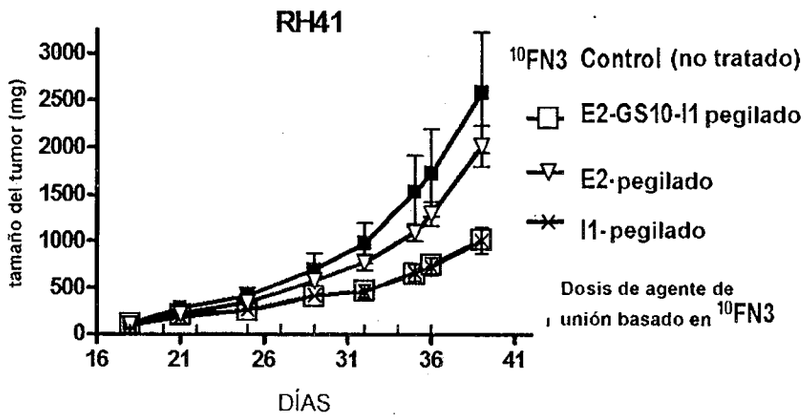


Figura 33

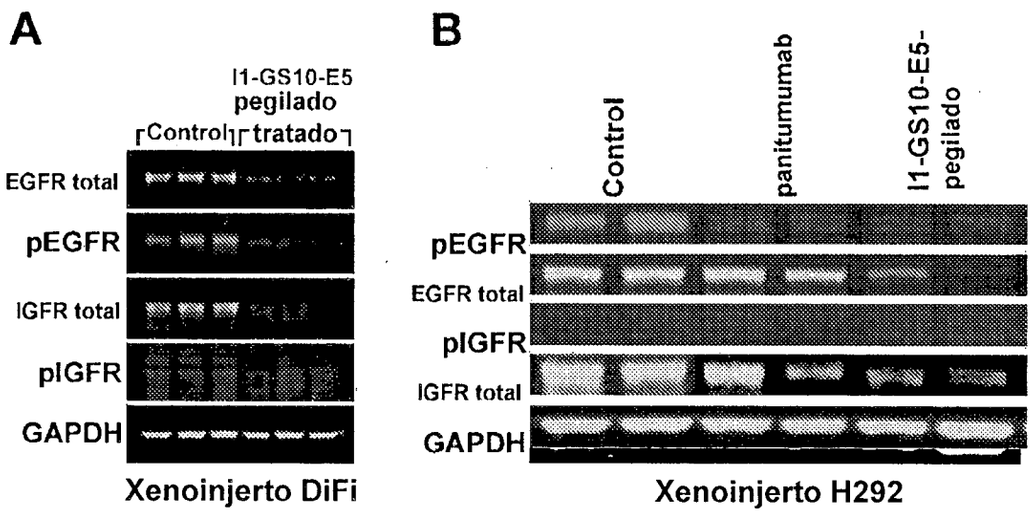


Figura 34

bucle BC bucle DE

MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPGGVRTATISGL

bucle FG

KPGVDYTITVYAVTDYMHSEYRQYPISINYRTEIDKPSQHHHHHH

Figura 35

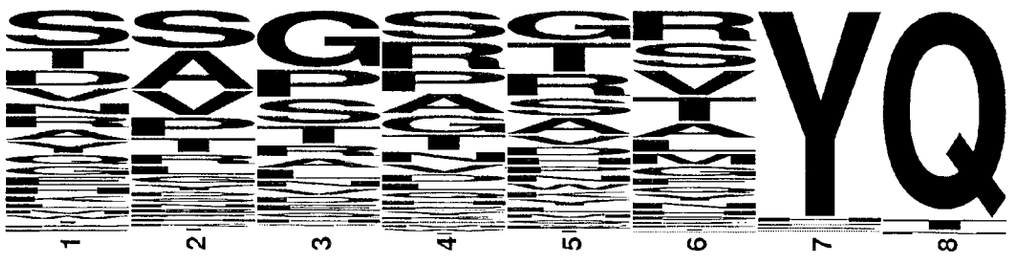


Figura 36



Figura 37



Figura 38



Figura 39

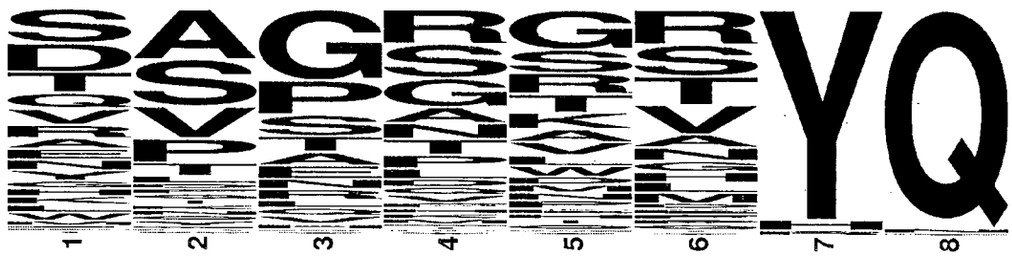


Figura 40



Figura 41



Figura 42



	a	b	c	d	e	f	g	h	i	j	k	l
NOMBRE DE CLÓN	ICW de pEGFR de A431 (nM)*	ICW de pEGFR de A431 (nM)*	ELISA de pEGFR de H292 (nM)*	ELISA de pEGFR de H292 (nM)*	Degrada EGFR	Degrada IGFR	EGFR KD (nM)	IGFR KD (nM)	ELISA de bloqueo de EGF (nM)	Inhibición de formación de colonias (nM)	Tm	% Monómero
E1-GS10-I1 pegilado	297	295	123	4	+	+	57.9	2.43	238	---	49	>95%
E3-GS10-I1 pegilado	42	40	10	6	++	++	10.4	0.74	89	---	52.5	>95%
E2-GS10-I1 pegilado	77	78	32	0.3	++	(-)	10.1	1.17	25	560	57.5	>95%
E4-GS10-I1 pegilado	12±0	12±2	1.3±0.5	0.4±0.2	(-)	(-)	4.77	0.77	19.5	5	55.5	>95%
E96-GS10-I1 pegilado	61±1	54±21	10±1	0.4	(-)	(-)	24.2	0.96	43.8	---	55	>95%
E5-GS10-I1 pegilado	44±1	47±7	12±4	0.4	+	+	12.4	1.16	119.3	---	54.5	>95%
E85-GS10-I1 pegilado	15±0	15±2	4±1	0.3	(-)	+	4.76	0.75	65.9	---	55.5	>95%
E90-GS10-I1 pegilado	65±0	63±9	10±1	0.4	---	---	13.5	1.5	69.1	---	49.5	>95%
E105-GS10-I1 pegilado	56±0	61±6	15±4	0.5	++	++	9.28	1.35	75	---	58.5	>95%
E105-GS10-I1 pegilado	61±11	49±17	16±6	0.5	---	---	7.65	1.19	93.8	---	56.5	>95%
I1-GS10-E5 pegilado	54±33	58±13	12±4	0.4±0.1	+	++	7.66	0.4	150.8	1	56	>95%
I1-GS10-E85 pegilado	22±15	23±4	8±3	0.7±0.5	(-)	(-)	5.97	0.43	37.8	---	58	>95%
I1-GS10-E4 pegilado	12±4	13±1	4±1	0.2	(-)	+	3.63	0.46	38.1	6	60	>95%
I1-GS10-E105 pegilado	53±9	48±3	13±3	0.5±0.2	++	++	4.28	0.37	61.2	---	59.5	>95%
I1-GS10-E112 pegilado	116	94	16	0.3	---	---	3.35	0.38	104.3	---	62.5	>95%
cetuximab	5±4	9±1	5±3	---	++	---	0.39	---	1	770	---	---
panitumumab	6±4	5±2	5±2	---	++	---	0.05	---	24.4	140	---	---
nimotuzumab	>3	>3	>3	---	+	---	1	---	13.6	---	---	---
I1	---	---	---	0.4±0.2	---	(-)	---	0.11	---	15.510	65.3	>95%

Figura 43

Figura 44

Dosis	Molécula		HL_Lambda_z (h)	Cmax (ug/ml)	AUCINF_obs (hr*ug/ml)	Cl_F_obs (ml/h/kg)	Vz_F_obs (ml/kg)	MRTINF_obs (h)
100 mg/kg	E4-GS10-I1 pegilado	N	3	3	3	3	3	3
		Media	18,5	521,1	20811,4	4,8	128,3	34,1
		SD	2,6	75,7	2058,7	0,5	6,4	2,0
		Mín	16,6	434,2	18824,8	4,4	122,4	31,8
		Máx	21,5	573,0	22935,3	5,3	135,2	35,6
		CV%	14,0	14,5	9,9	9,8	5,0	6,0
	I1-GS10-E5 pegilado	N	3	3	3	3	3	3
		Media	20,9	719,5	25730,1	3,9	117,4	33,0
		SD	2,3	90,4	2983,3	0,4	4,1	2,2
		Mín	18,6	623,7	23362,5	3,4	114,9	30,6
		Máx	23,2	803,4	29080,9	4,3	122,1	34,8
		CV%	11,0	12,6	11,6	11,1	3,5	6,7
	I1-GS10-E4 pegilado	N	3	3	3	3	3	3
		Media	15,2	757,1	28344,0	3,6	77,7	34,5
		SD	0,6	202,9	2777,8	0,4	6,7	2,0
		Mín	14,6	533,9	25411,7	3,2	70,3	32,4
		Máx	15,9	930,4	30936,0	3,9	83,1	36,5
		CV%	4,1	26,8	9,8	10,0	8,6	5,9
10mg/kg	E4-GS10-I1 pegilado	N	3	3	3	3	3	3
		Media	12,7	67,2	1721,2	6,0	108,4	19,6
		SD	1,4	12,9	336,7	1,3	15,1	0,9
		Mín	11,6	52,5	1338,0	5,1	95,5	18,7
		Máx	14,3	76,8	1969,5	7,5	125,0	20,6
		CV%	11,0	19,2	19,6	21,8	13,9	4,8
	I1-GS10-E5 pegilado	N	2	2	2	2	2	2
		Media	19,0	80,9	2345,6	4,4	118,7	23,7
		SD	1,5	3,2	526,4	1,0	17,1	0,6
		Mín	17,9	78,7	1973,4	3,7	106,6	23,3
		Máx	20,1	83,2	2717,8	5,1	130,8	24,1
		CV%	8,2	3,9	22,4	22,4	14,4	2,5
	I1-GS10-E4 pegilado	N	3	3	3	3	3	3
		Media	12,1	85,9	1857,1	5,6	95,5	19,6
		SD	1,6	15,4	420,2	1,1	9,7	0,9
		Mín	10,7	69,6	1581,1	4,3	85,0	18,6
		Máx	13,8	100,2	2340,7	6,3	104,1	20,4
		CV%	12,9	17,9	22,6	20,1	10,2	4,7

Figura 45

SEC ID N°	AGENTE DE UNIÓN	% de inhibición a 100 nM	Secuencia de Aminoácidos
219	E6	80.0	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPYDVYTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
220	E7	89.4	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPYDVHTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
221	E8	92.4	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPYDLTTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
222	E9	77.3	MGVSDVPRDLEVVAATPTSLLISWEANPSRYQYYRITYGETGGNSPVQEFTVPHDLNTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
223	E10	84.7	MGVSDVPRDLEVVAATPTSLLISWYPGSRTYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYY HPATYEHEYHAHPISINYRTEIDKPSQ
224	E11	83.7	MGVSDVPRDLEVVAATPTSLLISWTPANKSYQYYRITYGETGGNSPVQEFTVPYDGTTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHEYPISINYRTEIDKPSQ
225	E12	76.5	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPHDVYTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
226	E13	86.7	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPGQVYTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
227	E14	80.4	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPYDVTTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
228	E15	88.8	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPHDLRTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
229	E16	97.7	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPYDLVTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHESPISINYRTEIDKPSQ
230	E3	87.5	MGVSDVPRDLEVVAATPTSLLISWLPGKLRYQYYRITYGETGGNSPVQEFTVPHDLRTATISGLKPGVDYTITVYAVTNMM HVEYSEYPISINYRTEIDKPSQH
231	E1	85.9	MGVSDVPRDLEVVAATPTSLLISWVAGAEDYQYYRITYGETGGNSPVQEFTVPHDLVTATISGLKPGVDYTITVYAVTDMM HVEYTEHPISINYRTEIDKPSQ
232	E17	75.5	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPGMVHTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHESPISINYRTEIDKPSQ
233	E18	91.1	MGVSDVPRDLEVVAATPTSLLISWFVTHVAYQYYRITYGETGGNSPVQEFTVPGGLSTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ

SEC ID Nº	AGENTE DE UNIÓN	% de inhibición a 100 nM	Secuencia de Aminoácidos
234	E19	84.6	MGVSDVPRDLEVVAATPTSLLISWETESNAYQYYRITYGETGGNSPVQEFTVPGQIYTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
235	E20	80.2	MGVSDVPRDLEVVAATPTSLLISWMTSPSVYQYYRITYGETGGNSPVQEFTVPGPVQTATISGLKPGVDYTITVYAVTDYK EHQHAPHQYTAHPISINYRTEIDKPSQ
236	E2	80.5	MGVSDVPRDLEVVAATPTSLLISWDSGRGSYQYYRITYGETGGNSPVQEFTVPGPVHTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHESPISINYRTEIDKPSQ
237	E22	83.7	MGVSDVPRDLEVVAATPTSLLISWSTGRTTYQYYRITYGETGGNSPVQEFTVPHDLDTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
238	E23	81.1	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPYDVITATISGLKPGVDYTITVYAVTDMM HVEYAEYPISINYRTEIDKPSQ
239	E24	90.3	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPGQVPTATISGLKPGVDYTITVYAVTDSY NPATHEYKYHQTPISINYRTEIDKPSQ
240	E25	77.1	MGVSDVPRDLEVVAATPTSLLISWGYQSGGYTYYRITYGETGGNSPVQEFTVPHDLRTATISGLKPGVDYTITVYAVTDYA YKEYQEHPISINYRTEIDKPSQ
241	E26	75.4	MGVSDVPRDLEVVAATPTSLLISWWIGIPVYQYYRITYGETGGNSPVQEFTVPYDGKTATISGLKPGVDYTITVYAVTDMM HVEYAEYPISINYRTEIDKPSQ
242	E27	94.6	MGVSDVPRDLEVVAATPTSLLISWSKGSKSYQYYRITYGETGGNSPVQEFTVPYHVYTATISGLKPGVDYTITVYAVTDYY NPATYEYIYLTTPISINYRTEIDKPSQ
243	E28	85.3	MGVSDVPRDLEVVAATPTSLLISWNPGSKSYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDFY NPDTHEYLYNQYPISINYRTEIDKPSQ
244	E29	87.9	MGVSDVPRDLEVVAATPTSLLISWQPGTTHYQYYRITYGETGGNSPVQEFTVPYDLMTATISGLKPGVDYTITVYAVTDYY NPNTYEYIYLTTPISINYRTEIDKPSQ
245	E30	87.3	MGVSDVPRDLEVVAATPTSLLISWAIGTIVYQYYRITYGETGGNSPVQEFTVPAGVYTATISGLKPGVDYTITVYAVTDYY DWATHEYNYHTAPISINYRTEIDKPSQ
246	E31	75.8	MGVSDVPRDLEVVAATPTSLLISWTYNDGSYQYYRITYGETGGNSPVQEFTVPYAVYTATISGLKPGVDYTITVYAVTDFY NPATYEYIYHTTPISINYRTEIDKPSQ
247	E32	86.0	MGVSDVPRDLEVVAATPTSLLISWVSLVGFYQYYRITYGETGGNSPVQEFTVPGGVHTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
248	E33	75.8	MGVSDVPRDLEVVAATPTSLLISWASRKEVYQYYRITYGETGGNSPVQEFTVPGWLNTATISGLKPGVDYTITVYAVTDYM HVEYAEYPISINYRTEIDKPSQ

SEC ID Nº	AGENTE DE UNIÓN	% de inhibición a 100 nM	Secuencia de Aminoácidos
249	E34	80.4	MGVSDVPRDLEVVAATPTSLLISWLAPFWRYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
250	E35	90.2	MGVSDVPRDLEVVAATPTSLLISWTPPGHQHQYYRITYGETGGNSPVQEFTVPGQVTTATISGLKPGVDYTITVYAVTDYY NPATHYYTYYTTPISINYRTEIDKPSQ
251	E36	81.3	MGVSDVPRDLEVVAATPTSLLISWESGSRTYQYYRITYGETGGNSPVQEFTVPGGVHTATISGLKTGVDYTITVYAVTDYK PHADGPHTYHEYPISINYRTEIDKPSQ
252	E37	80.8	MGVSDVPRDLEVVAATPTSLLISWERTSTHYQYYRITYGETGGNSPVQEFTVPGRVYTATISGLKPGVDYTITVYAVTDYY NPATHEYKYHQTPISINYRTEIDKPSQ
253	E38	89.8	MGVSDVPRDLEVVAATPTSLLISWNARTDAYQYYRITYGETGGNSPVQEFTVPRDLETATISGLKPGVDYTITVYAVTDYK PHADGPHTYQESPISINYRTEIDKPSQ
254	E39	76.7	MGVSDVPRDLEVVAATPTSLLISWQVSAFRYQYYRITYGETGGNSPVQEFTVPGMVSTATISGLKPGVDYTITVYAVTDYK PHADGPHTYSEYPISINYRTEIDKPSQ
255	E40	89.6	MGVSDVPRDLEVVAATPTSLLISWVLGRRVYQYYRITYGETGGNSPVQEFTVPGAVYTATISGLKPGVDYTITVYAVTDYF NPATHEYQYELTPISINYRTEIDKPSQ
256	E41	75.2	MGVSDVPRDLEVVAATPTSLLISWTPPNSGHNYYRITYGETGGNSPVQEFTVPHDLTTATISGLKPGVDYTITVYAVTDYY NPNTYEYTYQFTPISINYRTEIDKPSQ
257	E42	77.3	MGVSDVPRDLEVVAATPTSLLISWVVPNWMYQYYRITYGETGGNSPVQEFTVPGMLETATISGLKPGVDYTITVYAVTDYY NPTTYEYTYFTYPISINYRTEIDKPSQ
258	E43	75.0	MGVSDVPRDLEVVAATPTSLLISWSGGFMRYQYYRITYGETGGNSPVQEFTVPGQVYTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
259	E44	83.3	MGVSDVPRDLEVVAATPTSLLISWDSEGPSYQYYRITYGETGGNSPVQEFTVPYAVYTATISGLKPGVDYTITVYAVTDYY NPRTHELFFQQYPISINYRTEIDKPSQ
260	E45	80.4	MGVSDVPRDLEVVAATPTSLLISWQVPRPMYQYYRITYGEKGGNSPVQEFTVPHDLRTATISGLKPGVDYTITVYAVTDYY DPTSNLYNYNQTPISINYRTEIDKPSQ
261	E46	77.0	MGVSDVPRDLEVVAATPTSLLISWQVGSVVYQYYRITYGETGGNSPVQEFTVPRDVLTATISGLKPGVDYTITVYAVTDYK PKPDGPHIYQAVPISINYRTEIDKPSQ
262	E47	76.9	MGVSDVPRDLEVVAATPTSLLISWNPASKDYQYYRITYGETGGNSPVQEFTVPGQVPTATISGLKPGVDYTITVYAVTDFY NPATHEYKYDSTPISINYRTEIDKPSQ
263	E48	88.6	MGVSDVPRDLEVVAATPTSLLISWRSSATAYQYYRITYGETGGNSPVQEFTVPGRVYTATISGLKPGVDYTITVYAVTDFF NWATHEYIYHSTPISINYRTEIDKPSQ

SEC ID Nº	AGENTE DE UNIÓN	% de inhibición a 100 nM	Secuencia de Aminoácidos
264	E49	83.5	MGVSDVPRDLEVVAATPTSLLISWHSGPREYQYYRITYGETGGNSPVQEFTVPGQVYTATISGLKPGVDYTITVYAVTDFF NPITHYYYYELTPISINYRTEIDKPSQ
265	E50	77.4	MGVSDVPRDLEVVAATPTSLLISWTVGLSVYQYYRITYGETGGNSPVQEFTVPGMVSTATISGLKPSVDYTITVYAVTDYK PHADGPHTYHEYPISINYRTEIDKPSQ
266	E51	82.8	MGVSDVPRDLEVVAATPTSLLISWGGHRAVYQYYRITYGETGGNSPVQEFTVPGAVYTATISGLKPGVDYTITVYAVTDYY NPDTHEYKYHQYPISINYRTEIDKPSQ
267	E52	75.3	MGVSDVPRDLEVVSATPTSLLISWQVPRPMYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYW FKEYREDPISINYRTEIDKPSQ
268	E53	79.8	MGVSDVPRDLEVVAATPTSLLISWSVGGMIYQYYRITYGETGGNSPVQEFTVPGMVTTATISGLKPGVDYTITVYAVTDYY NPATHEYKYHQTPISINYRTEIDKPSQ
113, donde X = Ser	E5	99.1	MGVSDVPRDLEVVAATPTSLLISWWAPVDRYQYYRITYGETGGNSPVQEFTVPRDVYTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
269	E54	76.1	MGVSDVPRDLEVVAATPTSLLISWKASYTGYNYYRITYGETGGNSPVQEFTVPRDVMTATISGLKPGVDYTITVYAVTDFY NPDTHQYTYRRIPISINYRTEIDKPSQ
270	E55	99.1	MGVSDVPRDLEVVAATPTSLLISWSVGQVFYQYYRITYGETGGNSPVQEFTVPYDVYTATISGLKPGVDYTITVYAVTDYY NPATHEYKYHQTPISINYRTEIDKPSQ
271	E56	84.2	MGVSDVPRDLEVVAATPTSLLISWYSGDYHYQYYRITYGETGGNSPVQEFTVPHDLETATISGLKPGVDYTITVYAVTDYY NPATHYYKYEQTPISINYRTEIDKPSQ
272	E57	75.5	MGVSDVPRDLEVVAATPTSLLISWIVQGGRYQYYRITYGETGGNSPVQEFTVPGMVTTATISGLKPGVDYTITVYAVTDYY NPSTHEYKYHQTPISINYRTEIDKPSQ
273	E58	79.7	MGVSDVPRDLEVVAATPTSLLISWSAVRWRYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDFY NPRTHVYIYDQFPISINYRTEIDKPSQ
274	E59	76.3	MGVSDVPRDLEVVAATPTSLLISWRARRLQYQYYRITYGETGGNSPVQEFTVPGMVTTATISGLKPGVDYTITVYAVTDFY NPATMEYTYQRTPISINYRTEIDKPSQ
275	E60	100.0	MGVSDVPRDLEVVAATPTSLLISWLQPLWRYQYYRITYGETGGNSPVQEFTVPGGLDTATISGLKPGVDYTITVYAVTDYK PHVDGPHAYHEYPISINYRTEIDKPSQ
276	E61	79.8	MGVSDVPRDLEVVAATPTSLLISWDASQGNYQYYRITYGETGGNSPVQEFTVPGAVKTATISGLKPGVDYTITVYAVTDFF NPATHEYIYHTTPISINYRTEIDKPSQ
277	E62	78.9	MGVSDVPRDLEVVAATPTSLLISWCLDGQLYQYYRITYGETGGNSPVQEFTVPGSIVTATISGLKPGVDYTITVYAVTDWY NLATHEYNYRVTPISINYRTEIDKPSQ

SEC ID Nº	AGENTE DE UNIÓN	% de inhibición a 100 nM	Secuencia de Aminoácidos
278	E63	76.2	MGVSDVPRDLEVVAATPTSLLISWDTSGASYQYYRITYGETGGNSPVQEFTVPYSVYTATISGLKPGVDYTITVYAVTDYY DPDSHYYNYNMVPISINYRTEIDKPSQ
279	E64	78.2	MGVSDVPRDLEVVAATPTSLLISWDSGNGTYQYYRITYGETGGNSPVQEFTVPYRVYTATISGLKPGVDYTITVYAVTDYY NPATHEYTYELRPISINYRTEIDKPSQ
280	E65	80.7	MGVSDVPRDLEVVATTPTSLLISWRPTSQVYQYYRITYGETGGNSPVQEFTVPYNVYTATISGLKPGVDYTITVYAVTDFF NYATHEYIYHTIPISINYRTEIDKPSQ
281	E66	75.0	MGVSDVPRDLEVVAATPTSLLISWKSYGSAYQYYRITYGETGGNSPVQEFTVPGDLQTATISGLKPGVDYTITVYAITDYY NPDTHEYKYHVSPISINYRTEIDKPSQ
282	E67	75.3	MGVSDVPRDLEVVAATPTSLLISWSSVMGLYQYYRITYGETGGNSPVQEFTVPYDVYTATISGLKPGVDYTITVYAVTDYY NPSTYEYKYNTTPISINYRTEIDKPSQ
283	E68	78.5	MGVSDVPRDLEVVAATPTSLLISWKTEPGRHQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDWY NLVSHEYVYHTTPISINYRTEIDKPSQ
284	E69	85.1	MGVSDVPRDLEVVAATPTSLLISWHAGMAVYQYYRITYGETGGNSPVQEFTVPGDVLTATISGLKPGVDYTITVYAVTDFF NPVTHEYMYHTIPISINYRTEIDKPSQ
285	E70	76.8	MGVSDVPRDLEVVAATPTSLLISWVSARGRYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYY NLETYEYHYYRTPISINYRTEIDKPSQ
286	E71	80.4	MGVSDVPRDLEVVAATPTSLLISWWFGTSSYQYYRITYGETGGNSPVQEFTVPGDLKTATISGLKPGVDYTITVYAVTDYF NPVTHEYEYHTTPISINYRTEIDKPSQ
287	E72	82.8	MGVSDVPRDLEVVAATPTSLLISWSATRTLYQYYRITYGETGGNSPVQEFTVPYDVHTATISGLKPGVDYTITVYAVTDYY NMVTYEYNYHLTPISINYRTEIDKPSQ
288	E73	78.8	MGVSDVPRDLEVVVATPTSLLISWIKLLGGYQYYRITYGETGGNSPVQEFTVPGPVYTATISGLKPGVDYTITVYAVTDFF NPRTHEYQYHTTPISINYRTEIDKPSQ
289	E74	80.9	MGVSDVPRDLEVVAATPTSLLISWRASGGLYQYYRITYGETGGNSPVQEFTVPGSVNTATISGLKPGVDYTITVYAVTDFY NPATYEYIYHTTPISINYRTEIDKPSQ
290	E75	76.5	MGVSDVPRDLEVVAATPTSLLISWAAGRATYQYYRITYGETGGNSPVQEFTVPYDVTTATISGLKPGVDYTITVYAVTDFY NPATHEYYYETTPISINYRTEIDKPSQ
291	E76	79.0	MGVSDVPRDLEVVAATPTSLLISWYSQPLTYQYYRITYGETGGNSPVQEFTVPHDVNTATISGLKPGVDYTITVYAVTDFY NPETHEYTYHLTPISINYRTEIDKPSQ
292	E77	81.1	MGVSDVPRDLEVVAATPTSLLISWSSATRPYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDFF NPTTHEYYYHTTPISINYRTEIDKPSQ

SEC ID Nº	AGENTE DE UNIÓN	% de inhibición a 100 nM	Secuencia de Aminoácidos
293	E78	76.9	MGVSDVPRDLEVVAATPTSLLISWSVERSVYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYY NPSTHEYNYLTTPISINYRTEIDKPSQ
294	E79	99.2	MGVSDVPRDLEVVAATPTSLLISWQDTSSYHQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYF NPSTHEYIYRTIPISINYRTEIDKPSQ
295	E80	89.6	MGVSDVPRDLEVVAATPTSLLISWSSSHRRYQYYRITYGETGGNSPVQEFTVPGSVATATISGLKPGVDYTITVYAVTDYF NPDTHEYLYHATPISINYRTEIDKPSQ
296	E81	75.1	MGVSDVPRDLEVVAATPTSLLISWDNNSNSYQYYRITYGETGGNSPVQEFTVPYDLRTATISGLKPGVDYTITVYAVTDYK PHTEGEHTYHESPISINYRTEIDKPSQ
297	E82	77.2	MGVSDVPRDLEVVAATPTSLLISWRVLVDMYQYYRITYGETGGNSPVQEFTVPGGVLTATISGLKPGVDYTITVYAVTDYK PHVDGPHTYYESPISINYRTEIDKPSQ
298	E83	90.7	MGVSDVPRDLEVVAATPTSLLISWMFVGMSYQYYRITYGETGGNSPVQEFTVPYGVHTATISGLKPGVDYTITVYAVTDYF NPATHEYIYHVTPISINYRTEIDKPSQ
299	E84	86.5	MGVSDVPRDLEVVAATPTSLLISWTLHRKNYQYYRITYGETGGNSPVQEFTVPGGVVTATISGLKPGVDYTITVYAVTDYY NPATHEYDYRTTPISINYRTEIDKPSQ
300	E85	89.3	MGVSDVPRDLEVVAATPTSLLISWTQGSTHYQYYRITYGETGGNSPVQEFTVPGMVYTATISGLKPGVDYTITVYAVTDYF DRSTHEYKYRTTPISINYRTEIDKPSQ
107, donde X = Ser	E4	94.3	MGVSDVPRDLEVVAATPTSLLISWHERDGSRQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYF NPTTHEYIYQTTPISINYRTEIDKPSQ
301	E86	84.7	MGVSDVPRDLEVVAATPTSLLISWDSGENNYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYY NPKTHEYNYLTIPISINYRTEIDKPSQ
302	E87	87.0	MGVSDVPRDLEVVAATPTSLLISWGSPLIEYQYYRITYGETGGNSPVQEFTVPGGLSTATISGLKPGVDYTITVYAVTDYF NPATHEYTYHVSPISINYRTEIDKPSQ
303	E88	89.3	MGVSDVPRDLEVVAATPTSLLISWSATNKTYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYF NPTTHEYIYQTTPISINYRTEIDKPSQ
304	E89	82.6	MGVSDVPRDLEVVAATPTSLLISWDDPAANRQYYRITYGETGGNSPVQEFTVPYDLRTATISGLKPGVDYTITVYAVTDYY NPATHQYKYSQSPISINYRTEIDKPSQ
305	E90	81.3	MGVSDVPRDLEVVAATPTSLLISWYWEGLPYQYYRITYGETGGNSPVQEFTVPRDVNTATISGLKPGVDYTITVYAVTDWY NPDTHEYIYHTIPISINYRTEIDKPSQ
306	E91	84.7	MGVSDVPRDLEVVAATPTSLLISWSAPWRTYQYYRITYGETGGNSPVQEFTVPYDVYTATISGLKPGVDYTITVYAVTDYL NPNTLEYTYQRIPISINYRTEIDKPSQ

SEC ID Nº	AGENTE DE UNIÓN	% de inhibición a 100 nM	Secuencia de Aminoácidos
307	E92	88.5	MGVSDVPRDLEVVAATPTSLLISWQAANHSYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDFF NPVTHEYKYRTIPISINYRTEIDKPSQ
308	E93	76.9	MGVSDVPRDLEVVAATPTSLLISWDSGRGSYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHEYPISINYRTEIDKPSQ
309	E94	78.7	MGVSDVPRDLEVVAATPTSLLISWNNGGRNYQYYRITYGETGGNSPVQEFTVPYDVYTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHEYPISINYRTEIDKPSQ
310	E95	98.0	MGVSDVPRDLEVVAATPTSLLISWVVPQGMYQYYRITYGETGGNSPVQEFTVPGGVSTATISGLKPGVDYTITVYAVTDYF NPATHEYNYHSIPISINYRTEIDKPSQ
311	E96	91.7	MGVSDVPRDLEVVAATPTSLLISWASNRGTYQYYRITYGETGGNSPVQEFTVPGGVSTATISGLKPGVDYTITVYAVTDAF NPTTHEYNYFTTPISINYRTEIDKPSQ
312	E97	89.3	MGVSDVPRDLEVVAATPTSLLISWLPGKLRYQYYRITYGETGGNSPVQEFTVPHDLRTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
313	E98	75.8	MGVSDVPRDLEVVAATPTSLLISWDAPTSRYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHEYPISINYRTEIDKPSQ
314	E99	84.7	MGVSDVPRDLEVVAATPTSLLISWDAPTSRYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHEYPISINYRTEIDKPSQ
315	E100	83.3	MGVSDVPRDLEVVAATPTSLLISWTPANKSYQYYRITYGETGGNSPVQEFTVPHDLVTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHEYPISINYRTEIDKPSQ
316	E101	90.9	MGVSDVPRDLEVVAATPTSLLISWDAPAVTYQYYRITYGETGGNSPVQEFTVPHDLVTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
317	E102	80.0	MGVSDVPRDLEVVAATPTSLLISWTPANKSYQYYRITYGETGGNSPVQEFTVPHDLVTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHESPISINYRTEIDKPSQ
318	E103	76.3	MGVSDVPRDLEVVAATPTSLLISWTPANKSYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTNMM HVEYSEYPISINYRTEIDKPSQ
319	E104	89.3	MGVSDVPRDLEVVAATPTSLLISWDAGAVTYQYYRITYGETGGNSPVQEFTVPHDLVTATISGLKPGVDYTITVYAVTDHK PHADGPHTYHEYPISINYRTEIDKPSQ
320	E105	87.0	MGVSDVPRDLEVVAATPTSLLISWDAPTSRYQYYRITYGETGGNSPVQEFTVPGGLSTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
321	E106	84.0	MGVSDVPRDLEVVAATPTSLLISWDAPAVTYQYYRITYGETGGNSPVQEFTVPYDVYTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHEYPISINYRTEIDKPSQ

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SEC ID Nº	AGENTE DE UNIÓN	% de inhibición a 100 nM	Secuencia de Aminoácidos
322	E107	75.8	MGVSDVPRDLEVVAATPTSLLISWDSGRGSYQYYRITYGETGGNSPVQEFTVPYDVYTATISGLKPGVDYTITVYAVTDMM HVEYTEHPISINYRTEIDKPSQH
323	E108	80.0	MGVSDVPRDLEVVAATPTSLLISWDAPAVTYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
324	E109	90.9	MGVSDVPRDLEVVAATPTSLLISWDAPTSRYQYYRITYGETGGNSPVQEFTVPHDLVTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
325	E110	81.3	MGVSDVPRDLEVVAATPTSLLISWDAGAVTYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHESPISINYRTEIDKPSQ
326	E111	85.5	MGVSDVPRDLEVVAATPTSLLISWDAPTSRYQYYRITYGETGGNSPVQEFTVPHDLVTATISGLKPGVDYTITVYAVTNMM HVEYSEYPISINYRTEIDKPSQ
327	E112	86.2	MGVSDVPRDLEVVAATPTSLLISWDAGAVTYQYYRITYGETGGNSPVQEFTVPGGVRTATISGLKPGVDYTITVYAVTDYK PHADGPHTYHEYPISINYRTEIDKPSQ

Figura 46

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                21        30                  51  56                  76        87
WT   EVVAATPTSLLI SWDAPAVTVR YYRITYGETGGNSPVQEFTV PGSKST ATISGLKPGVDYTITVYAV TGRGDSPASSK      P ISINYRT
I1   EVVAATPTSLLI SWSARLKVAR YYRITYGETGGNSPVQEFTV PKNVYT ATISGLKPGVDYTITVYAV TRFRDYQ         P ISINYRT
E1   EVVAATPTSLLI SWVAGAEDYQ YYRITYGETGGNSPVQEFTV PHDLVT ATISGLKPGVDYTITVYAV TDMMHVEYTEH       P ISINYRT
E2   EVVAATPTSLLI SWDSGRGSYQ YYRITYGETGGNSPVQEFTV PGPVHT ATISGLKPGVDYTITVYAV TDHKPHADGPHTYHESP ISINYRT
E3   EVVAATPTSLLI SWLPGKLRYQ YYRITYGETGGNSPVQEFTV PHDLRT ATISGLKPGVDYTITVYAV TNMMHVEYSEY      P ISINYRT
E4   EVVAATPTSLLI SWHERDGSRQ YYRITYGETGGNSPVQEFTV PGGVRT ATISGLKPGVDYTITVYAV TDYFNPTTHEYIYQTTP ISINYRT
E5   EVVAATPTSLLI SWWAPVDRYQ YYRITYGETGGNSPVQEFTV PRDVYT ATISGLKPGVDYTITVYAV TDYKPHADGPHTYHESP ISINYRT
E85  EVVAATPTSLLI SWTQGSTHYQ YYRITYGETGGNSPVQEFTV PGMVYT ATISGLKPGVDYTITVYAV TDYFDRSTHEYKYRTTP ISINYRT
E90  EVVAATPTSLLI SWYWEGLPYQ YYRITYGETGGNSPVQEFTV PRDVNT ATISGLKPGVDYTITVYAV TDWYNPDTHEYIYHTIP ISINYRT
E96  EVVAATPTSLLI SWASNRGTYQ YYRITYGETGGNSPVQEFTV PGGVST ATISGLKPGVDYTITVYAV TDAFNPTTHEYNYFTTP ISINYRT
E105 EVVAATPTSLLI SWDAPTSRYQ YYRITYGETGGNSPVQEFTV PGGLST ATISGLKPGVDYTITVYAV TDYKPHADGPHTYHESP ISINYRT
E112 EVVAATPTSLLI SWDAGAVTYQ YYRITYGETGGNSPVQEFTV PGGVRT ATISGLKPGVDYTITVYAV TDYKPHADGPHTYHEYP ISINYRT
```

Figura 47

SEC ID Nº	AGENTE DE UNIÓN	SECUENCIA DE NUCLEÓTIDOS
328	I1 (con Cola Cys)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTGCGCGTCTG AAAGTTGCGCGATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTAAAAACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAGGTTCCGCGACTACCAG CCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCACCACCACCACCAC
329	E6	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGTCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
330	E7	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT CATACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGTCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
331	E8	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACCTG ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
332	E9	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGAAGCTAACCCT TCTCGTTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG AACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
333	E10	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTACCCAGGATCT CGCACCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACTACCATCCGGCT ACTTACGAACATGAATACCATGCTCATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
334	E11	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACCCCTGCTAAT AAATCTTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGGT ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
335	E12	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

SEC ID Nº	AGENTE DE UNIÓN	SECUENCIA DE NUCLEÓTIDOS
336	E13	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCAGGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
337	E14	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
338	E15	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
339	E16	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
340	E3	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTTGCCGGGCAAG CTGAGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAACATGATGCATGTTGAA TACTCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
341	E1	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGTGGCCGGGGCG GAGGACTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACATGATGCATGTTGAA TACACTGAACATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
342	E17	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGGTT CACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
343	E18	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTTCGTGACGCAC GTCGCCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTCTG TCCACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

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344	E19	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGAGACGGAGAGC AACGCGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCAGATC TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
345	E20	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGATGACGTCGCCC TCGGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCCGGTT CAGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACAAAGAACATCAG CATGCTCCGCATCAGTACACTGCTCATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
346	E2	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATTCAGGACGA GGTTCCTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCCGGTT CATACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
347	E22	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCAACAGGTCGC ACAACTTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
348	E23	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT ATCACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACATGATGCATGTTGAA TACGCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
349	E24	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCAGGTT CCAACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTCTTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
350	E25	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTCGGGCTACCAAAGT GGCGGCTATACCTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACGCTTACAAAGAA TACCAGGAACATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
351	E26	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTGGATCGGCATC CCGGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGGT AAAACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACATGATGCATGTTGAA TACGCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC

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352	E27	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTAAAGGTTCA AAATCTTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACCATGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTATAACCCGGCT ACTTACGAATACATATACCTTACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
353	E28	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAATCCCGGCTCC AAAAGCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTACAATCCGGAT ACTCATGAATACCTATACAATCAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
354	E29	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAACCCGGCACC ACACATTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACCTG ATGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGAAT ACTTATGAGTATATATACTTGACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
355	E30	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGCCATCGGCACC ATCGTCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGCTGGTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACGACTGGGCT ACTCATGAATACAATTACCACACCGCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
356	E31	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACTTATAATGAT GGCAGCTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGCTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTACAATCCGGCT ACATATGAATACATATATCACACGACACCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
357	E32	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGTCTCCCTCGTG GGCTTCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CATACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
358	E33	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGCCTCGAGGAAG GAGGTCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTTGGTTG AACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACATGCATGTTGAA TACGCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
359	E34	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTTGGCGCCCTTC TGGCGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

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360	E35	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACACCACCAGGA CATCAACATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCAGGTT ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCAGCT ACTCACTATTACACTTATTATACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
361	E36	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGAGTCGGGGTCC AGGACGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CATACAGCTACCATCAGCGGCCTTAAAACTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
362	E37	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGAGAGGACCTCC ACCCACTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCGTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
363	E38	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAATGCTCGCACC GACGCTTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCGTGACCTG GAAACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCTCATGCG GACGGACCGCATACTTACCAAGAGTCGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
364	E39	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTGAGCGCG TTCCGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGGTT TCTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACTCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
365	E40	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGTGCTGGGCAGG AGGGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGCTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTCAACCCAGCT ACCCATGAATACCAATACGAGCTTACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
366	E41	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACTCCACCCAAT TCTGGTCATAATTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGAAT ACCTATGAATACACATATCAATTCACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
367	E42	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGTCGTCCCGAAC TGGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGCTG GAAACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTATAACCCGACT ACGTATGAATACACATACTTTACCTATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

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368	E43	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCCGGCGGGTTC ATGCGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCAGGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
369	E44	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATTCCGAAGGT CCTTCTTATCAATATTACCGCATCACTTACGGCGAAAAAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGCTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGAGA ACGCATGAATTATTTTTCCAGCAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
370	E45	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACGACCCGACA TCTAATCTGTACAATTACAACCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
371	E46	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTGGGCTCG GTGGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCGTGACGTT CTGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGAAGCCT GACGGTCCACATATATACCAGGCAGTGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
372	E47	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAACCCTGCTTCT AAAGACTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCAGGTT CCGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTACAACCCGGCT ACTCATGAGTATAAATATGACTCGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
373	E48	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAGATCATCAGCA ACCGCCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCGTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTCAACTGGGCC ACTCATGAGTACATATACCACTCAACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
374	E49	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCATTCCGGTCCA CGAGAATATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCAGGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTCAACCCGATT ACACATTACTATTACTACGAGCTGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
375	E50	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACGGTGGGCCTG AGCGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGGTT TCTACAGCTACCATCAGCGGCCTTAAACCTAGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

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376	E51	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGGGGGGCACCGG GCGGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGCTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACTACAACCCGGAT ACTCATGAATACAAATACCATCAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
377	E52	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTTCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGTTCCGCGT CCGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACTGGTTCAAGGAA TACCGTGAAGACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
378	E53	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAGCGTCGGGGGC ATGATCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGGTT ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
379	E5	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTGGGCCCCCGTC GACCGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCGTGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
380	E5 (con cola Cys)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTGGGCCCCCGTC GACCGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCGTGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCACCACCAC CACCAC
381	E54	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAAAGCCAGCTAT ACCGGCTACAACTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCGTGACGTT ATGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTCTACAATCCGGAT ACTCATCAATACACATACCGTCGCATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
382	E55	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCGGTGGGCCAG GTCTTCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACTACAACCCGGCT ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
383	E56	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTACTCTGGTGAT TACCATTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GAAACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGGCT ACTCATTACTACAAGTACGAGCAGACACCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

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384	E57	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTTGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGATCGTCCAGGGG GGGCGCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGGTT ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCTTCA ACTCATGAATACAAATACCATCAGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
385	E58	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCGGCCGTCCGC TGGCGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTACAACCCGCGT ACTCATGTATACATATACGATCAGTTCCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
386	E59	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAGGGCCAGGCGC TTGCAGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGGTT ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTACAACCCGGCT ACTATGGAGTACACATATCAGCGGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
387	E60	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTTGCAGCCCCTC TGGAGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTCTG GACACAGCTACCATCAGCGGACTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGTT GACGGTCCCCATGCTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
388	E61	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCCTCCCAG GGGAACTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGCTGTT AAAACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTCAACCCGGCT ACTCATGAATACATATACCATACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
389	E62	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTGCCTCGACGGG CAGTTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTTCTATC GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTGGTACAACCTCGCG ACTCATGAATACAACTACCGTGTGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
390	E63	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACACTTCAGGT GCTTCATATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACTCTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACGACCCTGAT TCGCATTATTACAACTACAATATGGTTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
391	E64	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATTCTGGTAAT GGTACTTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACCGTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGGCT ACTCACGAATATACATACGAGCTGCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

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392	E65	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTACCACCCCCACCAGCCTGCTGATCAGCTGGCGGCCCACCAGC CAGGTCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACAACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTTAACTATGCT ACTCACGAATACATATACCATACCATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
393	E66	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAAGTCGTACGGG TCGGCCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGACCTG CAGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTATCACTGACTATTACAACCCGGAT ACACATGAGTATAAATACCATGTGTCGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
394	E67	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCGTCGGTGATG GGGTTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCTTCT ACTTATGAATACAAATACAATACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
495	E68	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAAAACAGAACCA GGCCGCCACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTGGTACAACCTGGTT TCTCATGAATACGTATACCATACTACCCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
395	E69	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCACGCCGGCATG GCGGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGACGTT CTGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTCAATCCGGTT ACTCATGAATACATGTATCATACGATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
396	E70	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGTGTCCGCGAGG GGGCGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCTAGAA ACTTATGAATATCATTACTATCGCACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
397	E71	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTGGTTCGGCACC TCGTCCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGACCTG AAAACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTTAACCCCGTT ACTCATGAATACGAATATCATACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
398	E72	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCCGCGACCCGG ACCCTGTACCAATATTACCGAATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT CATACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACATGGTT ACTTATGAATACAACTACCATCTTACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

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399	E73	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGTTGCCACCCCCACCAGCCTGCTGATCAGCTGGACCAAGTTGTTG GGCGGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCCTGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTCAACCCTCGT ACTCATGAATATCAATATCACACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
400	E74	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAGGGCGTCGGGC GGGCTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTTCTGTT AACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTACAACCCGGCT ACTTATGAGTACATATACCATACCACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
401	E75	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGCGGCCGGGCGC GCCACGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT ACTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTACAACCCGGCT ACTCATGAATACTACTATGAGACCACGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
402	E76	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTACTCGCAGCCC TTGACGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACGTT AACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTCTACAACCCGGAG ACACATGAATACACTTACCACCTGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
403	E77	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAGTTCTGCAACA AGACCTTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTCAACCCGACT ACGCACGAATACTATTATCATACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
404	E78	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCCGTCGAGAGG TCCGTGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGTCT ACTCATGAATACAATTACCTCACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
405	E79	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAAGATACCTCC AGTTATCATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTCAACCCGTCT ACCCATGAATACATCTACCGTACCATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
406	E80	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTAGCTCTCAT CGCCGCTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTTCGGTT GCTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTCAACCCAGAC ACTCATGAATACCTATACCATGCCACCCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

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407	E81	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATAATAATTCT AACTCATATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACCTG CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCTCATACT GAGGGTGAGCATACTTATCATGAATCGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
408	E82	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCGCGTGTTGGTC GACATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CTGACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGTT GACGGGCCGCACACCTACTATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
409	E83	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGATGTTCGTGGGG ATGTCCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGGTGTT CATACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTCAACCCGGCT ACGCATGAATACATCTACCATGTGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
410	E84	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACGCTGCACCGG AAGAACTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGGCA ACTCATGAATACGACTACCGAACAACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
411	E85	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTTCTGATCAGCTGGACACAAGGCAGT ACTCATTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTATGGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTCGACCGCTCT ACTCATGAGTATAAATACCGTACGACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
412	E4	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCACGAACGTGAC GGAAGTAGACAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTTAACCCGACT ACACATGAATACATATATCAGACAACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
413	E86	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACTCCGGTGAA AACAATTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGAAG ACTCATGAATATAATTATCTTACTATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
414	E87	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGGGAGCCCCTTG ATCGAGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTCTG TCTACAGCTACCATCAGCGGCCTCAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTCAACCCGGCT ACTCATGAATACACATACCATGTGAGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

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415	E88	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTGCAACAAAC AAAACTTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTTAACCCGACT ACACATGAATACATATATCAGACAACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
416	E89	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATGACCCAGCT GCAAACCGACAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACCTG CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTACAACCCGGCT ACCCATCAATACAAATACTCTCAGAGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
417	E90	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTACTGGGAGGGG CTGCCCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCGTGACGTT AACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTGGTACAACCCCGAC ACCCATGAGTATATATACCATACGATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
418	E91	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAGCGCGCCGTGG CGGACCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTAAACCCTAAC ACGCTTGAATACACCTACCAGCGCATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
419	E92	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAGGCGGCCAAC CACTCGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTTTTTCAATCCTGTC ACTCATGAATACAAATACCGTACAATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
420	E93	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATTCAGGACGA GGTTCCTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCACGCT GACGGTCCGCACACTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
421	E94	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGAATAACGGAGGA CGCAATTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCACGCT GACGGTCCGCACACTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
422	E95	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGTCGTGCCGCAG GGGATGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT TCTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATTTCAACCCGGCA ACCCATGAATACAATTATCATTCAATTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

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423	E96	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGCGAGCAACCGG GGGACGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT TCTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACGCTTTCAACCCAACT ACTCATGAATACAATTATTTTACAACTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
424	E97	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTTGCCGGGCAAG CTGAGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
425	E98	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCAACC TCCCGCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
426	E99	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCAACC TCCCGCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCACGCT GACGGTCCGCACACTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
427	E100	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACCCCTGCTAAT AAATCTTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
428	E101	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCGGCT GTTACTTACCAGTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
429	E102	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACCCCTGCTAAT AAATCTTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
430	E103	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGACCCCTGCTAAT AAATCTTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAACATGATGCATGTTGAA TACTCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC

SEC ID Nº	AGENTE DE UNIÓN	SECUENCIA DE NUCLEÓTIDOS
431	E104	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTGGTGCT GTTACTTACCAGTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GTTACACCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
432	E105	ATGGGACTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCAACC TCCCGCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTCTG TCCACACCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
433	E106	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCGGCT GTTACTTACCAGTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCACGCT GACGGTCCGCACACTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
434	E107	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATTCAGGACGA GGTTCCTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTTACGACGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACATGATGCATGTTGAA TACACTGAACATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
435	E108	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCGGCT GTTACTTACCAGTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
436	E109	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCAACC TCCCGGCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
437	E110	ATCGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTGGTGCT GTTACTTACCAGTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
438	E111	ATCGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTCCAACC TCCCGGCTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGACCTG GTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAACATGATGCATGTTGAA TACTTCCGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC

SEC ID Nº	AGENTE DE UNIÓN	SECUENCIA DE NUCLEÓTIDOS
439	E112	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGACGCTGGTGCT GTTACTTACCAGTATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTATAAACCGCACGCT GACGGTCCGCACACTTACCATGAATATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC
440	E113	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTATCCTGGCCAA CCAACATATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCATTGTGCCTTACCTGGTT TACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACTACGCTTACAAAGAA TACTCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCACCACCAC
441	E114	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGCAAAGTTCAACC AGCCAATATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTGGTGTT CGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCGCATGCT GACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCACCAC CACCAC

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Figura 48

SEC ID Nº	AGENTE DE UNIÓN	SEC DE ADN
442	E3-GS10-I1	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTTGCCGGGCA AGCTGAGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGA CCTGCGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAACATGATGCAT GTTGAATACTCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAAGGTAGCGGCTCTGGTTCCGGCAGCGGCT CCGGCAGCGGCTCTGGCAGCGGTTCTGGTTCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAG CCTGCTGATCAGCTGGTCTGCGCGTCTGAAAGTTGCGCGATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCT GTCCAGGAGTTCACTGTGCCTAAAAACGTTTACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTG TGTATGCTGTCACTAGGTTCCGCGACTACCAGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCA CCACCACCACCAC
443	I1-GS10-E3	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTGCGCGTC TGAAAGTTGCGCGATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTAAAAA CGTTTACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAGGTTCCGCGAC TACCAGCCAATTTCCATTAATTACCGCACAGAAATTGACAAAGGTAGCGGCTCTGGTTCCGGCAGCGGCTCCGGCAGCGGCT CTGGCAGCGGTTCTGGTTCCGTTCTGATGTGCCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAG CTGGTTGCCGGGCAAGCTGAGGTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTC ACTGTGCCTCATGACCTGCGTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCA CTAACATGATGCATGTTGAATACTCTGAATACCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCA CCACCACCACCAC
444	E1-GS10-I1	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGTGGCCGGGG CGGAGGACTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTCATGA CCTGGTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACATGATGCAT GTTGAATACACTGAACATCCAATTTCCATTAATTACCGCACAGAAATTGACAAAGGTAGCGGCTCTGGTTCCGGCAGCGGCT CCGGCAGCGGCTCTGGCAGCGGTTCTGGTTCCGTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAG CCTGCTGATCAGCTGGTCTGCGCGTCTGAAAGTTGCGCGATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCT GTCCAGGAGTTCACTGTGCCTAAAAACGTTTACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTG TGTATGCTGTCACTAGGTTCCGCGACTACCAGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCA CCACCACCACCAC
445	I1-GS10-E1	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTGCGCGTC TGAAAGTTGCGCGATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTAAAAA CGTTTACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAGGTTCCGCGAC TACCAGCCAATTTCCATTAATTACCGCACAGAAATTGACAAAGGTAGCGGCTCTGGTTCCGGCAGCGGCTCCGGCAGCGGCT CTGGCAGCGGTTCTGGTTCCGTTCTGATGTGCCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAG CTGGGTGGCCGGGCGGAGGACTACCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTC ACTGTGCCTCATGACCTGGTTACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCA CTGACATGATGCATGTTGAATACACTGAACATCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCA CCACCACCACCAC

SEC ID Nº	AGENTE DE UNIÓN	SEC DE ADN
446	E2-GS10-I1	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGGATTCAGGAC GAGGTTCCTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTCC GGTTCATACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTGACCATAAACCG CATGCTGACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAAAGGTAGCGGCTCTG GTTCCGGCAGCGGCTCCGGCAGCGGCTCTGGCAGCGGTTCTGGTTCCGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGC TGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTGCGCGTCTGAAAGTTGCGCGATATTACCGCATCACTTACGGCGAAACA GGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTAAAAACGTTTACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTG ATTATACCATCACTGTGTATGCTGTCACTAGGTTCCGCGACTACCAGCCAATTTCCATTAATTACCGCACAGAAATTGACAA ACCATGCCAGCACCACCACCACCACCAC
447	I1-GS10-E2	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAGCTGGTCTGCGCGTC TGAAAGTTGCGCGATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTAAAAA CGTTTACACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCACTAGGTTCCGCGAC TACCAGCCAATTTCCATTAATTACCGCACAGAAATTGACAAAGGTAGCGGCTCTGGTTCCGGCAGCGGCTCCGGCAGCGGCT CTGGCAGCGGTTCTGGTTCCGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGATCAG CTGGGATTCAGGACGAGGTTCCTATCAATATTACCGCATCACTTACGGCGAAACAGGAGGCAATAGCCCTGTCCAGGAGTTC ACTGTGCCTGGTCCGGTTCATACAGCTACCATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCA CTGACCATAAACCGCATGCTGACGGTCCGCATACTTACCATGAATCTCCAATTTCCATTAATTACCGCACAGAAATTGACAA ACCATGCCAGCACCACCACCACCACCAC
448	E5-GS10-I1	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAGGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTTCTTGGTGGGCACCGG TTGATCGTTATCAGTATTATCGCATCACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCTCGCGA CGTTTATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTACGCCGTTACCGATTATAAACCG CATGCAGATGGTCCGCATACCTATCATGAAAGCCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCG GTTCAGGTAGCGGATCAGGTTCTGGTTCTGGTAGTGGTAGCGGCAGCGTTTCAGATGTGCCTCGCGACCTGGAAGTGGTGGC AGCCACACCGACTTCTCTGCTGATTAGCTGGTCTGCACGTCTGAAAGTTGCCCGTTATTACCGTATTACTTATGGCGAAACA GGCGGAAATAGCCCTGTGCAAGAATTTACCGTGCCGAAAAATGTGTACACAGCCACCATCTCTGGCCTGAAACCTGGCGTGG ACTACACAATCACAGTTTATGCAGTGACCCGTTTTCGTGATTATCAGCCGATCAGCATCAATTATCGTACAGAGATCGATAA ACCGTGCCAGCATCACCACCATCATCAC
449	E85-GS10-I1	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAGGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTTCTTGGACCCAGGGTA GCACACATTATCAGTATTATCGCATCACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCTGGTAT GGTTTATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTACGCCGTTACCGATTATTTCGAT CGGTCCACCCATGAATATAAATATCGGACCACCCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCG GTTCAGGTAGCGGATCAGGTTCTGGTTCTGGTAGTGGTAGCGGCAGCGTTTCAGATGTGCCTCGCGACCTGGAAGTGGTGGC AGCCACACCGACTTCTCTGCTGATTAGCTGGTCTGCACGTCTGAAAGTTGCCCGTTATTACCGTATTACTTATGGCGAAACA GGCGGAAATAGCCCTGTGCAAGAATTTACCGTGCCGAAAAATGTGTACACAGCCACCATCTCTGGCCTGAAACCTGGCGTGG ACTACACAATCACAGTTTATGCAGTGACCCGTTTTCGTGATTATCAGCCGATCAGCATCAATTATCGTACAGAGATCGATAA ACCGTGCCAGCATCACCACCATCATCAC

SEC ID Nº	AGENTE DE UNIÓN	SEC DE ADN
450	E4-GS10-I1	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAGGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTTCTTGGCATGAACGTG ATGGTAGCCGTCAGTATTATCGCATCACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCTGGCGG TGTTCGTACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTACGCCGTTACCGATTATTTCAAT CCGACCACCCATGAATATATTTATCAGACCACCCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCG GTTCAGGTAGCGGATCAGGTTCTGGTTCTGGTAGTGGTAGCGGCAGCGTTTCAGATGTGCCTCGCGACCTGGAAGTGGTGGC AGCCACACCGACTTCTCTGCTGATTAGCTGGTCTGCACGTCTGAAAGTTGCCCGTTATTACCGTATTACTTATGGCGAAACA GGCGGAAATAGCCCTGTGCAAGAATTTACCGTGCCGAAAAATGTGTACACAGCCACCATCTCTGGCCTGAAACCTGGCGTGG ACTACACAATCACAGTTTATGCAGTGACCCGTTTTCGTGATTATCAGCCGATCAGCATCAATTATCGTACAGAGATCGATAA ACCGTGCCAGCATCACCACCATCATCAC
451	E90-GS10-I1	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAGGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTTCTTGGTATTGGGAAG GTCTGCCGTATCAGTATTATCGCATCACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTCACCGTTCCTCGCGA CGTTAATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTACGCCGTTACCGATTGGTACAAC CCTGATACCCATGAATATATTTATCATACCATTCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCG GTTCAGGTAGCGGATCAGGTTCTGGTTCTGGTAGTGGTAGCGGCAGCGTTTCAGATGTGCCTCGCGACCTGGAAGTGGTGGC AGCCACACCGACTTCTCTGCTGATTAGCTGGTCTGCACGTCTGAAAGTTGCCCGTTATTACCGTATTACTTATGGCGAAACA GGCGGAAATAGCCCTGTGCAAGAATTTACCGTGCCGAAAAATGTGTACACAGCCACCATCTCTGGCCTGAAACCTGGCGTGG ACTACACAATCACAGTTTATGCAGTGACCCGTTTTCGTGATTATCAGCCGATCAGCATCAATTATCGTACAGAGATCGATAA ACCGTGCCAGCATCACCACCATCATCAC
452	E96-GS10-I1	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAGGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTTCTTGGGCAAGCAATC GTGGCACCTATCAGTATTATCGCATCACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCTGGCGG TGTTTCTACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTACGCCGTTACCGATGCATTTAAT CCGACCACCCATGAATATAATTATTTTACCACCCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCG GTTCAGGTAGCGGATCAGGTTCTGGTTCTGGTAGTGGTAGCGGCAGCGTTTCAGATGTGCCTCGCGACCTGGAAGTGGTGGC AGCCACACCGACTTCTCTGCTGATTAGCTGGTCTGCACGTCTGAAAGTTGCCCGTTATTACCGTATTACTTATGGCGAAACA GGCGGAAATAGCCCTGTGCAAGAATTTACCGTGCCGAAAAATGTGTACACAGCCACCATCTCTGGCCTGAAACCTGGCGTGG ACTACACAATCACAGTTTATGCAGTGACCCGTTTTCGTGATTATCAGCCGATCAGCATCAATTATCGTACAGAGATCGATAA ACCGTGCCAGCATCACCACCATCATCAC
453	E105-GS10-I1	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAGGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTTCTTGGGATGCACCGA CCTCTCGTTATCAGTATTATCGCATCACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCTGGCGG TCTGAGCACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTACGCCGTTACCGATTATAAACCG CATGCAGATGGTCCGCATACCTATCATGAAAGCCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCG GTTCAGGTAGCGGATCAGGTTCTGGTTCTGGTAGTGGTAGCGGCAGCGTTTCAGATGTGCCTCGCGACGTGGAAGTGGTGGC AGCCACACCGACTTCTCTGCTGATTAGCTGGTCTGCACGTCTGAAAGTTGCCCGTTATTACCGTATTACTTATGGCGAAACA GGCGGAAATAGCCCTGTGCAAGAATTTACCGTGCCGAAAAATGTGTACACAGCCACCATCTCTGGCCTGAAACCTGGCGTGG ACTACACAATCACAGTTTATGCAGTGACCCGTTTTCGTGATTATCAGCCGATCAGCATCAATTATCGTACAGAGATCGATAA ACCGTGCCAGCATCACCACCATCATCAC

SEC ID Nº	AGENTE DE UNIÓN	SEC DE ADN
454	E112-GS10-I1	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAGGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTTCTTGGGATGCAGGTG CAGTTACCTATCAGTATTATCGCATCACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCTGGCGG TGTTCGTACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTACGCCGTTACCGATTATAAACCG CATGCAGATGGTCCGCATACCTATCATGAATATCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCG GTTCAGGTAGCGGATCAGGTTCTGGTTCTGGTAGTGGTAGCGGCAGCGTTTCAGATGTGCCTCGCGACCTGGAAGTGGTGGC AGCCACACCGACTTCTCTGCTGATTAGCTGGTCTGCACGTCTGAAAGTTGCCCGTTATTACCGTATTACTTATGGCGAAACA GGCGGAAATAGCCCTGTGCAAGAATTTACCGTGCCGAAAAATGTGTACACAGCCACCATCTCTGGCCTGAAACCTGGCGTGG ACTACACAATCACAGTTTATGCAGTGACCCGTTTTCGTGATTATCAGCCGATCAGCATCAATTATCGTACAGAGATCGATAA ACCGTGCCAGCATCACCACCATCATCAC
455	I1-GS10-E5	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAAGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTAGCTGGTCTGCACGTC TGAAAGTTGCCCGTTATTATCGCATTACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCGAAAAA TGTTTATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTATGCAGTTACCCGTTTTCGTGAT TATCAGCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCGGTTCTGGTAGCGGTTCAGGTTCTGGTT CTGGTAGTGGTAGCGGCAGCGTTTCAGACGTGCCTCGTGATTTAGAAGTGGTGGCAGCCACACCGACCTCACTGCTGATTTC TTGGTGGGCACCGGTTGATCGTTATCAGTATTATCGCATCACATACGGCGAAACAGGCGGAAATAGCCCTGTGCAAGAATTC ACCGTACCGCGTGATGTGTATACCGCCACAATTTCTGGTTTAAAACCTGGCGTGGACTACACAATCACAGTTTATGCCGTGA CCGATTATAAACCGCATGCAGATGGTCCGCATACCTATCATGAAAGCCCGATCTCTATCAATTATCGCACAGAGATCGATAA ACCGTGTCAGCATCACCACCATCATCAC
456	I1-GS10-E85	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAAGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTAGCTGGTCTGCACGTC TGAAAGTTGCCCGTTATTATCGCATTACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCGAAAAA TGTTTATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTATGCAGTTACCCGTTTTCGTGAT TATCAGCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCGGTTCTGGTAGCGGTTCAGGTTCTGGTT CTGGTAGTGGTAGCGGCAGCGTTTCAGACGTGCCTCGTGATTTAGAAGTGGTGGCAGCCACACCGACCTCACTGCTGATTTC TTGGACCCAGGGTAGCACACATTATCAGTATTATCGCATCACATACGGCGAAACAGGCGGAAATAGCCCTGTGCAAGAATTC ACCGTACCGGGTATGGTGTATACCGCCACAATTTCTGGTTTAAAACCTGGCGTGGACTACACAATCACAGTTTATGCCGTGA CCGATTATTTCGATCGCAGCACCCATGAATATAAATATCGTACCACCCCGATCTCTATCAATTATCGCACAGAGATCGATAA ACCGTGTCAGCATCACCACCATCATCAC
457	I1-GS10-E4	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAAGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTAGCTGGTCTGCACGTC TGAAAGTTGCCCGTTATTATCGCATTACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCGAAAAA TGTTTATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTATGCAGTTACCCGTTTTCGTGAT TATCAGCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCGGTTCTGGTAGCGGTTCAGGTTCTGGTT CTGGTAGTGGTAGCGGCAGCGTTTCAGACGTGCCTCGTGATTTAGAAGTGGTGGCAGCCACACCGACCTCACTGCTGATTTC TTGGCATGAACGTGATGGTAGCCGTCAGTATTATCGCATCACATACGGCGAAACAGGCGGAAATAGCCCTGTGCAAGAATTC ACCGTACCGGGTGGTGTTCGTACCGCCACAATTTCTGGTTTAAAACCTGGCGTGGACTACACAATCACAGTTTATGCCGTGA CCGATTATTTCAATCCGACCACCCACGAATATATTTATCAGACCACCCCGATCTCTATCAATTATCGCACAGAGATCGATAA ACCGTGTCAGCATCACCACCATCATCAC

SEC ID Nº	AGENTE DE UNIÓN	SEC DE ADN
458	I1-GS10-E105	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAAGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTAGCTGGTCTGCACGTC TGAAAGTTGCCCGTTATTATCGCATTACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCGAAAAA TGTTTATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTATGCAGTTACCCGTTTTCGTGAT TATCAGCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCGGTTCTGGTAGCGGTTCAGGTTCTGGTT CTGGTAGTGGTAGCGGCAGCGTTTCAGACGTGCCTCGTGATTTAGAAGTGGTGGCAGCCACACCGACCTCACTGCTGATTTC TTGGGATGCACCGACCAGCCGTTATCAGTATTATCGCATCACATACGGCGAAACAGGCGGAAATAGCCCTGTGCAAGAATTC ACCGTACCGGGTGGTCTGAGCACCGCCACAATTTCTGGTTTAAAACCTGGCGTGGACTACACAATCACAGTTTATGCCGTGA CCGATTATAAACCGCATGCAGATGGTCCGCATACCTATCATGAAAGCCCGATCTCTATCAATTATCGCACAGAGATCGATAA ACCGTGTCAGCATCACCACCATCATCAC
459	I1-GS10-E112	ATGGGTGTTTCTGATGTTCCGCGTGATCTGGAAGTTGTTGCAGCAACCCCGACCAGCCTGCTGATTAGCTGGTCTGCACGTC TGAAAGTTGCCCGTTATTATCGCATTACCTATGGTGAAACCGGTGGTAATTCTCCGGTTCAGGAATTTACCGTTCCGAAAAA TGTTTATACCGCAACCATTAGCGGTCTGAAACCGGGTGTTGATTACACCATTACCGTTTATGCAGTTACCCGTTTTCGTGAT TATCAGCCGATTAGCATTAACTATCGCACCGAAATTGATAAAGGTAGCGGTAGCGGTTCTGGTAGCGGTTCAGGTTCTGGTT CTGGTAGTGGTAGCGGCAGCGTTTCAGACGTGCCTCGTGATTTAGAAGTGGTGGCAGCCACACCGACCTCACTGCTGATTTC TTGGGATGCCGGTGCAGTTACCTATCAGTATTATCGCATCACATACGGCGAAACAGGCGGAAATAGCCCTGTGCAAGAATTC ACCGTACCGGGTGGTGTTCGTACCGCCACAATTTCTGGTTTAAAACCTGGCGTGGACTACACAATCACAGTTTATGCCGTGA CCGATTATAAACCGCATGCAGATGGTCCGCATACCTATCATGAATATCCGATCTCTATCAATTATCGCACAGAGATCGATAA ACCGTGTCAGCATCACCACCATCATCAC
460	I1-GSGCGS8-E5	ATGGGCGTGAGTGATGTTCCGCGTGATCTGGAAGTGGTTGCAGCAACCCCGACGAGCCTGCTGATTAGCTGGTCTGCCCGCC TGAAAGTGGCACGTTATTACCGCATCACCTACGGCGAAACGGGCGGTAACTCTCCGGTTCAGGAATTTACCGTGCCGAAAAA TGTTTATACCGCAACGATTAGCGGCCTGAAACCGGGTGTGGATTATACCATCACGGTGTACGCGGTTACCCGTTTCCGCGAT TACCAGCCGATTAGCATCAACTATCGTACGGAAATTGAAAAAGGCTCTGGTTGCGGCAGTGGTAGCGGCTCTGGTAGTGGCA GCGGTTCTGGCAGTGGTAGCGTGTCTGACGTCCCGCGCGACCTGGAAGTTGTTGCAGCGACCCCGACCAGCCTGCTGATTAG TTGGTGGGCCCCGGTGGATCGTTACCAGTATTACCGCATCACCTATGGCGAAACCGGTGGTAACAGCCCGGTGCAAGAATTT ACCGTGCCGCGTGATGTTTATACCGCGACCATCTCTGGTCTGAAACCGGGCGTTGACTACACGATTACCGTTTACGCGGTTA CCGATTATAAACCGCATGCCGATGGTCCGCATACGTACCACGAAAGTCCGATTAGCATCAATTATCGGACCGAACATCACCA TCACCATCAC
461	I1-GS10-E5-GSGC	ATGGGCGTGTCTGATGTTCCGCGTGATCTGGAAGTGGTTGCGGCCACCCCGACGAGTCTGCTGATTAGCTGGTCTGCCCGCC TGAAAGTGGCACGTTATTACCGCATCACCTACGGCGAAACGGGCGGTAACAGCCCGGTTCAGGAATTTACCGTGCCGAAAAA TGTTTATACCGCAACGATTTCTGGCCTGAAACCGGGTGTGGATTATACCATCACGGTGTACGCGGTTACCCGTTTCCGCGAT TACCAGCCGATTAGCATCAACTATCGTACGGAAATTGAAAAAGGCAGTGGTAGCGGCTCTGGTAGTGGCAGCGGTTCTGGCA GTGGTAGCGGCTCTGGTAGTGTAAGCGACGTCCCGCGCGATCTGGAAGTGGTTGCAGCGACCCCGACGAGCCTGCTGATTTC TTGGTGGGCCCCGGTGGATCGTTACCAGTATTACCGCATCACCTATGGCGAAACCGGTGGCAATTCTCCGGTGCAAGAATTC ACCGTGCCGCGTGATGTTTATACCGCGACGATTAGCGGTCTGAAACCGGGCGTTGACTACACGATTACCGTGTACGCGGTTA CCGATTATAAACCGCATGCCGATGGTCCGCATACGTACCACGAATCTCCGATTAGTATCAATTATCGGACCGAAGGCAGTGG TTGCCATCACCATCACCATCAC

SEC ID Nº	AGENTE DE UNIÓN	SEC DE ADN
462	I1(S62C)-GS10-E5	ATGGGCGTGAGTGATGTTCCGCGTGATCTGGAAGTGGTTGCAGCAACCCCGACGAGCCTGCTGATTAGCTGGTCTGCCCGCC TGAAAGTGGCACGTTATTACCGCATCACCTACGGCGAAACGGGCGGTAACAGCCCGGTTCAGGAATTTACCGTGCCGAAAAA TGTTTATACCGCAACGATTTGCGGCCTGAAACCGGGTGTGGATTATACCATCACGGTGTACGCGGTTACCCGTTTCCGCGAT TACCAGCCGATTAGCATCAACTATCGTACGGAAATTGAAAAAGGCAGTGGTAGCGGCTCTGGTAGTGGCAGCGGTTCTGGCA GTGGTAGCGGCTCTGGTAGTGTAAGCGACGTCCCGCGCGACCTGGAAGTTGTTGCAGCGACGCCGACGAGCCTGCTGATCTC TTGGTGGGCCCCGGTGGATCGTTACCAGTATTACCGCATCACCTATGGCGAAACCGGTGGTAACTCTCCGGTGCAAGAATTT ACCGTGCCGCGTGATGTTTATACCGCGACGATTTCTGGTCTGAAACCGGGCGTTGACTACACGATTACCGTTTACGCGGTTA CCGATTATAAACCGCATGCCGATGGTCCGCATACGTACCACGAATCTCCGATTAGTATCAATTATCGGACCGAACATCACCA TCACCATCAC
463	I1-GS10-E5(S62C)	ATGGGCGTGAGTGATGTTCCGCGTGATCTGGAAGTGGTTGCAGCAACCCCGACGAGCCTGCTGATTAGCTGGTCTGCCCGCC TGAAAGTGGCACGTTATTACCGCATCACCTACGGCGAAACGGGCGGTAACTCTCCGGTTCAGGAATTTACCGTGCCGAAAAA TGTTTATACCGCAACGATTAGCGGCCTGAAACCGGGTGTGGATTATACCATCACGGTGTACGCGGTTACCCGTTTCCGCGAT TACCAGCCGATTAGCATCAACTATCGTACGGAAATTGAAAAAGGCAGTGGTAGCGGCTCTGGTAGTGGCAGCGGTTCTGGCA GTGGTAGCGGCTCTGGTAGTGTAAGCGACGTCCCGCGCGACCTGGAAGTTGTTGCAGCGACGCCGACGAGCCTGCTGATCTC TTGGTGGGCCCCGGTGGATCGTTACCAGTATTACCGCATCACCTATGGCGAAACCGGTGGTAACAGCCCGGTGCAAGAATTT ACCGTGCCGCGTGATGTTTATACCGCGACGATTTGTGGTCTGAAACCGGGCGTTGACTACACGATTACCGTTTACGCGGTTA CCGATTATAAACCGCATGCCGATGGTCCGCATACGTACCACGAATCTCCGATTAGTATCAATTATCGGACCGAACATCACCA TCACCATCAC
464	I1(S91C)-GS10-E5	ATGGGCGTGAGTGATGTTCCGCGTGATCTGGAAGTGGTTGCAGCAACCCCGACGAGCCTGCTGATTAGCTGGTCTGCCCGCC TGAAAGTGGCACGTTATTACCGCATCACCTACGGCGAAACGGGCGGTAACTCTCCGGTTCAGGAATTTACCGTGCCGAAAAA TGTTTATACCGCAACGATTAGCGGCCTGAAACCGGGTGTGGATTATACCATCACGGTGTACGCGGTTACCCGTTTCCGCGAT TACCAGCCGATTTGCATCAACTATCGTACGGAAATTGAAAAAGGCAGTGGTAGCGGCTCTGGTAGTGGCAGCGGTTCTGGCA GTGGTAGCGGCTCTGGTAGTGTAAGCGACGTCCCGCGCGACCTGGAAGTTGTTGCAGCGACGCCGACGAGCCTGCTGATCTC TTGGTGGGCCCCGGTGGATCGTTACCAGTATTACCGCATCACCTATGGCGAAACCGGTGGTAACAGCCCGGTGCAAGAATTT ACCGTGCCGCGTGATGTTTATACCGCGACCATCTCTGGTCTGAAACCGGGCGTTGACTACACGATTACCGTTTACGCGGTTA CCGATTATAAACCGCATGCCGATGGTCCGCATACGTACCACGAATCTCCGATTAGTATCAATTATCGGACCGAACATCACCA TCACCATCAC
465	I1-GS10-E5(S91C)	ATGGGCGTGAGCGATGTTCCGCGTGATCTGGAAGTGGTTGCAGCAACCCCGACCAGCCTGCTGATTAGCTGGTCTGCCCGCC TGAAAGTGGCACGTTATTACCGCATCACCTACGGCGAAACGGGCGGTAACAGTCCGGTTCAGGAATTTACCGTGCCGAAAAA TGTTTATACCGCAACGATTAGCGGCCTGAAACCGGGTGTGGATTATACCATCACGGTGTACGCGGTTACCCGTTTCCGCGAT TACCAGCCGATTAGCATCAACTATCGTACGGAAATTGAAAAAGGCAGTGGTAGCGGCTCTGGTAGTGGCAGCGGTTCTGGCA GTGGTAGCGGCTCTGGTAGTGTAAGCGACGTCCCGCGCGACCTGGAAGTTGTTGCAGCGACGCCGACCAGCCTGCTGATCAG TTGGTGGGCCCCGGTGGATCGTTACCAGTATTACCGCATCACCTATGGCGAAACCGGTGGTAACAGCCCGGTGCAAGAATTC ACCGTGCCGCGTGATGTTTATACCGCGACCATCTCTGGTCTGAAACCGGGCGTTGACTACACGATTACCGTTTACGCGGTTA CCGATTATAAACCGCATGCCGATGGTCCGCATACGTACCACGAAAGCCCGATTTGCATCAATTATCGGACCGAACATCACCA TCACCATCAC

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-064214- -00000-0000
Fecha: 2011-05-24 17:24:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1286

PATENTE DE INVENCIÓN ☐ **MODELO DE UTILIDAD** ☐ **Art 33 Decisión 486/00**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☐ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Prosperidad para todos

Bogotá D.C.,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO
Apoderado(a) y/o Representante de
BRISTOL - MYERS SQUIBB COMPANY

REFERENCIA	Radicación No.	11 064214
	Solicitud internacional	PCT/US2009/065765
	Fecha inicio fase nacional	24/06/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	№ 12407

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. Con respecto al resumen y de conformidad con lo dispuesto en el artículo 31 D. 486 en el cual se establece que el resumen consiste en una síntesis de la divulgación técnica contenida en la solicitud de patente, debe adecuar el resumen a los dispuesto en dicha norma, teniendo en cuenta que el extracto permitirá precisar el objeto de la invención, sus elementos característicos y el campo de aplicación.

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se consideraró abandonada y perderá su prelación.

Continua en la página siguiente...

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5 , 7 y 10 PBX: 5870000
Sede CAN: Av. Cra 50 No. 26-55 int. 2 Tel: 5880070
Call Center 5920400. Línea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (C)

11 AGO. 2011

El anterior requerimiento fue notificado por fijación en lista de fecha_____.
adpa11