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CARRERA 7 # 71 – 21 TORRE B – PISO 4
BOGOTÁ – COLOMBIA
TEL. (571) 744 22 00
FAX. (571) 742 22 00
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E S D

RESPUESTA A OFICIO 4663 DE 20 ABRIL 2007

REF Expediente No 07 021 258 - Solicitud de Patente FASE NACIONAL Corresp a la Solicitud Internacional PCT/US2005/031401
a favor de **GENENTECH, INC**
Titulada ANTAGONISTAS ANTIBETA7 HUMANIZADOS Y USOS PARA ESTOS

JUAN PABLO CADENA SARMIENTO, vecino de Bogotá, portador de la tarjeta profesional No 57492, obrando como apoderado de la sociedad **GENENTECH, INC**, según lo acredita el documento de Poder presentado en esa División, para dar cumplimiento al requerimiento notificado por fijación en lista el 20 de abril de 2007 y de acuerdo con los Artículos 38 y 39 de la Decisión 486 de la Comisión de la Comunidad Andina, Artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Unica de la SIC, me permito anexar al presente escrito los siguientes documentos

1 Documento donde consta la cesión del derecho a la Patente otorgado por los inventores al solicitante, debidamente apostillado, junto con su correspondiente traducción al castellano

2 Reporte de Examen Preliminar Internacional sobre la Patentabilidad (Formas PCT/IB/373 y PCT/ISA/237)

3 Extracto para publicación y Tarjeta de Archivo Temático

De la señora jefe atentamente,

JUAN PABLO CADENA SARMIENTO
C C No 80 410 337 de Usaquén
Cra 7 No 71-21, Torre B, Piso 4

Bogotá, 8 de junio de 2007
CHP/MEVaac

5897

Industria y Comercio
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO TEMÁTICO

PATENTE DE INVENCION _X_ PCT _X_ MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) N° de solicitud 07 021258 (22) Fecha de solicitud 02-03-2007
(51) Clasificación Internacional

(71)Solicitante(s) GENENTECH INC

(72) Inventor(es Mark S. DENNIS Sherman FONG

(74) Agente JUAN PABLO CADENA SARMIENTO

(30) Prioridad	(31) No Prioridad	(32) Fecha	(33) País
	60/607,377	03-09-2004	US

FIGURA CARACTERISTICA
6 x 6 cm

(85) Fecha inicio fase nacional 03-04-2007
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud 02-09-2005
No de solicitud PCT/US2005/031401

(87) Publicación internacional
Fecha. 09-03-2006
No Publicación WO/2006/026759 A3

(54) Título **ANTAGONISTAS ANTI-BETA7 HUMANIZADOS Y USOS PARA ESTOS**

(57) Reivindicación(es)

1 Un polipéptido o anticuerpo de unión anti-beta7 que comprende

(a) Al menos una secuencia HVR seleccionada del grupo que consiste de
(i) HVR L1 que comprende las secuencias A1-A11 en donde A1-A11 es RASESVDTYLH (SEQ ID NO:1)
(ii) HVR-L2 que comprende la secuencia B1 B8 en donde B1 B8 es KYASQSIS (SEQ ID NO:2)
(iii) HVR-L3 que comprende la secuencia C1 C10 en donde C1 C10 es QQGNSLLPNT (SEQ ID NO 3)
(iv) HVR-H1 que comprende la secuencia D1 D10, en donde D1 D10 es GFFITNNYWG (SEQ ID NO:4)
(v) HVR-H2 que comprende la secuencia E1-E17, en donde E1-E17 es GYISYSGSTSYNPSLKS (SEQ ID NO 5)
(vi) HVR-H3 que comprende la secuencia F1-F11 en donde F1 F11 es MTGSSGYFDF (SEQ ID NO:6)

CONTINUA AL RESPALDO

26 Un anticuerpo anti-beta7 humanizado o fragmento de unión beta7 de este, en donde la afinidad monovalente del anticuerpo al fragmento de unión al beta7 humano es sustancialmente el mismo o mayor que la afinidad monovalente de un anticuerpo que comprende las secuencias variables de cadena ligera y cadena pesada como se describió en la Fig 1A (SEQ ID NO:10) y/o la Fig 1B (SEQ ID NO:11), o la Fig 9A (SEQ ID NO:12) y/o la Fig 9B (SEQ ID NO:13)

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

(21) N° de solicitud 07 021 258 22) Fecha de solicitud 02-03-2007 (30) Prioridad (31) No Prioridad (32) Fecha (33) País 60/607,377 03-09-2004 US	(51) Int Cl (71)Solicitante(s) GENENTECH INC (72) Inventor(es) Mark S DENNIS, Sherman FONG (74) Agente JUAN PABLO CADENA SARMIENTO
(85) Fecha inicio fase nacional 03-04-2007 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud 02-09-2005 No de solicitud PCT/US2005/031401	(87) Publicación internacional Fecha 09-03-2006 N° publicación WO/2006/026759 A3
(54) Título **ANTAGONISTAS ANTI-BETA7 HUMANIZADOS Y USOS PARA ESTOS**	

Reivindicación(es)

1 Un polipéptido o anticuerpo de unión anti-beta7 que comprende

(a) Al menos una secuencia HVR seleccionada del grupo que consiste de

(i) HVR-L1 que comprende las secuencias A1-A11 en donde A1-A11 es RASESVDTYLH (SEQ ID NO 1)

(ii) HVR-L2 que comprende la secuencia B1 B8 en donde B1-B8 es KYASQSIS (SEQ ID NO 2)

(iii) HVR-L3 que comprende la secuencia C1 C10 en donde C1-C10 es QQGNSLLPNT (SEQ ID NO 3)

(iv) HVR-H1 que comprende la secuencia D1-D10, en donde D1 D10 es GFFITNNYWG (SEQ ID NO 4)

(v) HVR-H2 que comprende la secuencia E1 E17 en donde E1-E17 es GYISYSGSTSYNPSLKS (SEQ ID NO 5)

(vi) HVR-H3 que comprende la secuencia F1 F11 en donde F1 F11 es MTGSSGYFDF (SEQ ID NO 6)

26 Un anticuerpo anti-beta7 humanizado o fragmento de unión beta7 de este, en donde la afinidad monovalente del anticuerpo al fragmento de unión al beta7 humano es sustancialmente el mismo o mayor que la afinidad monovalente de un anticuerpo que comprende las secuencias variables de cadena ligera y cadena pesada como se describió en la Fig 1A (SEQ ID NO 10) y/o la Fig 1B (SEQ ID NO 11) o la Fig 9A (SEQ ID NO 12) y/o la Fig 9B (SEQ ID NO 13)

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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

CONLEY Deirdre L.
MS 49
1 DNA Way
South San Francisco, California 94080
ETATS-UNIS D AMERIQUE

Date of mailing *(day/month/year)* 15 March 2007 (15.03.2007)	
Applicant's or agent's file reference P2159R1	IMPORTANT NOTICE

International application No	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/031401	02 September 2005 (02.09.2005)	03 September 2004 (03.09.2004)

Applicant
GENENTECH, INC et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer
Beate Giffo-Schmitt

e-mail: pt03.pct@wipo.int

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference P2159R1	FOR FURTHER ACTION	See Item 4 below
International application No. PCT/US2005/031401	International filing date (*day/month/year*) 02 September 2005 (02.09.2005)	Priority date (*day/month/year*) 03 September 2004 (03.09.2004)
International Patent Classification (IPC) (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant GENENTECH INC		

1 This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- ☒ Box No. I — Basis of the report
- ☐ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

4 The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis*.2).

	Date of issuance of this report 06 March 2007 (06.03.2007)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Beate Giffo-Schmitt
Facsimile No. +41 22 338 82 70	e-mail pt03.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/031401	02.09.2005	03.09.2004

International Patent Classification (IPC) or both national classification and IPC
INV C07K16/28 A61K39/395 C07K16/18

Applicant
GENENTECH, INC

1 This opinion contains indications relating to the following items

- ☒ Box No I Basis of the opinion
- ☐ Box No II Priority
- ☒ Box No III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No VII Certain defects in the international application
- ☐ Box No VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA.	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Inon, A Telephone No. +49 89 2399-8174

Form PCT/ISA/237 (Cover Sheet) (April 2005)

WRITTEN PINI N F THE INTERNATIONAL SEARCHING AUTH RITY

International application No.
PCT/US2005/031401

S979

Box No. I Basis of the opinion

1 With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b))

2 With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☒ on paper

☒ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed

☐ filed together with the international application in electronic form

☒ furnished subsequently to this Authority for the purposes of search

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4 Additional comments

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Box No III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos 2,3,5-50

because

☒ the said international application, or the said claims Nos. 35-48 (IA) relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☒ the description claims or drawings *(indicate particular elements below)* or said claims Nos. 2,3,5-50 (N.IS, IA) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing, the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter* 1(a) or (b)

☐ a meaningful opinion could not be formed without the tables related to the sequence listings, the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

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Box No V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement

1 Statement

Novelty (N)	Yes	Claims	3,9-35
	No	Claims	1,2,4-8,36-50
Inventive step (IS)	Yes	Claims	
	No	Claims	1-50
Industrial applicability (IA)	Yes	Claims	1-35,49,50
	No	Claims	

2 Citations and explanations

see separate sheet

Box No VI Certain documents cited

1 Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Item I

I 1 The sequence listing pages 1-13 filed with letter of 24 04.2006 do not form part of the application (Rule 13ter 1(f) PCT)

Item III

IIL1 With respect to claims 2, 3, 5-25, 36-50

The polypeptides or antibodies of claims 2, 3, 5-25, 36-50 are defined by comprising "at least one variant HVR, wherein the variant HVR comprises modification of at least one residue of any of the sequences depicted in SEQ ID NO 1, 2, 3, 4, 5, or 6" Therefore, claims 2, 3, 5-25 relate to an extremely large number of possible molecules and are unclear within the meaning of Article 6 PCT In order to determine the scope of the claims the skilled person would have to test all known and yet unknown antibodies on their binding activity to beta7 and further identify the CDR sequences As this screening program represents certainly an undue burden, the scope of claims 2, 3, 5-25 is not clear In the present case, the claims so lack clarity, that a meaningful search over the whole of the claimed scope is impossible Consequently, the search, and thus the examination, has been carried out for those parts of the claims which in view of the application as a whole appear to be clear, namely those parts relating to anti-beta7 antibodies in general and anti-beta7 antibodies comprising the CDRs as referred to SEQ ID NO 1-9, and 63-68 Same applies to claims 36-50 referring to the antibodies of the claims cited above

III 2 With respect to claims 26-50

Claims 26-35 relate to a humanized anti-beta7 antibody which has a desired property or effect, I e the monovalent affinity of the antibody to human beta7 is the same as or greater than monovalent affinity of an antibody defined by the sequences as referred to SEQ ID NO 10-13 Said claims do not meet the requirements of Article 6 PCT in that the matter for which protection in sought is not clearly defined The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result In order to determine the scope of the claims the skilled person would have to test all known and yet unknown antibodies on their binding affinity to beta7 As this screening program represents certainly an undue burden, the scope of claims 26-35 is not clear In the present case, the claims so lack clarity, that a meaningful search over the whole of the

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claimed scope is impossible Consequently, the search, and thus the examination, has been carried out for those parts of the claims which in view of the application as a whole appear to be clear, namely those parts relating to anti-beta7 antibodies having the requested binding affinity, i e the antibody variants referred to as FIB 504.5, 504 16, 504 32 (p 114 Table 3) Same applies to claims 36-50 referring to the antibodies of the claims cited above

III.3 With respect to claims 36-48

Claims 36-48 relate (at least in part, as far as an in vivo method is concerned) to subject-matter considered by this Authority to be covered by the provisions of Rule 67 1(iv) PCT Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(I) PCT)

Item V

V 1 Reference is made to following documents

D1 D PICARELLA ET AL. 'Monoclonal antibodies specific for beta 7 integrin and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) reduce inflammation in the colon of scid mice reconstituted with CD45RBhigh CD4+ T cells', JOURNAL OF IMMUNOLOGY, 1 March 1997 (1997-03-01), vol 158, no 5, pages 2099-2106

D2 WO9624673 (LEUKOSITE, INC) 15 August 1996 (1996-08-15)

D3 X. SUN ET AL. 'beta7 Integrins contribute to skin graft rejection', TRANSPLANTATION, 27 October 2002 (2002-10-27), vol 74, no 8, pages 1202-1203

D4 M TIDSWELL ET AL. 'Structure-function analysis of the integrin beta 7 subunit Identification of domains involved in adhesion to MAdCAM-1', JOURNAL OF IMMUNOLOGY, 01 August 1997 (1997-08-01), vol 159, no 3, pages 1497-1505

D5 WO0040604 (THE BRIGHAM AND WOMEN'S HOSPITAL, INC) 13 July 2000 (2000-07-13)

D6 C V LEE ET AL. 'High-affinity Human Antibodies from Phage-displayed Synthetic Fab Libraries with a Single Framework Scaffold', JOURNAL OF MOLECULAR BIOLOGY, 23 July 2003 (2004-07-23), vol 340, no 5, pages 1073-1093

D7 METHODS IN MOLECULAR BIOLOGY, Humana Press Inc, Totowa, USA, Ed

12 | 899

BKC LO, ISBN 1-58829-092-1, Release date December 2003, PART III 'Antibody Expression and Optimization, Chapters 18-21 'Directed mutagenesis of antibody variable domains' (p 319), 'Antibody affinity maturation by chain shuffling' (p 327), 'Antibody affinity maturation by random mutagenesis' (p 343), Developing a minimally immunogenic humanized antibody by SDR grafting' (p. 361)

D8 H WU ET AL. 'Stepwise in vitro affinity maturation of Vitaxin, an alphavbeta3-specific humanized mAb', PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, 26 May 1998 (1998-05-26), vol 95, no 11, pages 6037-6042

D9 C RADER ET AL. 'A phage display approach for rapid antibody humanization Designed combinatorial V gene libraries', PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, 21 July 1998 (1998-07-21), vol 95, no 15, pages 8910-8915

D10 W -P YANG ET AL 'CDR walking mutagenesis of the affinity maturation of a potent human anti-HIV-1 antibody into the picomolar range', JOURNAL OF MOLECULAR BIOLOGY, 1995, vol 254, no 3, pages 392-403

D11 J HANES ET AL. 'Picomolar affinity antibodies from a fully synthetic naive library selected and evolved by ribosome display', NATURE BIOTECHNOLOGY, December 2000 (2000-12-00), vol. 18, no 12, pages 1287-1292

D12 J L. TORAN ET AL. 'Improvement in affinity and HIV-1 neutralization by somatic mutation in the heavy chain first complementarity-determining region of antibodies triggered by HIV-1 infection', EUROPEAN JOURNAL OF IMMUNOLOGY, January 2001 (2001-01-00), vol 31, no 1, pages 128-137

D13 WO2005080432 (GENENTECH, INC) 01 September 2005 (2005-09-01)

V 2 Novelty (Article 33(2) PCT)

V.2.1 With respect to claim 1, 4, 5, and 36-50

The subject-matter of claims 1, 4, 5, and 36-50 refers to anti-beta7 antibodies comprising CDRs as referred to SEQ ID NO 1-6. It appears that the parent antibody FIB 504 comprises said CDRs as it is shown in Fig 1A and 1B Therefore, the disclosure of D1-D5 describing FIB 504 and its binding characteristic as well as its effect on various diseases is considered novelty destroying for the subject-matter of claims 1, 4, 5, and 36-50 Thus, claims 1, 4, 5, and 36-50 do not meet the requirements of Article 33(2) PCT

V.2 2 With reapect to claims 2, 6, 7, 8, 36-50

The subject-matter of claim 2 refers to HVR variants comprising modification of at least one residue of any of the sequences depicted in SEQ ID NO: 1, 2, 3, 4, 5, or 6 An upper limit of the number of modified residues is not given Therefore, all residues may be modified Thus, each and every anti-beta7 antibody, humanized or not, falls under the subject-matter of claim 2 Therefore, claims 2, 6, 7, 8, 36-50 lacks novelty over D1-D5 (D2 e g discloses humanized antibodies derived from FIB 504 which are used to treat inflammatory bowel diseases p. 6 l. 7-29, D5 e g discloses humanized FIB 504 antibodies p. 9 l 15-18, p 22 l 15-26)

V.2.3 With respect to claims 3 and 9-35

The subject-matter of claims 3 and 9-35, as far as it is clear and searched, does not appear to be disclosed in the available prior art documents Therefore, claims 3 and 9-35 are considered novel in the sense of Article 33(2) PCT

V.3 Inventive step (Article 33(3) PCT)

V.3 1 With respect to claims 3 and 9-35

The subject-matter of claims 3 and 9-35 differs from D2 or D5 in that the sequence of the CDRs of the anti-beta7 antibody is different. The technical problem to be solved may be regarded as providing a humanized anti-beta7 antibody with an altered affinity than the parent rat antibody (FIB 504) (the binding affinity of the antibody referred to as 504.16 is less than that of the parent antibody) Methods for affinity maturation of antibodies are known to the person skilled in the art. D6, e g., describes a method for producing anti-mVEGF antibodies with picomolar affinities, I e 0 016 nM (see also D7-D12) Therefore, it would be a routine procedure for the skilled person, starting form the known antibody Fib 504, to produce a humanized antibody with an altered, or even with an higher, affinity for beta7 Thus, the subject-matter of claims 3 and 9-35 is not considered inventive in the sense of Article 33(3) PCT

Though, if the antibodies of the present application defined by the sequences of six CDRs would show a surprising effect in vivo, then the antibodies and the use of said antibodies for preparing a medicament would be considered inventive However, the present application lacks comparative experimental data to support a surprising effect.

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V.4 Industrial applicability (Article 33(4) PCT)

V 4 1 With respect to claims 1-35, 49, and 50

The subject-matter of claims 1-35, 49 and 50 appear to be susceptible of industrial application

V 4.2 With respect to claims 36-48

The subject-matter of claims 36-48 is considered (at least in part) to be a method of treatment by therapy of the human or animal body

For the assessment of the present claims 36-48 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.5 Further remarks

V.5.1 With respect to claims 2-50

The subject-matter of claim 2 and of all claims being dependent on claim 2 is unclear, since claim 2 refers to the variants of HVR of claim 1, but does not comprise the HVR as defined in claim 1, since said variants comprise "modification of at least one residue of any of the sequences depicted in SEQ ID NO 1, 2, 3, 4, 5, or 6. Therefore, claims 2-50 do not meet the requirements of Article 6 PCT

V.5.2 With respect to claim 1

The subject-matter of claim 1 reads "HVR-L3 comprising sequence C1-C10, wherein C1-C10 is QQGNSLLPNT (SEQ ID NO:3) However, the sequence referred to as SEQ ID NO 3 in the sequence listing is C1-C9 QQGNSLPNT (see also claims 5 and 34 and Figure 1 where it reads QQGNSLPNT)

Item VI

VI 1 With respect to document D13

The examination report has been based on an assumed valid priority for the present

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application Should the priority of the present application not be valid, the above cited document D13 would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT) Furthermore, should the present application be entered into the regional phase, the document D13 could be relevant to the question of novelty

AS' 103303

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APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1 Country *United States of America*

This public document

2 has been signed by N Williams

3 acting in the capacity of Certifying Officer

4 bears the seal/stamp of Patent and Trademark Office

Certified

5 at Washington, D C

6 the twenty-first of May, 2007

7 by ~~Assistant~~ *Authentication Officer United States Department of State*

8 No 07023527-15

9 Seal/Stamp

10 Signature

Denitra T Hawkins

7x604

A 7059285

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

March 26, 2007

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON APRIL 27, 2005

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

N WILLIAMS
Certifying Officer

605
TB

U.S DEPARTMENT OF COMMERCE
Patent and Trademark Office

RECORDATION FORM COVER SHEET
PATENTS ONLY

Atty Dkt No: PE2159

Commissioner for Patents: Please record the attached original documents or copy thereof

1 Name of conveying party(ies)

Sherman Fong
Mark S Dennis

Additional name(s) of conveying party(ies) attached? _ Yes X No

2 Name and address of receiving party(ies)

Name GENENTECH, INC.
Internal Address
Street Address 1 DNA Way
City South San Francisco State California
ZIP 94080-4990

Additional name(s) & address(es) attached? _ Yes X No

3 Nature of conveyance

X Assignment Merger
Security Agreement
Change of Name
Other

Execution Date April 22, 2005, April 26, 2005

4 Application number(s) or patent number(s)

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)
60/607,377

B Patent No.(s)

Additional numbers attached? Yes X No

5 Name and address of party to whom correspondence concerning document should be mailed

Deirdre L. Conley, Ph D
GENENTECH, INC
1 DNA Way
South San Francisco, CA 94080

6 Total number of applications and patents involved. 1

7 Total fee (37 CFR 3 41) $ 40.00
_ Enclosed
X Authorized to be charged to deposit account

8 Deposit account number
07-0630

DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief the foregoing information is true and correct and any attached copy is a true copy of the original document.

Deirdre L. Conley, Ph.D.
Name of Person Signing
Registration No 36,487

Signature

April 27, 2005
Date

Total number of pages comprising cover sheet, attachments and document 4

Revised (04/11/05)

606
OT

Docket No PR2159

ASSIGNMENT

WHEREAS, Sherman Fong a citizen of USA, residing at 18 Baslnside Way, Alameda CA 94502 and Mark S Dennis, a citizen of USA residing at 120 Plymouth, San Carlos, CA 94070 (hereinafter "ASSIGNORS") have invented a new and useful invention in

HUMANIZED FB504 AND USES THEREFOR

for which a provisional application Serial No 60/607,377 (Docket No PR2159) has been filed by them on September 3, 2004, and

WHEREAS, GENENTECH INC a corporation organized and existing under and by virtue of the laws of the State of Delaware, having a place of business at 1 DNA Way, South San Francisco, California 94080-4990 is desirous of acquiring an interest in and to said invention and in and to the Letters Patents to be obtained therefor,

NOW THEREFORE be it known by all whom it may concern,

That for good and valuable consideration the receipt of which is hereby acknowledged the said ASSIGNORS have and do hereby sell, assign, transfer and set over unto the said GENENTECH, INC , its successors and assigns, the full and exclusive right, title and interest including all rights under the Paris Convention for the Protection of Industrial Property, in and to said invention and in and to any and all Letters Patents to be granted and issued therefor or any continuation division renewal or substitute thereof and as to Letters Patents any reissue or re-examination thereof, not only for, to and in the United States of America, its territories and possessions, but for, to and in all other countries, and it has been and is hereby authorized and requested that the appropriate government agencies issue said Letters Patents to said GENENTECH, INC , in accordance with this Assignment.

Said ASSIGNORS covenant and agree to cooperate with GENENTECH, INC , to enable said GENENTECH, INC to enjoy to the fullest extent the right, title and interest herein conveyed in the United States and foreign countries Such cooperation by said ASSIGNORS includes prompt production of pertinent facts and documents, giving of testimony, execution of petitions oathe, specificatbons declarations or other papers and other assistance all to the extent deemed necessary or desirable by said GENENTECH, INC , (a) for perfecting the right title and interest herein conveyed, (b) for prosecuting any of said applications, (c) for filing and prosecuting applications for reissuance of any of said patents, (d) for interference or other priority proceedings involving said invention, and (e) for legal proceedings involving said invention and any applications therefor and any patents granted thereon, including without limitation opposition proceedings cancellation proceedings, priority contests public use proceedings, infringement actions and court actions, provided, however, that the expense incurred by said ASSIGNORS in providing such cooperation shall be paid for by said GENENTECH INC

The terms and covenants of this assignment shall inure to the benefit of said GENENTECH, INC , its successors, assigns and other legal representatives, and shall be binding upon said ASSIGNORS their respective heirs legal representatives and assigns

Said ASSIGNORS hereby warrant and represent that they have not entered and will not enter into any assignment, contract, or understanding in conflict herewith

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IN WITNESS WHEREOF we undersign as follows,

South San Francisco

Dated 4/26/05

Sherman Fong

Sherman Fong

South San Francisco

Dated _____

Mark S Dennis

608

IN WITNESS WHEREOF we undersign as follows,

South San Francisco

Dated _____

Sherman Fong

South San Francisco

Dated 4-22-05

Mark S Dennis

TRADUCCION AL ESPAÑOL del Documento de Cesión a **GENENTECH, INC** firmado por los cedentes y el cesionario

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APOSTILLA

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

1 País Estados Unidos de Amérca

Este documento público

2 ha sido firmado por N Williams

3 actuando en capacidad de Funcionario que Certifica

4 lleva el sello/timbre de la Oficina de marcas y patentes

Certificado

5 en Washington D C

6 el veintiuno de Mayo de 2007

7 por el Funcionario de autenticación, Departamento de Estado de Estados Unidos

8 No 07023527-15

9 Sello/timbre

10 Firma

(Firma)

Denitra T Hawkins

[sello]

670

LOS ESTADOS UNIDOS DE AMÉRICA
A TODO AQUEL QUE PUEDA LLEGARLE LA PRESENTE

DEPARTAMENTO DE COMERCIO DE ESTADOS UNIDOS
Oficina de Marcas y Patentes de Estados Unidos

Marzo 26 de 2007

ESTE ES PARA CERTIFICAR QUE EL ANEXO ES UNA COPIA VERDADERA DE LOS ARCHIVOS DE ESTA OFICINA DE UN DOCUMENTO ARCHIVADO EL 27 DE ABRIL DE 2005

Por autoridad del
Subsecretario de Comercio para la Propiedad Intelectual
y Director de la Oficina de Marcas y Patente de Estados Unidos

N WILLIAMS
Funcionario que Certifica

Hay un sello que dice
Oficina de Marcas y Patentes de Estados Unidos
Departamento de Comercio

25

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HOJA DE PORTADA DEL FORMULARIO DE REGISTRO

SOLAMENTE PATENTES

Departamento de Comercio
Oficina de Marcas y Patentes
Expediente de abogado No. PR2027

Comisionado Asistente para patentes Por favor archive los documentos originales anexos o copias de los mismos

1 Nombre de la(s) parte(s) cedente(s)

Sherman Fong
Mark S Dennis

¿Se anexa(n) nombre(s) adicional(es) de parte(s) cedente(s)? _ Si X No

2 Nombre y dirección de la(s) parte(s) receptora(s)

Nombre GENENTECH, INC

Dirección interna.

Dirección 1 DNA Way

Ciudad South San Francisco Estado California

ZIP 94080-4990

¿Se anexan Nombre(s) y dirección(es) adicional(es)? _ Si X No

3. Naturaleza del traspaso:

X Cesión Fusión

Acuerdo de Seguridad

Cambio de Nombre

Otro:

Fecha de Ejecución Abril 22, 2005, Abril 26, 2005

4 Numero(s) de solicitud o número(s) de patente

Si este documento se presenta junto con una nueva solicitud, la fecha de ejecución de la solicitud es.

A. Solicitud de patente No(s).
60/607,377

B Patente No(s).

¿Se anexan números adicionales? _ Si X No

5. Nombre y dirección de la parte a quien se le debe enviar la correspondencia.

Deirdre L. Conley, Ph d
GENENTECH INC
1DNA Way
South San Francisco, CA 94080

6 Numero total de solicitudes y patentes involucradas 1

7 Tarifa total (37 C F R 3 41) $40 00

__ Adjunta
X Autorizado para cargarla a cuenta de depósito

8 Número de cuenta de Depósito
07-0630

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9 Declaración y firma
hasta donde se y creo, la información anterior es verdadera y correcta y cualquier copia anexa es una copia verdadera del documento original

Deirdre L. Conley, Ph.d	(Firma)	Abril 27, 2005
Nombre de la persona que firma Registro No 36 487	Firma	Fecha

Número total de páginas que comprenden portada anexos y documento 4

PATENTE
700174448 ROLLO 016173 CUADRO 0349

6-12

CESIÓN

CONSIDERANDO QUE, Sherman Fong, un ciudadano de los E U.A , residente en 19 Basinside Way, Alameda, CA 94502, y Mark S Dennis, un ciudadano de los E U.A , residente en 120 Plymouth, San Carlos, CA 94070 (en adelante referidos como "CEDENTE"), han inventado una invención nueva y útil

FIB504 HUMANIZADA Y USOS PARA LA MISMA

para la cual se presentó la solicitud provisional con Serie No 60/607,377 (Expediente No PR2159) por ellos el 3 de Septiembre de 2004, y

CONSIDERANDO QUE, GENENTECH, INC , una corporación organizada y existente bajo y por virtud de las leyes del Estado de Delaware que tiene oficinas en 1 DNA Way, South San Francisco, California 94080-4990, está deseosa de adquirir un interés en y para dicha invención, y en y para las patentes que se obtendrán de la misma,

AHORA, POR LO TANTO, téngase por sabido por todo aquel que le concierna

Que por una consideración buena y valiosa el recibo de la cual se reconoce por la presente, dicho CEDENTE ha y por la presente vende, cede, transfiere y traspasa a dicha GENENTECH, INC sus sucesores y cesionarios, el derecho, título e interés completo y exclusivo incluyendo todos los derechos bajo la Convención de Paris para la Protección de la Propiedad Industrial, en y para dicha invención, y en y para cualquiera y todas las patentes que se concedan y emitan para la misma o cualquier continuación, división, renovación, o sustitución de la misma, y en cuanto a patentes cualquier reemisión o reexaminación de las mismas, no solo para, por y en los Estados Unidos de América, sus territorios y posesiones, sin para, por y en todos los otros países, y se ha y por la presente se autoriza y solicita que las agencias gubernamentales respectivas emitan dichas patentes a GENENTECH, INC de acuerdo con esta cesión

Dicho CEDENTE garantiza y acuerda cooperar con GENENTECH, INC , para posibilitar a dicha GENETECH, INC , a disfrutar hasta su máxima extensión el derecho, título e interés aquí cedido en Estados Unidos y los países extranjeros Tal cooperación por dichos CEDENTE incluye la pronta producción de hechos y documentos pertinentes, dando testimonio, ejecutando peticiones, juramentos, especificaciones, declaraciones u otros documentos, y otra ayuda todas hasta el punto considerado necesario o deseable por dichas GENETECH, INC (a) para perfeccionar el derecho, título e interés aquí cedido, (b) para procesar cualquiera de dichas solicitudes, (c) para presentar y procesar solicitudes de reemisión de cualquiera de dichas patentes, (d) para procesos de interferencia u otros procesos de prioridad que involucran dicha invención, y (e) para procedimientos legales que involucran dicha invención y cualquier solicitud de la misma y cualquier patente concedida sobre la misma, incluyendo sin limitación procedimientos de oposición, procedimientos de cancelación, disputas de prioridad, procesos de uso público, acciones de violación y acciones de la corte, con la condición que los gastos incurridos por dicho CEDENTE al proporcionar dicha cooperación deban ser pagados por GENETECH, INC

Los términos y garantías de esta cesión deben lastimar a beneficio de dicha GENETECH, INC sus sucesores, cesionarios y otros representantes legales, y deberá ser obligante sobre dichos CEDENTE, sus respectivos herederos, representantes legales y cesionarios

Dicho CEDENTE por la presente garantiza y manifiesta que no ha entrado y no entrará en ninguna cesión, contrato o entendimiento en conflicto con la presente

PATENTE
ROLLO 016173 CUADRO 0350

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EN TESTIMONIO DE LO CUAL suscribimos como sigue

South San Francisco

4/26/05
Fecha

(Firma)
Sherman Fong

South San Francisco

Fecha

Mark S Dennis

PATENTE
ROLLO 015520 CUADRO 0541

28
674

EN TESTIMONIO DE LO CUAL suscribimos como sigue

South San Francisco

Fecha

Sherman Fong

South San Francisco

4-22-05
Fecha

(firma)
Mark S Dennis

CERTIFICADO 04/27/2005

PATENTE
ROLLO 016173 CUADRO 0352