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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMI

E.

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D.

REF: Expediente No. PCT/13-115304

TÍTULO SOLICITADO: "PROTEÍNAS QUE PRESENTAN UN DOMINIO DE
UNIÓN A INTERLEUCINA-13"

PUBLICACIÓN: Gaceta 616 del 20/05/2010, N° de publicación 238.
Solicitud divisional.

SOLICITANTE: ABBVIE, INC.

APODERADO: ALICIA LLORED A RICAURTE.

TRÁMITE: Recurso de Reposición y en subsidio el de apelación en
contra de la Resolución 2477 de enero 28 de 2014 por la
cual se concede una patente de invención tramitada bajo
el número de expediente PCT/13-115304.

TITO NOÉ PARRA MURILLO, mayor de edad, identificado como aparece al pie de mi
firma, reconocido apoderado de la sociedad LAFRANCOL S.A.S. en el asunto de la
referencia, de manera respetuosa, y dentro de los términos de ley, presento Recurso de
Reposición y en subsidio de apelación contra la Resolución 2477 de enero 28 de 2014 por
la cual se concedió a la solicitud PCT/13-115304 el privilegio de patente de invención.

I. PETICIÓN

Sírvase, Señor Superintendente, reponer íntegramente la Resolución 2477 de enero 28 de
2014, por la cual se declaró infundada la oposición presentada y se otorgó el privilegio de
patente solicitado en el expediente de la referencia, y en su remplazo emitir otra que, con
fundamento en los argumentos expuestos en el escrito de observación y en el presente
escrito, declare fundada dicha oposición y niegue el privilegio de patente mencionado,

procediendo luego al definitivo archivo del expediente en cuestión.

II. ARGUMENTOS SOBRE LOS FUNDAMENTOS DE LA CONCESIÓN Y MOTIVOS DE INCONFORMIDAD

La Resolución 2477 de enero 28 de 2014, que concede el privilegio de patente de invención solicitado para el capítulo reivindicatorio del expediente 13-115304 titulado “**Proteínas que presentan un dominio de unión a interleucina-13**”, viola flagrantemente la Decisión 486 si se tiene en cuenta que existían motivos suficientes para afectar los requisitos de novedad y nivel inventivo de la solicitud en mención. Es evidente que el solicitante y la Resolución cometen un error cuando afirman que la oposición presentada por mi representada no muestra ningún tipo de argumento soportado técnicamente, ni desvirtúa la patentabilidad del objeto de estudio, declarándola infundada por cuanto, al momento de presentación del escrito de oposición se dejó en claro que para el presente caso nos encontramos frente a una combinación de compuestos, lo cual indudablemente afecta el requisito de nivel inventivo, éste mismo indispensable para acceder a cualquier beneficio patentario.

Así las cosas, me permito reiterar que la concesión de patente objeto del presente escrito se ve afectada por los documentos del estado del arte que fueron presentados inicialmente en el escrito de observación, por lo cual, basado en lo siguiente, solicito respetuosamente a ese Despacho dar análisis completo y a cabalidad sobre los siguientes documentos, los cuales sin lugar a dudas objetan la concesión en mención, toda vez que develan de manera expresa y sucinta lo que se pretende proteger en la presente solicitud.

Dicho así, me permito manifestar que agentes tales como Leflunomida, Temsirolimus, Ciclosporina, Mesalamina, entre muchos otros, han sido ampliamente divulgados en el sector químico-farmacéutico, y concretamente se han develado materias muy similares, las cuales ruego a ese Despacho analizar, en los siguientes documentos:

- DE 2854439
- US 4284786
- US 5362718
- US 4117118
- GB 751386

Así como resulta imprescindible manifestar que los anteriores documentos deben ser analizados a profundidad y cabalidad para así determinar finalmente si afectan o no la novedad y nivel inventivo de la presente solicitud, toda vez que en nuestra opinión se revelan materias muy similares, también es necesario reiterar que la solicitud de la referencia pretende proteger mediante el derecho patentario objetos que no son considerados invenciones. Es claro que una invención es toda creación humana que permita transformar la materia o energía que existe en la naturaleza, para su aprovechamiento por los seres humanos y satisfacer sus necesidades concretas. De igual modo, como ya se mencionó, según los parámetros de la Decisión 486 y normas concordantes, serán patentables las invenciones que cumplan con los requisitos de novedad, nivel inventivo y aplicación industrial. No obstante, puede observarse que la solicitud en comento pretende reivindicar combinaciones, las cuales no se consideran invenciones. En este sentido, la mezcla (Combinaciones) de productos (Moléculas) conocidos y su variación, bien sea en uso, forma, dimensión o de materia, NO se consideran invenciones por cuanto no son susceptibles de aplicación industrial, nivel inventivo y novedad, luego NO pueden acceder a beneficios patentarios. Por lo tanto, se suma una circunstancia más que imposibilita definitivamente la concesión de la solicitud en mención.

Y sobre el particular, es imprescindible señalar que un efecto sinérgico nuevo no se considera inventivo como tal, dado que puede ser obvio para una persona versada en la materia, cosa que sucede en el presente caso. En palabras del Doctor Carlos Correa, *“El efecto sinérgico entre dos o más drogas se puede considerar un “descubrimiento” y no una “invención”, dado que la sinergia ocurre en el cuerpo y se descubre a través de ensayos clínicos. Asimismo, cabe destacar que, en algunos casos, las reivindicaciones de combinaciones pueden equivaler, en términos prácticos, a reivindicaciones sobre tratamientos médicos (cuya patentabilidad está excluida en la mayoría de los países), cuando sólo brindan un método para administrar una combinación de drogas conocidas. Asimismo, la combinación de drogas para evitar la resistencia particular a una de ellas es una práctica normal en el desarrollo farmacéutico y, por lo general, es evidente para el hombre del oficio de nivel medio”* (Pautas para el examen de patentes farmacéuticas, CEIDIE, Pág. 8). En estos términos, está claro que nos encontramos frente a un tema totalmente sensible que merece toda la evaluación por cuanto las combinaciones deben considerarse excluidas de beneficios de patente.

Y en caso que ese Despacho decidiera insistir en el cabal cumplimiento de los requisitos exigidos para acceder al beneficio de patente, me permito allegar copia del International

Search Report y el respectivo Written Opinion Of The International Searching Authority, documentos en los cuales se resalta que la presente invención no cumple con los requisitos de novedad y nivel inventivo por cuanto existen documentos citados del estado del arte que afectan de manera definitiva tales exigencias. Lo anterior deja entrever, sin lugar a equívocos, que la presente solicitud no debió ser concedida, por lo cual es procedente la revocatoria de la Resolución objeto de este escrito.

En este sentido, reitero con el debido respeto la necesidad de analizar a profundidad los requisitos de novedad y nivel inventivo para así determinar si la presente solicitud es merecedora de concesión de privilegio de patente.

ANEXOS

International Search Report y el Written Opinion Of The International Searching Authority de la equivalente internacional WO 2008/127271.

En subsidio apelo.

Señor Superintendente,

TITO NOÉ PARRA MURILLO

C.C. 79.579.680 de Bogotá

T.P. 11168 del C. S de la J.

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(74) Agents: SESHADRI, Tara et al.; Abbott Bioresarch
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(US).

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ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL,
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LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW,
MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,
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FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL,
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Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments
- with sequence listing part of description published sepa-
rately in electronic form and available upon request from
the International Bureau

(88) Date of publication of the international search report:
9 April 2009

(54) Title: INTERLEUKIN -13 BINDING PROTEINS

(57) Abstract: The present invention encompasses IL- 13 binding proteins. Specifically, the invention relates to antibodies that are chimeric, CDR grafted and humanized antibodies. Preferred antibodies have high affinity for hIL-13 and neutralize hIL-13 activity in vitro and in vivo. An antibody of the invention can be a full-length antibody or an antigen-binding portion thereof. Method of making and method of using the antibodies of the invention are also provided. The antibodies, or antibody portions, of the invention are useful for detecting hIL-13 and for inhibiting hIL-13 activity, e.g., in a human subject suffering from a disorder in which hTL-13 activity is detrimental.

WO 2008/127271 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 07/19660

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - C12P 21/08; C07H 21/00 (2009.01) USPC - 530/388.23; 536/23.53 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(8) - C12P 21/08; C07H 21/00 (2009.01) USPC - 530/388.23; 536/23.53 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 424/158.1; 435/243; 435/252.33; 435/254.11; 435/254.2; 435/254.21; 435/325; 435/348; 435/349; 435/358; 435/365; 435/419; 435/69.6; 514/12; 530/350; 530/387.1; 530/387.3; 530/388.1; 530/391.3; 530/391.7; 536/23.53; 424/145.1; 530/388.23 435/69.1; 435/320 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WEST (PGPB,USPT,EPAB,JPAB): Interleukin-13, IL-13, antibody, binding protein, inhibitor, agonist, ligand, immunoglobulin, constant domain, light chain, heavy chain, crystallized antibody, carrier-free, controlled release, adjuvant, hyaluronidase. GenCore version 6.3 (all DB): SEQ ID NO:32, 33, 4, 6, 46, 47, 70, 71, 80, 81		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 2006/0063228 A1 (Kasalan, et al) 23 Mar 2006 (23.03.2006); abstract; SEQ ID NO: 23, 21, Table 1, pg 14, col 2; SEQ ID NO: 29, 27, pg 46, 47; claims 33, 43; Fig 19; para [0010], [0014], [0029], [0042], [0055], [0056], [0076], [0094], [0097], [0101], [0107], [0131], [0134], [0147], [0150], [0153], [0154], [0170], [0172], [0177], [0178], [0189], [0197]-[0199], [0206], [0212], [0216]-[0218], [0246], [0271], [0287], [0302]	1, 2, 16, 23-25, 27-33, 37-50, 52, 53, 58, 59, 61-69 26, 34-36, 40, 51, 54-57, 60
Y	US 2004/0096452 A1 (Denney) 20 May 20 2004 (20.03.2004); SEQ ID NO: 49 pg 53, 54; para [0336]	26
Y	US 2003/0175261 A1 (Weickmann) 18 Sep 2003 (18.09.2003); para [0060]	60
Y	US 2005/0147610 A1 (Ghayur, et al.) 07 Jul 2005 (07 07.2005); para [0104], [0105]	34-36, 40, 51, 54-57
A	US 2005/0065327 A1 (Monk, et al.) 24 Mar 2005 (24.03.2005)	1-69
☐ Further documents are listed in the continuation of Box C. ☐		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 03 Feb 2009 (03.02.2009)		Date of mailing of the international search report 09 FEB 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 07/19660

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Group I, claims 1-69, wherein claim 2 is limited to residues 31-35 of SEQ ID NO: 32; claim 4 - to the VH 25C8 variable domain CDR set; claim 6 - to VH 25C8 and VL 25C8 CDR sets; claim 8 - to SEQ ID NO: 6; claims 13 and 15 - to SEQ ID NO:70; claim 14- SEQ ID NO:70 and 71.

Group II+, claims 1-69. Should additional fee be paid, Applicant is invited to make an election of SEQ ID NOs of claims 4, 6, 8, 13-15 to be searched.

Group III, claims 70-103, drawn to an anti-IL13 isolated antibody or antigen binding fragment thereof.

***** SEE SUPPLEMENTAL PAGE TO CONTINUE *****

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
Claims 1-69, limited to VH 25C8 CDR, VH 13CS CDR, VL 13CS CDR Sets and SEQ ID NO: 70, 71, 80, 81.
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/US 07/19660

***** SUPPLEMENTAL PAGE *****

BOX III. Observations where unity of invention is lacking:

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Although Groups I-III do share the technical feature of an anti-IL 13 isolated antibody or antigen binding fragment thereof, this shared technical feature does not represent a contribution over the prior art of US 2006/0140948 A1 to Foltz, et al. (29 Jun 06) that teaches fully human monoclonal anti- IL-13 antibodies (abstract) inhibiting binding of IL-13 to IL-13 receptor alpha 1(para [0008]). As the above antibody were known at the time of the invention, as evidenced by the teaching of Foltz et al., this cannot be considered a special technical feature that would otherwise unify the groups.

In addition, the sequences of groups I and II+ are patentably distinct because they are unrelated sequences and antibodies comprising said sequences differ in structure and in biological activity.

Groups I-III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To: TARA SESHADRI
ABBOTT BIORESEARCH CENTER
100 RESEARCH DRIVE
WORCESTER, MA 01605-4314

Date of mailing
(day/month/year) **09 FEB 2009**

Applicant's or agent's file reference 8370.WO.O1		FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/US 07/19660	International filing date (day/month/year) 07 September 2007 (07.09.2007)	Priority date (day/month/year) 08 September 2006 (08.09.2006)	
International Patent Classification (IPC) or both national classification and IPC IPC(8) - C12P 21/08; C07H 21/00 (2009.01) USPC - 530/388.23; 536/23.53			
Applicant ABBOTT LABORATORIES			

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 43bis.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 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 66.1bis(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/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Date of completion of this opinion 03 February 2009 (03.02.2009)	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774
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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

PCT/US2007/019660 09.02.2009

International application No.

PCT/US 07/19660

Box No. 1 Basis of this opinion

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

- ☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

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

a. 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

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) 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.

5. Additional comments:

GenCore version 6.3 (all databases): SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:6, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:4, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:12, SEQ ID NO:20, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:23, SEQ ID NO:80, SEQ ID NO:81

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

PCT/US2007/019660 09.02.2009

PCT/US 07/19660

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☒ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

- ☐ complied with
- ☒ not complied with for the following reasons:

Group I, claims 1-69, wherein claim 2 is limited to residues 31-35 of SEQ ID NO: 32; claim 4 - to the VH 25C8 variable domain CDR set; claim 6 - to VH 25C8 and VL 25C8 CDR sets; claim 8 - to SEQ ID NO: 6; claims 13 and 15 - to SEQ ID NO:70; claim 14- SEQ ID NO:70 and 71.

Group II+, claims 1-69. Should additional fee be paid, Applicant is invited to make an election of SEQ ID NOs of claims 4, 6, 8, 13-15 to be searched.

Group III, claims 70-103, drawn to an anti-IL13 isolated antibody or antigen binding fragment thereof.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Although Groups I-III do share the technical feature of an anti-IL13 isolated antibody or antigen binding fragment thereof, this shared technical feature does not represent a contribution over the prior art of US 2006/0140948 A1 to Foltz, et al. (29 Jun 06) that teaches fully human monoclonal anti-IL-13 antibodies (abstract) inhibiting binding of IL-13 to IL-13 receptor alpha 1(para [0008]). As the above antibody were known at the time of the invention, as evidenced by the teaching of Foltz et al., this cannot be considered a special technical feature that would otherwise unify the groups.

In addition, the sequences of groups I and II+ are patentably distinct because they are unrelated sequences and antibodies comprising said sequences differ in structure and in biological activity.

Groups I-III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

- ☐ all parts
- ☒ the parts relating to claims Nos. 1-69, limited to VH 25C8, VH 13CS, VL 13CS CDR Sets, and SEQ ID 70, 71, 80, 81

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

PCT/US2007/019660 09.02.2009

PCT/US 07/19660

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

1. Statement

Novelty (N)	Claims	1-69	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	3-15, 17-22	YES
	Claims	1, 2, 16, 23-69	NO
Industrial applicability (IA)	Claims	1-69	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1, 2, 16, 23-25, 27-33, 37-39, 41-50, 52, 53, 58, 59, 61-69 lack an inventive step under PCT Article 33(3) as being obvious over US 2006/0063228 A1 to Kasaian, et al (hereinafter "Kasaian").

As to claims 1 and 16, Kasaian discloses a binding protein comprising an antigen binding domain, said binding protein capable of binding IL-13 (abstract), said antigen binding domain comprising at least one CDR comprising an amino acid sequence selected from the group consisting of (Table 1, pg 14, col 2):

CDR-H2: XI-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14-X15-X16-X17 (SEQ ID NO: 65) I wherein; X1 is S, X2 is I, X3 is S, X4 is S, X5 is G, X6 is G, X10 is Y, X11 is Y, X12 is P, X13 is D, X14 is S, X15 is V, X16 is K, X17 is G (SEQ ID NO:23, Table 1).

Kasaian does not disclose that X7 is S, Y or G; X8 is E, N, Y, V, or R; X9 is T, I, or K. However, Kasaian does disclose a minimum core CDR sequence wherein said amino acids is any naturally occurring amino acid (Table 1; "Xaa 5...9 can be any naturally occurring amino acid," SEQ 29; pg 47). Thus, it would have been obvious to a person of ordinary skill in the art how to select the defined amino acids in positions 5-7 without undue experimentation.

In addition, Kasaian further discloses CDR-L3: XI-X2-X3-X4-X5-X6-X7-X8-X9 (SEQ ID NO: 69), wherein; X1 is Q, X2 is Q, X4 is N, X5 is E, X6 is D, X7 is P, X8 is W, X9 is T (SEQ ID NO:21, Table 1).

Kasaian does not disclose that X3 of said CDR-L3 is H, G, Y, W, or N. However, Kasaian does disclose a minimum core CDR sequence wherein X3 is any naturally occurring amino acid (Table 1; "Xaa 1...3 can be any naturally occurring amino acid," SEQ ID NO:27; pg 46-47). Thus, it would have been obvious to a person of ordinary skill in the art how to select the defined amino acids in the third position without undue experimentation.

As to claim 2, Kasaian further discloses a CDR comprising an amino acid sequence QQXaaNTLPLT, wherein Xaa may be any naturally occurring amino acid (Table 1; "Xaa 1...3 can be any naturally occurring amino acid," SEQ ID NO:27; pg 46-47). Thus, it would have been obvious to a person of ordinary skill in the art how to select the defined amino acids in the third position without undue experimentation.

As to claim 23, Kasaian further discloses that said antibody construct further comprising an immunoglobulin constant domain (para [0010], [0029], [0101], [0172]).

As to claim 24, Kasaian further discloses that said binding protein is selected from the group consisting of a monoclonal antibody (mAb13.2, para [0014]), a humanized antibody (abstract).

As to claim 25, Kasaian further discloses that said binding protein comprises a heavy chain immunoglobulin constant domain selected from the group consisting of a human IgM constant domain, a human IgG1 constant domain, a human IgG2 constant domain, a human IgG3 constant domain, a human IgG4 constant domain (para [0010], [0029], [0101], [0107]).

As to claim 27, Kasaian discloses that said antibody conjugate further comprising an agent selected from the group consisting of: an immunoadhesion molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent (para [0131, "Antibodies can be conjugated by chemical methods with radionuclides, drugs, macromolecules, or other agents, or can be made as fusion proteins comprising one or more CDRs described herein.")

As to claim 28, Kasaian discloses that said agent is an imaging agent selected from the group consisting of a radiolabel (para [0131, "Antibodies can be conjugated by chemical methods with radionuclides...")

As to claim 29, Kasaian discloses that said imaging agent is a radiolabel selected from the group consisting of: ³H, ¹⁴C, ³⁵S, ⁹⁰Y, ⁹⁹Tc, ¹¹¹In, ¹²⁵I, ¹³¹I, ¹⁷⁷Lu, ¹⁸⁶Ho, and ¹⁵³Sm (para [0246]).

As to claim 30, Kasaian discloses that said agent is a therapeutic or cytotoxic agent selected from the group consisting of: an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, and an apoptotic agent. (para [0131, "Antibodies can be conjugated by chemical methods with radionuclides, drugs, macromolecules, or other agents, or can be made as fusion proteins comprising one or more CDRs described herein.")

SEE SUPPLEMENTAL BOX TO CONTINUE

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

PCT/US2007/019660 09.02.2009

International application No.

PCT/US.07/19660

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
There are two claims numbered 66, while claim 67 is missing. For the purpose of the search the second claim 66 is named "claim 67."

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PCT/US2007/019660 09.02.2009

International application No.

PCT/US 07/19660

Supplemental Box

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Continuation of:

Box No. V(2) Citations and Explanations:

As to claim 31, Kasaian discloses the antibody construct according to claim 24, wherein said binding protein possesses a glycosylation pattern (para [0134], "the antibody may be modified to have an altered glycosylation pattern (e.g., altered from the original or native glycosylation pattern). As used in this context, "altered" means having one or more carbohydrate moieties deleted, and/or having one or more glycosylation sites added to the original antibody. Addition of glycosylation sites to the presently disclosed antibodies may be accomplished by altering the amino acid sequence to contain glycosylation site consensus sequences; such techniques are well known in the art;" para [0153] "Polypeptides made in yeast or bacteria can be modified, e.g., glycosylation of appropriate sites;" claim 16, "The antibody, or antigen-binding fragment thereof, of claim 15 having a constant region mutated to decrease ... antibody glycosylation..."). Kasaian further discloses that "the antibody binds to a human antigen, e.g., IL-13" (para [0056]). Kasaian does not expressly disclose that said binding protein possesses a human glycosylation pattern. However, it would have been obvious to one of ordinary skill in the art to modify said antibody to possess a human glycosylation pattern to diminish immunogenic reaction of a human subject to whom said antibody are delivered.

As to claim 32, Kasaian discloses 32 the binding protein according to claim 1, wherein said binding protein is a crystallized binding protein. (para [0271], "The Fab fragments themselves were crystallized...")

As to claim 33, Kasaian discloses the antibody construct according to claim 23, wherein said antibody construct is a crystallized antibody construct (para [0271], "The Fab fragments themselves were crystallized...")

As to claim 37, Kasaian discloses an isolated nucleic acid encoding a binding protein amino acid sequence of claim 1 (para [0147], [0150]).

As to claim 38, Kasaian discloses an isolated nucleic acid encoding an antibody construct amino acid sequence of claim 23 (para [0042], [0147]).

As to claim 39, Kasaian discloses a vector comprising an isolated nucleic acid according to claim 38 (para [0154]).

As to claim 41, Kasaian discloses a host cell comprising a vector according to claim 39 (para [0153], [0154]).

As to claim 42, Kasaian discloses the host cell according to claim 41, wherein said host cell is a prokaryotic cell (para [0153] "It may be possible to recombinantly produce polypeptides in ... prokaryotes (e.g., Escherichia coli, Bacillus subtilis, and Salmonella typhimurium).

As to claim 43, Kasaian discloses the host cell according to claim 41, wherein said host cell is E. coli (para [0153], [0287]).

As to claim 44, Kasaian discloses the host cell according to claim 41, wherein said host cell is a eukaryotic cell (para [0153] "it may be possible to recombinantly produce polypeptides in lower eukaryotes such as yeast (e.g., Saccharomyces, Pichia, Kluyveromyces strains, and Candida strains).

As to claim 45, Kasaian discloses that said eukaryotic cell is selected from the group consisting of protist cell, animal cell, plant cell and fungal cell (para [0153], [0154]).

As to claim 46, Kasaian discloses that said eukaryotic cell is an animal cell selected from the group consisting of; a mammalian cell, an avian cell, and an insect cell (para [0153], [0154], [0302]).

As to claim 47, Kasaian discloses that said host cell is a CHO cell (PARA [0287]).

As to claim 48, Kasaian discloses that said host cell is COS (EXAMPLE 6, para [0302]).

As to claim 49, Kasaian discloses that said host cell is a yeast cell (para [0153]).

As to claim 50, Kasaian discloses that said yeast cell is Saccharomyces cerevisiae (para [0153]).

As to claim 52, Kasaian discloses a method of producing a protein capable of binding IL-13, comprising culturing a host cell of claim 41 in culture medium under conditions sufficient to produce a binding protein capable of binding IL-13 (para [0097], "When the antibody protein or biologically active portion thereof is recombinantly produced;" claim 43; para [0055], "Nucleic acids that include sequences encoding protein chains that include such variable domains can be expressed in mammalian cells, e.g., tissue culture cells;" para [0076], FIG. 19 "Fully humanized mAb13.2 (h13.2v2) retains full binding activity to IL-13").

As to claim 53, Kasaian discloses a protein produced according to the method of claim 52 (abstract, para [0097].

As to claim 58, Kasaian discloses a pharmaceutical composition comprising the binding protein of claim 1, and a pharmaceutically acceptable carrier (para [0170]; para [0177]).

As to claim 59, Kasaian discloses the pharmaceutical composition of claim 58 wherein said pharmaceutically acceptable carrier functions as adjuvant (para [0177]) useful to increase the absorption ([0189] "delivery enhancers such as surfactants can be used to further enhance pulmonary delivery. A "surfactant" as used herein refers to a compound having hydrophilic and lipophilic moieties that promote absorption of a drug by interacting with an interface between two immiscible phases") of said binding protein.

As to claim 61, Kasaian discloses the pharmaceutical composition of claim 58 further comprising at least one additional therapeutic agent for treating a disorder in which IL-13 activity is detrimental ([0218], "Examples of preferred additional therapeutic agents that can be coadministered and/or coformulated with one or more IL-13 antagonists.")

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Box No. V(2) Citations and Explanations and the preceding SUPPLEMENTAL BOX:

As to claim 62, Kasaian discloses the pharmaceutical composition of claim 61, wherein said additional agent is selected from the group consisting of: imaging agent, detectable label or reporter (para [0131], [0246]), therapeutic agent, anti-cytokine antibody or functional fragment thereof; detectable label or reporter; a TNF antagonist; an immunoglobulin, a beta agonist, an inhaled steroid, a cytokine antagonist (para [0218]).

As to claim 63, Kasaian discloses a method for reducing human IL-13 activity comprising contacting human IL-13 with the binding protein of claim 1 such that human IL-13 activity is reduced (abstract; para [0076], FIG. 19 "Fully humanized mAb13.2 (h13.2v2) retains full binding activity to IL-13").

As to claim 64, Kasaian discloses a method for reducing human IL-13 activity in a human subject suffering from a disorder in which IL-13 activity is detrimental (abstract), comprising administering to the human subject the binding protein of claim 1 such that human IL-13 activity in the human subject is reduced (para [0076], FIG. 19 "Fully humanized mAb13.2 (h13.2v2) retains full binding activity to IL-13").

As to claim 65, Kasaian discloses a method for treating a subject for a disease or a disorder in which IL-13 activity is detrimental by administering to the subject the binding protein of claim 1 such that treatment is achieved (abstract; para [0076], FIG. 19 "Fully humanized mAb13.2 (h13.2v2) retains full binding activity to IL-13").

As to claim 66, Kasaian discloses that said disorder is selected from the group consisting of respiratory disorders (para [0198], [0199]); other conditions involving airway inflammation (para [0094], [0197]); atopic dermatitis (para [0206]).

As to claim 67, Kasaian discloses that said disorder is selected from the group consisting of fibrotic lung disease (para [0212]); atopic dermatitis (para [0206]).

As to claim 68, Kasaian discloses a method of treating a patient suffering from a disorder in which IL-13 is detrimental (abstract, para [0216], [0217]) comprising the step of administering the binding protein of claim 1 before, concurrent, or after the administration of a second agent, wherein the second agent is selected from the group consisting of inhaled steroids; beta-agonists; antagonists of leukotrienes or leukotriene receptors (para [0218]).

As to claim 69, Kasaian discloses that said administering to the subject is by at least one mode selected from parenteral, subcutaneous, intravenous (para [0178]).

Claim 26 lack an inventive step under PCT Article 33(3) as being obvious over Kasaian, as above, in view of US 2004/0096452 A1 (Denney).

As to claim 26, Kasaian does not disclose an immunoglobulin constant domain having an amino acid sequence SEQ ID NO:4. This element is disclosed by Denney (pg 53, 54 SEQ ID NO: 49; para [0336]). It would have been obvious to one of ordinary skill in the art to combine variable domains taught by Kasaian with the constant domain taught by Denney because Denney explains that said constant region CK is the same as that found in the native proteins (para [0336], "The DNA sequence encoding the CK region is listed in SEQ ID NO:48; the amino acid sequence encoded by SEQ ID NO:48 is listed in SEQ ID NO:49") to diminish immunogenic reaction of a human subject to whom said antibody are delivered.

Claims 34-36, 40, 51, 54-57 lack an inventive step under PCT Article 33(3) as being obvious over Kasaian, as above, in view of US 2005/0147610 A1 to Ghayur, et al. (hereinafter "Ghayur").

As to claim 34, Kasaian does not disclose that said crystallized antibody construct is a carrier-free pharmaceutical controlled release crystallized antibody construct. This element is taught by Ghayur (para [0110], "a crystallized binding protein comprising any one of the binding proteins disclosed above, wherein the binding protein exists as a crystal. Preferably the crystal is a carrier-free pharmaceutical controlled release crystal").

As to claim 35, Ghayur further discloses that said antibody construct has a greater half life in vivo than the soluble counterpart of said antibody construct (para [0110]).

As to claim 36, Ghayur further discloses that said antibody construct retains biological activity after crystallization (para [0110]).

As to claim 40, Kasaian does not disclose that said vector is selected from the group consisting of pcDNA, pTT, pTT3, pEFBOS, pBV, pLY, and pBI. Said element, in the context of producing human antibody molecules for IL-18, is taught by Ghayur (para [0104], "a vector comprising the isolated nucleic acid disclosed above wherein said vector is selected from the group consisting of pcDNA; pTT (Durocher et al., Nucleic Acids Research 2002, Vol 30, No.2); pTT3 (pTT with additional multiple cloning site; pEFBOS (Mizushima, S. and Nagata, S., (1990) Nucleic acids Research Vol 18, No. 17); pBV; pJV; and pBJ"). It would have been obvious to one of ordinary skill in the art to employ vectors taught by Ghayur for producing IL-13 binding protein taught by Kasaian, because said vectors are convenient tools for protein expression in a variety of hosts, as taught by Ghayur (para [0105], "Preferably the host cell is a prokaryotic cell. More preferably the host cell is E. Coli. In a related embodiment the host cell is an eukaryotic cell. Preferably the eukaryotic cell is selected from the group consisting of protist cell, animal cell, plant cell and fungal cell. More preferably the host cell is a mammalian cell including, but not limited to, CHO and COS; or a fungal cell such as Saccharomyces cerevisiae; or an insect cell such as Sf9.")

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As to claim 51, although Kasalan discloses that said host cell is an insect cell (para [0154], "Polypeptides can also be produced in animal cells, e.g., insect," Kasalan does not expressly disclose that said insect cell is Sf9. This element, in the context of producing human antibody molecules for IL-18, is taught by Ghayur ((para [0105]). It would have been obvious to one of ordinary skill in the art to use Sf9 cells to produce anti-IL-13 antibody without undue experimentation.

As to claim 54, the combination of Kasalan and Ghayur discloses a composition for the release of a binding protein said composition comprising:
(a) a formulation, wherein said formulation comprises a crystallized binding protein (Ghayur, para [0110]), according to claim 33 (Kasalan, para [0271]) and an ingredient (Kasalan, para [0218], "Examples of preferred additional therapeutic agents that can be coadministered and/or coformulated with one or more IL-13 antagonists."); and
(b) at least one polymeric carrier (Kasalan, para [0170]; [0177], "The liquid form of the pharmaceutical composition may further contain ... polyethylene glycol.")

As to claim 55, Kasalan discloses the composition according to claim 54, wherein said polymeric carrier is poly (ethylene glycol) (para [0177]).

As to claim 56, Kasalan discloses the composition according to claim 54, wherein said ingredient is polyethylene glycol (para [0177]).

As to claim 57, Kasalan discloses a method for treating a mammal comprising the step of administering to the mammal an effective amount of the composition according to claim 54 (claim 33).

Claim 60 lack an inventive step under PCT Article 33(3) as being obvious over Kasalan, as above, in view of US 2003/0175261 A1 (Weickmann).

As to claim 60, Kasalan does not disclose that said adjuvant is hyaluronidase. However, Weickmann teaches that hyaluronidases are used as penetrants and adjuvants during a peptide administration (para [0060]). It would have been obvious to one of ordinary skill in the art to use hyaluronidase as an adjuvant per Weickmann to increase absorption of the binding protein.

Claims 3-15, 17-22 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed subject matter.

As to claims 3-12 and 15, prior art does not teach or fairly suggest the binding protein according to claim 1, wherein said binding protein comprises at least 3 CDRs (claim 3), and specifically does not teach the claimed variable domain CDR sets
VH 25C8 CDR Set (VH 25C8 CDR-H1, VH 25C8 CDR-H2, VH 25C8 CDR-H3 (Residues 31-35, 50-66, and 99-105 of SEQ ID NO:32);
VH 13CS CDR Set (VH 13C5 CDR-H1, VH 13C5 CDR-H2, VH 1305 CDR-H3 (Residues 32-38, 52-67, and 100-112 of SEQ ID NO: 46); or
VL 13CS CDR Set (VL 1305 CDR-L1, VL 13C5 CDR-L2, VL 1305 CDR-L3 (Residues 24-34, 50-56, 89-97 of SEQ ID NO:47) (claims 4-6).

As to claims 13, 14, 17-22, prior art does not teach or fairly suggest the binding protein according to claim 1, wherein said binding protein comprises at least one variable domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 70, 71, 80, 81.

Claims 1-69 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.