Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: **Expediente No. PCT/11-108934**

TÍTULO SOLICITADO: **"PROTEÍNAS DE UNIÓN A IL-17"**

PUBLICACIÓN: **Gaceta 641 del 30/03/2012, N° de publicación 314.**

SOLICITANTE: **ABBVIE INC.**

APODERADO: **ALICIA LLOREDA RICAURTE.**

TRÁMITE: **Recurso de Reposición y en subsidio el de apelación en contra de la Resolución 14592 de marzo 31 de 2015 por la cual se concede una patente de invención tramitada bajo el número de expediente PCT/11-108934.**

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 14592 de marzo 31 de 2015 por la cual se concedió a la solicitud PCT/11-108934 el privilegio de patente de invención.

I. PETICIÓN

Sírvase, Señor Superintendente, reponer íntegramente la Resolución 14592 de marzo 31 de 2015, 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 14592 de marzo 31 de 2015, que concede el privilegio de patente de invención solicitado para el capítulo reivindicatorio del expediente 11-108934 titulado "**Proteínas de unión a IL - 17**", 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 Infliximab, Adalimumab, Etaanercept, entre 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:

- **WO 9216553**
- **WO 9729131**
- **US 6090382**
- **WO 9406476**
- **US 5605690**

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 decidiere 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 2010/102251

En subsidio apelo.

Señor Superintendente,

TITO NOÉ BARRA MURILLO
C.C. 79.579.680 de Bogotá
T.P. 71168 del C. S de la J.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 9831.WO.O1	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 10/26424	International filing date *(day/month/year)* 05 March 2010 (05.03.2010)	(Earliest) Priority Date *(day/month/year)* 05 March 2009 (05.03.2009)
Applicant ABBOTT LABORATORIES		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the language, the international search was carried out 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)).

b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☒ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/26424

Box No. I **Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☒ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing 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.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/26424

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.: 106-133, 145-147, and 177-187
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

.....SEE EXTRA SHEET.....

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.:

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.:
1-69, wherein: claim 1 is limited to the CDR-H1 "DYEIH"; and wherein claims 2, 4, 6, 13, and 15 are limited to species which comprise the CDR-H1 "DYEIH" (see extra sheet for details)

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

International application No.
PCT/US 10/26424

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/395 (2010.01)
USPC - 424/145.1
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)-A61K 39/395 (2010.01)
USPC-424/145.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC-424/158.1; 530/388.23

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(PGPB,USPT,USOC,EPAB,JPAB); Google Patents; Google Scholar
IL-$, IL-17, IL-13, binding protein, antibody, chimeric, recombinant, humanized, crystallized, expression vector, coli, cho, cos, cerevisiae, mammalian, sf9, inflamm$, glycosylation, antagonisy, inhibitory, function, neutralizing

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0196371 A1 (KUESTNER et al.) 23 August 2007 (23.08.2007) (para [0005], [0027]-[0034], [0042], [0043], [0085], [0086], [0143], [0144], [0156], [0164], [0181], [0186], [0205], [0233], [0262], [0291], [0292], [0299], [0319], [0365], [0366], [0376], [0412], [0455])	1-3, 16, and 23-69
Y --- A	WO 2007/080174 A2 (ASHMAN et al.) 19 July 2007 (19.07.2007) (pg 17 para 2, SEQ ID NO:7,pg 19 para 2)	1-3, 16, and 23-69 --- 4-15, and 17-22
Y --- A	US 2008/0269467 A1 (ALLAN et al.) 30 October 2008 (30.10.2008) (para [0007]-[0028]) Table 2	1-3, 16, and 23-69 --- 4-15, and 17-22
Y	WO 2007/005608 A2 (LACY et al.) 11 January 2007 (11.01.2007) (pg 12 para 1, SEQ ID NO:2)	26
Y	WO 2002/072636 A2 (SHENOY et al.) 19 September 2002 (19.09.2002) (pg 1 ln 5-pg 2 ln 25; pg 8 ln 20-30; pg 9 ln 10-15; pg 21 ln 25-pg 22 ln 5)	32-36 and 54-57
A	US 2008/0219971 A1 (SMITH et al.) 11 September 2008 (11.09.2008) (para [0132], SEQ ID NO:34) 13, 14, and 17-22	13, 14, and 17-22

☐ 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	Date of mailing of the international search report
09 September 2010 (09.09.2010)	27 SEP 2010
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

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/26424

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2000/047625 A (SUNG et al.) 17 August 2000 (17.08.2000) (Fig. 6a. CDR2; pg 5 ln 15-20, SEQ ID NO: 22)	4-12, and 15
A	US 2007/0003567 A1 (PATERSON et al.) 04 January 2007 (04.01.2007) (Example 19, SEQ ID NO: 48) 4-12, and 15	4-12, and 15
A	WO 2004/110369 A2 (MCWHIRTER) 23 December 2004 (23.12.2004) (Claim 23, SEQ ID NO: 20) 4-12, and 15	4-12, and 15
A	SODERLIND et.al. Recombining germline-derived CDR sequences for creating diverse singleframework antibody libraries. Nature Biotechnology. August 2000. Vol 18, pages 852-856, especially the abstract and pg 852, col 2, para 1	1
A	YANG et al. CDR Walking Mutagenesis for the Affinity Maturation of a Potent Human Anti-HIV-1 Antibody into the Picomolar Range. J. Mol. Biol. (1995) Vol 254, pages 392-403, especially the abstract and pg 393-394	1

Form PCT/ISA/210 (continuation of second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/26424

Continuation of Box No. III Lack of Unity:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: Claims 1-69, drawn to a binding protein comprising an antigen binding domain capable of binding human IL-17, a nucleic acid encoding the binding protein, vectors and cells comprising the nucleic acid, compositions comprising the binding proteins, methods of producing the binding protein, and methods of administering the binding protein. The first invention of Group I+ will be searched and includes a binding protein comprising the CDR-H1 "DYEIH" (CDR1 of SEQ ID NO: 26, 28, and 34), i.e. claims 1-69, wherein claim 1 is limited to the CDR-H1 "DYEIH" , wherein claim 2 is limited to residues 31-35 of SEQ ID NO:26; 28, or 34, wherein claims 4 and 6 are limited to VH7D7, VH8C8, or VH10F7, and wherein claims 13 and 15 are limited to SEQ ID NOS: 60 or 61. Due to the number of sequences in this application, the additional inventions of Group I+ will be defined as necessary depending on Applicant's ultimate payment of additional fees. The additional sequences will be searched if applicant pays for each additional sequence or shows that the sequences share a special technical feature, i.e. a common structure or feature that defines a contribution over the prior art. Note that each additional sequence to be searched must be specified by the Applicant in the response to this invitation and must either (1) have an additional invention fee paid or (2) have a showing that the sequences share a common structure or feature that defines a contribution over the prior art

Group II+: Claims 70-105, 134-144, 148-176, and 188-201, drawn to a binding protein comprising an antigen binding domain capable of binding human IL-17, a nucleic acid encoding the binding protein, vectors and cells comprising the nucleic acid, compositions comprising the binding proteins, methods of producing the binding protein, and methods of administering the binding protein. Due to the number of sequences in this application, the additional inventions of Group II+ will be defined as necessary depending on Applicant's ultimate payment of additional fees. The additional sequences will be searched if applicant pays for each additional sequence or shows that the sequences share a special technical feature, i.e. a common structure or feature that defines a contribution over the prior art. Note that each additional sequence to be searched must be specified by the Applicant in the response to this invitation and must either (1) have an additional invention fee paid or (2) have a showing that the sequences share a common structure or feature that defines a contribution over the prior art

The groups listed above 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.

Group I+ and II+ share the technical feature of a binding protein comprising an antigen binding domain capable of binding human IL-17. However, this does not represent an improvement over the the prior art. Allen et al. (US 2008/0269467) teach a binding protein comprising an antigen binding domain capable of binding human IL-17 (abstract).

Although the inventions of Group I+ further share the technical feature of claim 1, this also does not represent an improvement over the prior art as Allen et al. further teach claim 1, i.e. a binding protein comprising the CDR-L2 of SEQ ID NO:923 ("KVSNRFS" present in Fabs 1-94 of Table 3 on pg 23).

Although the first named invention of Group I+ shares, with certain other inventions of Group I+, the feature of a CDR-H1 comprising SEQ ID NO: 919 (X1-X2-X3-X4-X5), this shared feature does not represent a special technical feature. Allen et al. teach a CDR-H1 consensus sequence, wherein X1 (X6) may be D, X2 (X7) may be Y, X4 (X9) may be I, and X5 (X10) may be H (SEQ ID NO: 244 below Table 2 on pg 23), each as claimed by Applicant. Although Allen et al. do not teach an X3 residue as claimed, this shared X3 residue does not represent a significant structural element because X3 represents unrelated alternative residues (E or G) which do not belong to a recognized class of amino acid residues, i.e. they are not known as conservative substitutes.

Accordingly, unity of invention is lacking.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: LEON R. YANKWICH
YANKWICH & ASSOCIATES, P.C.
201 BROADWAY
CAMBRIDGE, MA 02139

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* 27 SEP 2010
Applicant's or agent's file reference 9831.WO.O1	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 10/26424	05 March 2010 (05.03.2010)	05 March 2009 (05.03.2009)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 39/395 (2010.01)
USPC - 424/145.1

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 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 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/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	09 September 2010 (09.09.2010)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/26424

Box No. I 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 43*bis*.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 sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☒ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☒ together with the international application in electronic form

      ☐ 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 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:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US 10/26424

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. 106-133, 145-147, and 177-187

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 106-133, 145-147, and 177-187 are so unclear that no meaningful opinion could be formed *(specify)*:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ 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 said claims Nos. 106-133, 145-147, and 177-187

☐ 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 Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/26424

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 appicable 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:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: Claims 1-69, drawn to a binding protein comprising an antigen binding domain capable of binding human IL-17, a nucleic acid encoding the binding protein, vectors and cells comprising the nucleic acid, compositions comprising the binding proteins, methods of producing the binding protein, and methods of administering the binding protein. The first invention of Group I+ will be searched and includes a binding protein comprising the CDR-H1 "DYEIH" (CDR1 of SEQ ID NO: 26, 28, and 34), i.e. claims 1-69, wherein claim 1 is limited to the CDR-H1 "DYEIH", wherein claim 2 is limited to residues 31-35 of SEQ ID NO:26; 28, or 34, wherein claims 4 and 6 are limited to VH7D7, VH6C6, or VH10F7, and wherein claims 13 and 15 are limited to SEQ ID NOS: 60 or 61. Due to the number of sequences in this application, the additional inventions of Group I+ will be defined as necessary depending on Applicant's ultimate payment of additional fees. The additional sequences will be searched if applicant pays for each additional sequence or shows that the sequences share a special technical feature, i.e. a common structure or feature that defines a contribution over the prior art. Note that each additional sequence to be searched must be specified by the Applicant in the response to this invitation and must either (1) have an additional invention fee paid or (2) have a showing that the sequences share a common structure or feature that defines a contribution over the prior art

Group II+: Claims 70-105, 134-144, 149-176, and 188-201, drawn to a binding protein comprising an antigen binding domain capable of binding human IL-17, a nucleic acid encoding the binding protein, vectors and cells comprising the nucleic acid, compositions comprising the binding proteins, methods of producing the binding protein, and methods of administering the binding protein. Due to the number of sequences in this application, the additional inventions of Group II+ will be defined as necessary depending on Applicant's ultimate payment of additional fees. The additional sequences will be searched if applicant pays for each additional sequence or shows that the sequences share a special technical feature, i.e. a common structure or feature that defines a contribution over the prior art. Note that each additional sequence to be searched must be specified by the Applicant in the response to this invitation and must either (1) have an additional invention fee paid or (2) have a showing that the sequences share a common structure or feature that defines a contribution over the prior art

The groups listed above 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.

Group I+ and II+ share the technical feature of a binding protein comprising an antigen binding domain capable of binding human IL-17. However, this does not represent an improvement over the the prior art. Allen et al. (US 2008/0269467) teach a binding protein comprising an antigen binding domain capable of binding human IL-17 (abstract).

Although the inventions of Group I+ further share the technical feature of claim 1, this also does not represent an improvement over the prior art as Allen et al. further teach claim 1, i.e. a binding protein comprising the CDR-L2 of SEQ ID NO:923 ("KVSNRFS" present in Fabs 1-94 of Table 3 on pg 23).
Although the first named invention of Group I+ shares, with certain other inventions of Group I+, the feature of a CDR-H1 comprising SEQ ID NO: 919 (X1-X2-X3-X4-X5), this shared feature does not represent a special technical feature. Allen et al. teach a CDR-H1 consensus sequence, wherein X1 (X6) may be D, X2 (X7) may be Y, X4 (X9) may be I, and X5 (X10) may be H (SEQ ID NO: 244 below Table 2 on pg 23), each as claimed by Applicant. Although Allen et al. do not teach an X3 residue as claimed, this shared X3 residue does not represent a significant structural element because X3 represents unrelated alternative residues (E or G) which do not belong to a recognized class of amino acid residues, i.e. they are not known as conservative substitutes.
Accordingly, unity of invention is lacking.

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 species which comprise the CDR-H1 "DYEIH"

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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)	Claims	1-69	YES
	Claims	none	NO
Inventive step (IS)	Claims	4-15, and 17-22	YES
	Claims	1-3, 16, and 23-69	NO
Industrial applicability (IA)	Claims	1-69	YES
	Claims	none	NO

2. Citations and explanations:

Claims 1-3, 16, 23-25, 27-31, 37-53, and 58-69, lack an inventive step under PCT Article 33(3) as being obvious over US 2008/0269467 A1 to Allan et al. (hereinafter "Allan") in view of US 2007/0196371 A1 to KUESTNER et al. (hereinafter "Kuestner"), in further view of WO 2007/080174 A2 to ASHMAN et al. (hereinafter "Ashman").

As per claim 1, Allan discloses a binding protein comprising an antigen binding domain capable of binding human IL-17 (abstract), said antigen binding domain comprising a CDR-H1 of SEQ ID NO: 919 (X1-X2-X3-X4-X5), wherein X1 (X6) may be D, X2 (X7) may be Y, X4 (X9) may be I, and X5 (X10) may be H (SEQ ID NO: 244 below Table 2 on pg 23; also see Fab# 80-87 and 89-106 of Table 2 for specific examples of CDR-H1 which comprises the claimed X1, X2, X4, and X5 residues). However, Allan does not teach that the CDR-H1 comprises DYEIH, i.e. does not teach that X3 can be E.

Kuestner discloses a binding protein comprising an antigen binding domain capable of binding human IL-17 (para [0005], [0181]), and further discloses that IL-17 and IL-13 are related cytokine mediating inflammatory processes which contribute to tissue and cell damage and diseases such as inflammatory bowel disease (para [0455]) but does not teach that the CDR-H1 comprises DYEIH.

Ashman discloses a binding protein comprising an antigen binding domain capable of binding human IL-13 (pg 14 para 7), wherein said antigen binding domain comprises at least one CDR comprising an amino acid sequence selected from the group consisting of: CDR-HI. XI -X2-X3-X4,-X5 (SEQ ID NO: 919) , wherein; XI is D ; X2 is Y; X3 is E ; X4 is I; X5 is H (pg 16, para 4, the CDRHI of SEQ ID NO: 1; also see pg 17 para 2, SEQ ID NO:7, residues 31-35).

It would have been obvious to one of ordinary skill in the art to provide the IL-17antibody of Allan and further to substitute X3 with E, as suggested by Kuestner and Ashman to obtain the invention as claimed. Given the finite number of residues in CDRs such as the CDR-H1 of Allan, it would have been well within the technical grasp of a skilled artisan to produce and test variants of the CDR-H1, such as single-residue mutants, with a reasonable expectation of success, as it was well known in the art to do so, for example, using phage display techniques. Further, one skilled in the art would have considered DYEIH as a possible CDR-H1 because it was known in the art, as taught by Ashman, albeit in an antibody which binds the related interleukin IL-13 and it was well known in the art that CDRs can be applied in binding proteins which bind distinct to antigens when combined with different CDRs and/or framework. One would have been motivated to do so in order to improve the capacity of the antibody to inhibit cytokine mediating inflammatory processes which contribute to tissue and cell damage and diseases such as inflammatory bowel disease, as taught by Kuestner.

As per claim 2, Ashman discloses wherein said at least one CDR comprises residues 31-35 of SEQ ID NO:26; (pg 17 para 2, SEQ ID NO:7, residues 31-35).

As per claim 3, Ashman discloses wherein said binding protein comprises at least 3 CDRs (pg 19 para 2).

As per claim 16, Kuestner discloses wherein the binding protein binds IL-17 (para [0005]).

As per claim 23, Kuestner discloses wherein said IL-1 7 binding protein construct further comprising a linker polypeptide or an immunoglobulin constant domain (para [0186]).

As per claim 24, Kuestner discloses wherein said binding protein is selected from the group consisting of; an immunoglobulin molecule (para [0181]), a monoclonal antibody (para [0181]), a chimeric antibody,(para [0186]) a CDR-grafted antibody (para [0230]), a humanized antibody (para [0230]), a Fab (para [0042]), or a scFv (para [0042]).

As per claim 25, Kuestner does not specify wherein said binding protein comprises a heavy chain immunoglobulin constant domain selected from the group consisting of; a human IgM constant domain, a human IgG 1 constant domain, a human IgG2 constant domain, a human IgG3 constant domain, a human IgG4 constant domain, a human IgE constant domain, and a human IgA constant domain. Constant domain fusions of all of these antibody classes were well known in the art and would have been obvious to one of ordinary skill in the art.

As per claim 27, Kuestner disclosese an IL-17 binding protein conjugate further comprising an agent selected from the group consisting of; an immunoadhesion molecule, a therapeutic agent, or an imaging agent (para [0085], [0086], [0233]).

As per claim 28, Kuestner discloses wherein said agent is an imaging agent selected from the group consisting of a radio label, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin (para [0086]).

**********continued in supplemental box**********

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In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box No. V. 2. Citations and explanations:

As per claim 29, Keustner does not specify wherein said imaging agent is a radiolabel selected from the group consisting of 3H, 14C, 35S, 90Y, 99Tc 111In, 125I, 131I, 177Lu, 166Ho, and 153Sm, but such labels would have been obvious to one of ordinary skill in the art because they were commonly employed radioisotope labels.

As per claim 30, Kuestner discloses wherein said agent is a therapeutic or cytotoxic agent is a toxin (para [0085]).

As per claim 31, Kuestner does not specify wherein said binding protein possesses a human glycosylation pattern, but does specify humanized antibodies to avoid immunological rejection of the protein. It would have been obvious to one of ordinary skill in the art to produce the antibody with a human glycosylation pattern to avoid immunological rejection in humans.

As per claim 37, Kuestner discloses an isolated nucleic acid encoding a binding protein amino acid sequence (para [0027]-[0034]).

As per claim 38, Kuestner discloses an isolated nucleic acid encoding an IL-17 binding protein construct amino acid sequence (para [0027] -[0034])..

As per claim 39, Kuestner discloses a vector comprising an isolated nucleic acid according to claim 37 or 38 (para [0143], [0144]).

As per claim 40, neither Allan, Kuestner, nor Ashman discloses wherein said vector is selected from the group consisting of pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, and pBJ. PcDNA at least, was a well known and widely used expression vector, and would have been an obvious expression vector to one of ordinary skill in the art.

As per claim 41, Kuestner discloses a host cell comprising a vector (para [0164]).

As per claim 42, Kuestner discloses wherein said host cell is a prokaryotic cell (para [0164]).

As per claim 43, Kuestner discloses wherein said host cell is E. coli (para [0164]).

As per claim 44, Kuestner discloses wherein said host cell is a eukaryotic cell (para [0412]).

As per claim 45, Kuestner discloses wherein said eukaryotic cell is an animal cell, (para [0412]).

As per claim 46, Kuestner discloses wherein said eukaryotic cell is a mammalian cell, (para [0412]).

As per claim 47, Kuestner discloses wherein said host cell is a CHO cell (para [0376]).

As per claim 48, Kuestner discloses wherein said host cell is COS (para [0412]).

As per claim 49, Kuestner discloses wherein said host cell is a yeast cell (para [0365], [0366]).

As per claim 50, Kuestner discloses wherein said yeast cell is Saccharomyces cerevisiae (para [0365], [0356]]).

As per claim 51, Kuestner discloses wherein said host cell is an insect Sf9 cell (para [0156]).

As per claim 52, Kuestner discloses method of producing a protein capable of binding IL-17, comprising culturing a host cell in culture medium under conditions sufficient to produce a binding protein capable of binding IL-17 (para [0412]).

As per claim 53, Kuestner discloses protein produced according to the method (para [0412])

As per claim 58, Kuestner discloses pharmaceutical composition comprising the binding protein, and a pharmaceutically acceptable carrier (para [0043], [0205]).

As per claim 59, Kuestner discloses wherein said pharmaceutically acceptable carrier functions as adjuvant useful to increase the absorption or dispersion of said binding protein (para [0319], liposomes).

As per claim 60, neither Allan, Kuestner, nor Ashman discloses wherein said adjuvant is hyaluronidase, but such an adjuvant would have been obvious to one of ordinary skill in the art because it was a well known and commercially available adjuvant as disclosed in the instant application (pg 132 ln 20-30).

As per claim 61, Kuestner discloses at least one additional therapeutic agent for treating a disorder in which IL-17 activity is detrimental (para [0291], tacrolimus).

As per claim 62, Kuestner discloses wherein said additional agent is selected from the group consisting of: therapeutic agent, imaging agent, cytotoxic agent (para [0085], [0086]).

As per claim 63, Kuestner discloses a method for reducing human IL-17 activity comprising contacting human IL-17 with the binding protein of claim 1 such that human IL-17 activity is reduced (para [0291]).

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In case the space in any of the preceding boxes is not sufficient.

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Box No. V. 2. Citations and explanations:

As per claim 64, Kuestner discloses a method for reducing human IL-17 activity in a human subject suffering from a disorder in which IL-17 activity is detrimental, comprising administering to the human subject the binding protein of claim 1 such that human IL-17 activity in the human subject is reduced (para [0291]).

As per claim 65, Kuestner discloses a method for treating a subject for a disease or a disorder in which IL-17 activity is detrimental by administering to the subject the binding protein such that treatment is achieved (para [0291]).

As per claim 66, Kuestner discloses wherein said disorder is asthma (para [0292]).

As per claim 67, Kuestner discloses wherein said disorder is rheumatoid arthritis (para [0262]).

As per claim 68, Kuestner discloses a method of treating a patient suffering from a disorder in which IL-17 is detrimental comprising the step of administering the binding protein of claim I before, concurrent, or after the administration of a second agent, wherein the second agent is Il-11 (para [0299]).

As per claim 69, Kuestner discloses wherein said administering to the subject is by at least one mode selected from subcutaneous, or intravenous (para [0299]).

Claim 26 lacks an inventive step under PCT Article 33(3) as being obvious over Allan in view of Kuestner and Ashman, and further in view of WO 2007/005608 A2 (LACY et al.).

As per claim 26, neither Allan, Kuestner, nor Ashman discloses an immunoglobulin constant domain having an amino acid sequence selected from the group consisting of: SEQ ID NO:3 SEQIDNO:4 SEQIDNO:5 and SEQ IDNO:6.
Lacy discloses humanised antibodies comprising an immunoglobulin constant domain having an amino acid sequence of: SEQ ID NO:3 (pg 12 para 1, SEQ ID NO:2). It would have been obvious to one of ordinary skill in the art to use the Ig constant domain taught by Lacy, in the binding proteins aught by Kuestner and Ashman, to obtain the invention as claimed, because it presents the binding activity in a human antibody context.

Claims 32-36 and 54-57, lack an inventive step under PCT Article 33(3) as being obvious over Allan inview of Kuestner and Ashman, and further in view of WO 2002/072636 A2 to SHENOY et al. (hereinafter "Shenoy").

As per claim 32, neither Allan, Kuestner, nor Ashman discloses wherein said binding protein is a crystallized binding protein.
Shenoy discloses pharmaceutical compositions comprising crystallized binding proteins (pg 1 ln 5-pg 2 ln 25). It would have been obvious to one of ordinary skill in the art to produce the binding proteins taught by Kuestner and Ashman, in crystallized form, as taught by Shenoy, to obtain the invention as claimed, because it provides proteins in high concentration, stability and purity.

As per claim 33, neither Allan, Kuestner, nor Ashman discloses wherein said IL-17 binding protein construct is a crystallized IL-17 binding protein construct.
Shenoy discloses pharmaceutical compositions comprising crystallized binding proteins (pg 1 ln 5-pg 2 ln 25). It would have been obvious to one of ordinary skill in the art to produce the binding proteins taught by Kuestner and Ashman, in crystallized form, as taught by Shenoy, to obtain the invention as claimed, because it provides proteins in high concentration, stability and purity.

As per claim 34, Shenoy discloses wherein said crystallized IL-17 binding protein construct is a carrier-free pharmaceutical controlled release crystallized IL-17 binding protein construct (pg 1 ln 5-pg 2 ln 25).

As per claim 35, Shenoy discloses wherein said IL-17 binding protein construct has a greater half life in vivo than the soluble counterpart of said IL-17 binding protein construct (pg 9 ln 10-15).

As per claim 36, Shenoy discloses wherein said IL-17 binding protein construct retains biological activity (pg 8 ln 20-30, antibodies are active upon dissolution).

As per claim 54, Shenoy discloses a composition for the release of a binding protein (pg 1 ln 5-pg 2 ln 25) said composition comprising: (a) a formulation, wherein said formulation comprises a crystallized binding protein, according to claim 33 (pg 1 ln 5-pg 2 ln 22), and an ingredient (pg 1 ln 5-pg 2 ln 22, excipient); and (b) at least one polymeric carrier (pg 1 ln 5-pg 2 ln 22).

As per claim 55, Shenoy discloses wherein said polymeric carrier is a polymer selected from one or more of the group consisting of: poly (acrylic acid), poly (cyanoacrylates), poly (amino acids), poly (anhydrides), poly (depsipeptide), poly (esters), poly (lactic acid), poly (lactic-co-glycolic acid) or PLGA, poly (bhydroxybutryate), poly (caprolactone), poly (dioxanone); poly (ethylene glycol), poly ((hydroxypropyl) methacrylamide, poly [(organo) phosphazene], poly (ortho esters), poly (vinyl alcohol), poly (vinylpyrrolidone), maleic anhydride- alkyl vinyl ether copolymers, pluronic polyols, albumin, alginate, cellulose and cellulose derivatives, collagen, fibrin, gelatin, hyaluronic acid, oligosaccharides, glycaminoglycans, sulfated polysaccharides, blends and copolymers thereof (pg 21 ln 25-pg 22 ln 5).

As per claim 56, Shenoy discloses wherein said ingredient is gelatin, (pg 22 ln 5).

As per claim 57, Shenoy discloses a method for treating a mammal comprising the step of administering to the mammal an effective amount of the composition (pg 1 ln 20-25).

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In case the space in any of the preceding boxes is not sufficient.

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Claims 4-12, and 15 meet the criteria set forth under PCT Article 33(2)-(3) because the prior art does not teach or fairly suggest the VH7D7, VH6C8, or VH10F7 CDR sets.

As per claim 4, Allan discloses a binding protein comprising an antigen binding domain capable of binding human IL-17 (abstract), said antigen binding domain comprising a CDR-H1 of SEQ ID NO: 919 (X1-X2-X3-X4-X5), wherein X1 (X6) may be D, X2 (X7) may be Y, X4 (X9) may be I, and X5 (X10) may be H (SEQ ID NO: 244 below Table 2 on pg 23; also see Fab# 80-87 and 89-106 of Table 2 for specific examples of CDR-H1 which comprises the claimed X1, X2, X4, and X5 residues). However, Allan does not teach that the CDR-H1 comprises DYEIH, i.e. does not teach that X3 can be E.

Ashman discloses VB 707 CDR-HI .residues 31-35 of SEQ ID NO :26 (pg 17 para 2, SEQ ID NO:7, residues 31-35) from the Vh7D7 set, but does not disclose wherein said at least 3 CDRs comprises a variable domain CDR set selected from the group consisting of:
VH 7D7/CDR Set
VB 707 CDR-HI .residues 31-35 of SEQ ID NO :26 (pg 17 para 2, SEQ ID NO:7, residues 31-35).
VB 707 CDR-H2 Residues 50-66 of SEQ IDNO:26
VB 707 CDR-H3 Residues 99-110 of SEQ IDNO:26

VH 6C6CDR Set.
VH.6C6.CDR-H1 Residues 31-35 of SEQ ID NO:28
VH.6C6.CDR-H2 Residues 50-66 of SEQ ID NO:28
VH.6C6.CDR-H3 Residues 99-108 of SEQ ID NO:28
or
VH 10F7 CDR set
VB10F7 CDR-HI Residues 31-35 of SEQ ID NO:34
VB10F7 CDR-H2 Residues 50-66 of SEQ ID NO:34
VB10F7 CDR-H3 Residues 99-110 of SEQ ID NO:34

WO 2000/047625 A to SUNG et al. discloses a CDR2 sequence that is 63.5% identical to residues 50-66 of SEQ ID NO:26 (Fig. 6a. CDR2; pg 5 ln 15-20, SEQ ID NO: 22).
US 2007/0003567 A1 to PATERSON et al. discloses a CDR sequence 76.3% identical to Residues 99-108 of SEQ ID NO:28 (Example 19, SEQ ID NO: 48).
WO 2004/110369 A2 to MCWHIRTER discloses a CDR 74% identical to Residues 50-66 of SEQ ID NO:34 (Claim 23, SEQ ID NO: 20).
However, the prior art does not teach or fairly suggest any of the complete CDR sets which include DYEIH.

Claims 5-12 meet the criteria set forth under PCT Article 33(2)-(3) for substantially the same reasons, because they depend from claim 4.

Claims 13, 14, and 17-22, meet the criteria set forth under PCT Article 33(2)-(3) because the prior art does not teach or fairly suggest an amino acid sequence selected from the group consisting of:SEQ ID NO:60 or SEQ ID NO:61.

As per claim 13, Allan discloses a binding protein comprising an antigen binding domain capable of binding human IL-17 (abstract), said antigen binding domain comprising a CDR-H1 of SEQ ID NO: 919 (X1-X2-X3-X4-X5), wherein X1 (X6) may be D, X2 (X7) may be Y, X4 (X9) may be I, and X5 (X10) may be H (SEQ ID NO: 244 below Table 2 on pg 23; also see Fab# 80-87 and 89-106 of Table 2 for specific examples of CDR-H1 which comprises the claimed X1, X2, X4, and X5 residues). However, Allan does not teach that the CDR-H1 comprises DYEIH, i.e. does not teach that X3 can be E.

Ashman does not disclose wherein said binding protein comprises at least one variable domain having an amino acid sequence selected from the group consisting of:SEQ ID NO:60 or SEQ ID NO:61.
The closes prior art, US 2008/0219971 A1 to SMITH et al., merely discloses a humanized antibody 82% identical to SEQ ID NO: 60 (para [0132], SEQ ID NO:34).

Claims 14, and 17-22 meet the criteria set forth under PCT Article 33(2)-(3) for substantially the same reasons, because they depend from claim 13.

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