PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* 20 AUG 2015

Applicant's or agent's file reference
X20280

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2015/030267	12 May 2015	19 May 2014

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 39/395 (2015.01)
CPC - A61K 2039/505 (2015.07)

Applicant ELI LILLY AND COMPANY

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 and 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.

Name and mailing address of the ISA/	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. 571-273-8300	05 August 2015	Blaine Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2015/030267

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:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

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 forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

SEQ ID NOs:1-13 were searched.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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

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

☐ the entire international application.

☒ claims Nos. 4-6, 10-18

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. 4-6, 10-18 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 4-6 and 10-18 are multiple dependent claims 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. 4-6, 10-18

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

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file 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 the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ 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

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

1. Statement

Novelty (N)	Claims	1-3, 7-9	YES
	Claims	None	NO
Inventive step (IS)	Claims	1-3, 7-9	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1-3, 7-9	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-3 and 7-9 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest:

Regarding claim 1, the prior art of record, individually or in combination, does not teach or fairly suggest an antibody that binds human Ang2 (SEQ ID NO: 7), comprising a light chain (LC) and a heavy chain (HC), wherein the light chain comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences KASQDVYIAVA (SEQ ID NO: 8), YWASTRDT (SEQ ID NO: 9), and HQYSSYPPT (SEQ ID NO: 10), respectively, and wherein the heavy chain comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3 consisting of the amino acid sequences GYSFTDYNMV (SEQ ID NO: 11), YIDPYNGGTGYNQKFEG (SEQ ID NO: 12), and ARTRDRYDVWYFDV (SEQ ID NO: 13), respectively.

Regarding claim 2, the prior art of record, individually or in combination, does not teach or fairly suggest an antibody, comprising a light chain (LC) and a heavy chain (HC), wherein the light chain comprises a light chain variable region (LCVR) and the heavy chain comprises a heavy chain variable region (HCVR), wherein the LCVR has the amino acid sequence given in SEQ ID NO: 3, and the HCVR has the amino acid sequence given in SEQ ID NO: 1.

Claim 3 depends from claim 1 or claim 2 and therefore meets the criteria set out in PCT Article 33(2)-(3) for at least the same reason as does claim 1 and claim 2.

Regarding claim 7, the prior art of record, individually or in combination, does not teach or fairly suggest a mammalian cell comprising a DNA molecule comprising a polynucleotide sequence encoding a polypeptide having an amino acid sequence of SEQ ID NO: 4 and a polynucleotide sequence encoding a polypeptide having an amino acid sequence of SEQ ID NO: 2, wherein the cell is capable of expressing an antibody comprising a light chain having an amino acid sequence of SEQ ID NO: 4 and a heavy chain having an amino acid sequence of SEQ ID NO: 2.

Claims 8 and 9 depend either directly or indirectly from claim 7 and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reason as does claim 7.

The following prior art is made of record to support and further define the reasons 1-3 and 7-9 meet the criteria set out in PCT Article 33 (2)-(3):

(i) US 2011/0027286 A1 to Thurston et al. (hereafter Thurston) discloses an antibody that binds human Ang2 (Para. [0005] The present invention provides human antibodies that bind to human Ang-2), but fails to explicitly disclose an antibody that binds human Ang2 (SEQ ID NO: 7), comprising a light chain (LC) and a heavy chain (HC), wherein the light chain comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences KASQDVYIAVA (SEQ ID NO: 8), YWASTRDT (SEQ ID NO: 9), and HQYSSYPPT (SEQ ID NO: 10), respectively, and wherein the heavy chain comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3 consisting of the amino acid sequences GYSFTDYNMV (SEQ ID NO: 11), YIDPYNGGTGYNQKFEG (SEQ ID NO: 12), and ARTRDRYDVWYFDV (SEQ ID NO: 13), respectively. Further, Thurston discloses an antibody (Para. [0005] The present invention provides human antibodies that bind to human Ang-2), but fails to explicitly disclose an antibody, comprising a light chain (LC) and a heavy chain (HC), wherein the light chain comprises a light chain variable region (LCVR) and the heavy chain comprises a heavy chain variable region (HCVR), wherein the LCVR has the amino acid sequence given in SEQ ID NO: 3, and the HCVR has the amino acid sequence given in SEQ ID NO: 1. Furthermore, Thurston discloses a cell comprising a DNA molecule comprising a polynucleotide sequence encoding an anti-Ang2 antibody (Para. [0015] In another aspect, the invention provides nucleic acid molecules encoding anti-Ang-2 antibodies or fragments thereof. Recombinant expression vectors carrying the nucleic acids of the invention, and host cells into which such vectors have been introduced, are also encompassed by the invention, as are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced), but fails to explicitly disclose a mammalian cell comprising a DNA molecule comprising a polynucleotide sequence encoding a polypeptide having an amino acid sequence of SEQ ID NO: 4 and a polynucleotide sequence encoding a polypeptide having an amino acid sequence of SEQ ID NO: 2, wherein the cell is capable of expressing an antibody comprising a light chain having an amino acid sequence of SEQ ID NO: 4 and a heavy chain having an amino acid sequence of SEQ ID NO: 2.

Supplemental Box

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

(ii) US 2010/0159587 A1 to Brinkmann et al. (hereafter Brinkmann) discloses an antibody that binds human Ang2 (Para. [0015] The present invention relates in part to an antibody which binds specifically to human angiopoietin-2 (ANG-2)), but fails to explicitly disclose an antibody that binds human Ang2 (SEQ ID NO: 7), comprising a light chain (LC) and a heavy chain (HC), wherein the light chain comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences KASQDVYIAVA (SEQ ID NO: 8), YWASTRDT (SEQ ID NO: 9), and HQYSSYPPT (SEQ ID NO: 10), respectively, and wherein the heavy chain comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3 consisting of the amino acid sequences GYSFTDYNMV (SEQ ID NO: 11), YIDPYNGGTGYNQKFEG (SEQ ID NO: 12), and ARTRDRYDVWYFDV (SEQ ID NO: 13), respectively.
Further, Brinkmann discloses an antibody (Para. [0015] The present invention relates in part to an antibody which binds specifically to human angiopoietin-2 (ANG-2)), but fails to explicitly disclose an antibody, comprising a light chain (LC) and a heavy chain (HC), wherein the light chain comprises a light chain variable region (LCVR) and the heavy chain comprises a heavy chain variable region (HCVR), wherein the LCVR has the amino acid sequence given in SEQ ID NO: 3, and the HCVR has the amino acid sequence given in SEQ ID NO 1. Furthermore, Brinkmann discloses a cell comprising a DNA molecule comprising a polynucleotide sequence encoding an anti-Ang2 antibody (Para. [0015] The present invention relates in part to an antibody which binds specifically to human angiopoietin-2 (ANG-2); Para. [0026] The invention further provides expression vectors containing nucleic acid according to the invention capable of expressing said nucleic acid in a prokaryotic or eukaryotic host cell, and host cells containing such vectors for the recombinant production of such an antibody), but fails to explicitly disclose a mammalian cell comprising a DNA molecule comprising a polynucleotide sequence encoding a polypeptide having an amino acid sequence of SEQ ID NO: 4 and a polynucleotide sequence encoding a polypeptide having an amino acid sequence of SEQ ID NO: 2, wherein the cell is capable of expressing an antibody comprising a light chain having an amino acid sequence of SEQ ID NO: 4 and a heavy chain having an amino acid sequence of SEQ ID NO: 2.

(iii) US 2006/0246071 A1 to Green et al. (hereafter Green) discloses an antibody that binds human Ang2 (Paras. [0013]-[0014] Embodiments of the invention relate to targeted binding agents that specifically bind to Angiopoietin-2 ... One embodiment of the invention, the targeted binding agent is a fully human antibody that binds to Ang-2), but fails to explicitly disclose an antibody that binds human Ang2 (SEQ ID NO: 7), comprising a light chain (LC) and a heavy chain (HC), wherein the light chain comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3 consisting of the amino acid sequences KASQDVYIAVA (SEQ ID NO: 8), YWASTRDT (SEQ ID NO: 9), and HQYSSYPPT (SEQ ID NO: 10), respectively, and wherein the heavy chain comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3 consisting of the amino acid sequences GYSFTDYNMV (SEQ ID NO: 11), YIDPYNGGTGYNQKFEG (SEQ ID NO: 12), and ARTRDRYDVWYFDV (SEQ ID NO: 13), respectively.
Further, Green discloses an antibody (Paras. [0013]-[0014] Embodiments of the invention relate to targeted binding agents that specifically bind to Angiopoietin-2 ... One embodiment of the invention, the targeted binding agent is a fully human antibody that binds to Ang-2), but fails to explicitly disclose an antibody, comprising a light chain (LC) and a heavy chain (HC), wherein the light chain comprises a light chain variable region (LCVR) and the heavy chain comprises a heavy chain variable region (HCVR), wherein the LCVR has the amino acid sequence given in SEQ ID NO: 3, and the HCVR has the amino acid sequence given in SEQ ID NO: 1.
Furthermore, Green discloses a cell comprising a DNA molecule comprising a polynucleotide sequence encoding an anti-Ang2 antibody (Para. [0032] Other embodiments of the invention include isolated nucleic acid molecules encoding any of the antibodies described herein, vectors having isolated nucleic acid molecules encoding anti-Ang-2 antibodies or a host cell transformed with any of such nucleic acid molecules. In addition, one embodiment of the invention is a method of producing an anti-Ang-2 antibody by culturing host cells under conditions wherein a nucleic acid molecule is expressed to produce the antibody followed by recovering the antibody), but fails to explicitly disclose a mammalian cell comprising a DNA molecule comprising a polynucleotide sequence encoding a polypeptide having an amino acid sequence of SEQ ID NO: 4 and a polynucleotide sequence encoding a polypeptide having an amino acid sequence of SEQ ID NO: 2, wherein the cell is capable of expressing an antibody comprising a light chain having an amino acid sequence of SEQ ID NO: 4 and a heavy chain having an amino acid sequence of SEQ ID NO: 2.

Claims 1-3 and 7-9 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.