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)*	26 JUL 2017
Applicant's or agent's file reference 41135-759601	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2017/016407	03 February 2017	04 February 2016

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 39/395; C07K 16/28; C07K 16/46; C07K 19/00; C12N 15/13 (2017.01)
CPC - A61K 38/00; A61K 2039/505; C07K 2317/565; C07K 2319/00 (2017.02)

Applicant THE CALIFORNIA INSTITUTE FOR BIOMEDICAL RESEARCH

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/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	05 July 2017	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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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: 51-56, 59, 74, 86, 87, 92, 96-108, 110, and 124 were searched.

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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. 4-22, 26-28, 32-37, 41-45

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. 4-22, 26-28, 32-37, 41-45 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 4-22, 26-28, 32-37, and 41-45 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. 4-22, 26-28, 32-37, 41-45

☐ 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.

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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, 23-25, 29-31, 38-40	YES
	Claims	None	NO
Inventive step (IS)	Claims	1-3, 23-25, 29-31, 38-40	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1-3, 23-25, 29-31, 38-40	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-3, 23-25, 29-31, and 38-40 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 comprising: a first amino acid sequence comprising SEQ ID NO: 74, and a second amino acid sequence comprising one or more of SEQ ID NOS: 54-56.

Claims 2 and 3 depend from claim 1, and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 1.

Regarding claim 23, the prior art of record, individually or in combination, does not teach or fairly suggest an antibody comprising a first amino acid sequence comprising: (a) one or more of SEQ ID NOS: 54-56; and (b) SEQ ID NO: 86, SEQ ID NO: 98, or an amino acid sequence having an unnatural amino acid replacing one or more amino acid residues of SEQ ID NO: 86.

Claims 24 and 25 depend from claim 23, and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 23.

Regarding claim 29, the prior art of record, individually or in combination, does not teach or fairly suggest an antibody comprising: (a) a first amino acid sequence comprising one or more of SEQ ID NOS: 54-56; and (b) an unnatural amino acid.

Claims 30 and 31 depend from claim 29, and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 29.

Regarding claim 38, the prior art of record, individually or in combination, does not teach or fairly suggest a composition comprising: (a) an amino acid sequence comprising one or more of SEQ ID NOS: 51-56 and an unnatural amino acid; and (b) a cell-targeting molecule linked to the amino acid sequence via the unnatural amino acid.

Claims 39 and 40 depend from claim 38, and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 38.

The following prior art is made of record to support and further define the reasons claims 1-3, 23-25, 29-31, and 38-40 meet the criteria set out in PCT Article 33(2)-(3):

(i) US 2014/0242080 A1 to Roche Glycart AG discloses an antibody comprising: a second amino acid sequence comprising one or more of SEQ ID NOS: 54-56 (Para. [0184] a T cell activating bispecific antigen binding molecule comprising (i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, comprising at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 270, SEQ ID NO: 271 and SEQ ID NO: 272 ... ; SEQ ID NO: 272 [14 amino acids] shows 100% sequence identity with SEQ ID NO: 56 of this instant application [14 amino acids]), but fails to disclose a first amino acid sequence comprising SEQ ID NO: 74. Further, Roche Glycart AG discloses an antibody comprising a first amino acid sequence comprising: (a) one or more of SEQ ID NOS: 54-56 ((Para. [0184] a T cell activating bispecific antigen binding molecule comprising (i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, comprising at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 270, SEQ ID NO: 271 and SEQ ID NO: 272 ... ; SEQ ID NO: 272 [14 amino acids] shows 100% sequence identity with SEQ ID NO: 56 of this instant application [14 amino acids]), but fails to disclose (b) SEQ ID NO: 86, SEQ ID NO: 98, or an amino acid sequence having an unnatural amino acid replacing one or more amino acid residues of SEQ ID NO: 86. Further still, Roche Glycart AG discloses an antibody comprising (a) a first amino acid sequence comprising one or more of SEQ ID NOS: 54-56 (Para. [0184] a T cell activating bispecific antigen binding molecule comprising (i) a first antigen binding moiety which is a Fab molecule capable of specific binding to CD3, comprising at least one heavy chain complementarity determining region (CDR) selected from the group consisting of SEQ ID NO: 270, SEQ ID NO: 271 and SEQ ID NO: 272 ... ; SEQ ID NO: 272 [14 amino acids] shows 100% sequence identity with SEQ ID NO: 56 of this instant application [14 amino acids]), but fails to disclose (b) an unnatural amino acid.

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Supplemental Box

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

(ii) WO 2007/058725 A2 to The Regents of the University of California discloses a composition comprising: (a) an amino acid sequence comprising one or more of SEQ ID NOS: 51-56 and an unnatural amino acid; and (b) a cell-targeting molecule linked to the amino acid sequence (Para. [0167] the present invention provides a mutant antibody comprising a first polypeptide sequence and a second polypeptide sequence. The first polypeptide sequence includes a portion of an antigen recognition domain, or the entire antigen recognition domain, as well as a mutant amino acid at a position which is within, or proximate to, the antigen recognition domain ... The second polypeptide sequence includes a first targeting moiety, and the second polypeptide sequence is attached via a linker (e.g. (Gly4Ser)3, or a covalent bond (ie zero-order linker)) to the first polypeptide sequence; Para. [0073] FIG. 42 shows the sequences for the VL chain of 2D12.5 (SEQ ID NO: 1) and the sequences for CDR1, CDR2, and CDR3 for the VL chain of 2D12.5 (SEQ ID NOS: 2, 3, and 4, respectively); Para. [0124] "Peptide," "polypeptide" or "protein" refers to a polymer in which the monomers are amino acids and are joined together through amide bonds, alternatively referred to as a polypeptide ... unnatural amino acids, for example, beta -alanine, phenylglycine and homoarginine are also included; SEQ ID NO: 3 [14 amino acids] shows 100% sequence identity with SEQ ID NO: 51 of this instant application [14 amino acids]), but fails to disclose (b) a cell-targeting molecule linked to the amino acid sequence via the unnatural amino acid.

Claims 1-3, 23-25, 29-31, and 38-40 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.