

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To: ROBIN L. TESKIN
BAKER, DONELSON, BEARMAN, CALDWELL
& BERKOWITZ, P.C.
901 K STREET, NW, SUITE 900
WASHINGTON, DC 20001

Date of mailing
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Applicant's or agent's file reference
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FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 22/82601

International filing date (day/month/year)

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ADD. C07K 2317/24, C07K 2317/31, C07K 2317/565

Applicant SURROZEN OPERATING, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.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 66.1bis(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.

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. 571-273-8300

Date of completion of this opinion

25 March 2023

Authorized officer

Kari Rodriguez

PCT Help Desk

Telephone No. 571-272-4300

**WRITTEN OPINION OF THE
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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(b)).

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.
b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.

5. Additional comments:

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

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

☐ the entire international application.

☒ claims Nos. 4-7, 10-34

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. 4-7, 10-34 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 4-7, 10-34 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. 4-7, 10-34

☐ 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}. I(a) or (b).

☐ See Supplemental Box for further details.

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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:

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 searched, the appropriate additional search fees must be paid.

Group I+, Claims 1-3, 8-9, directed to a multispecific antibody or antibody fragment. The antibody will be searched to the extent that the antibody encompasses wherein: (A) the VH1 comprises: (i) a heavy chain complementarity-determining region 1 (CDRH1) of SEQ ID NO:121, (ii) a heavy chain complementarity-determining region 2 (CDRH2) of SEQ ID NO:141, (iii) a heavy chain complementarity-determining region 3 (CDRH3) of SEQ ID NO:161; and the VL1 comprises: (iv) a light chain complementarity-determining region 1 (CDRL1) of SEQ ID NO:221, (v) a light chain complementarity-determining region 2 (CDRL2) of SEQ ID NO:241; and (vi) a light chain complementarity-determining region 3 (CDRL3) of SEQ ID NO:261, and (B) the VH2 comprises: (i) a CDRH1 of SEQ ID NO:321; (ii) a CDRH2 of SEQ ID NO:341, and (iii) a CDRH3 of SEQ ID NO:361 (note, these are the first claimed CDR sequences for the inventive antibody). The first named invention was determined based on the first claimed CDR sequences (claim 1) for the inventive antibody embodiment. This first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. It is believed that claims 1-3, 8-9 encompass this first named invention, and thus these claims will be searched without fee to the extent that the antibody encompasses wherein: (A) the VH1 comprises: (i) a heavy chain complementarity-determining region 1 (CDRH1) of SEQ ID NO:121, (ii) a heavy chain complementarity-determining region 2 (CDRH2) of SEQ ID NO:141, (iii) a heavy chain complementarity-determining region 3 (CDRH3) of SEQ ID NO:161; and the VL1 comprises: (iv) a light chain complementarity-determining region 1 (CDRL1) of SEQ ID NO:221, (v) a light chain complementarity-determining region 2 (CDRL2) of SEQ ID NO:241; and (vi) a light chain complementarity-determining region 3 (CDRL3) of SEQ ID NO:261, and (B) the VH2 comprises: (i) a CDRH1 of SEQ ID NO:321; (ii) a CDRH2 of SEQ ID NO:341, and (iii) a CDRH3 of SEQ ID NO:361. Additional antibody(ies) comprising additional CDR sequence(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected antibody(ies) comprising additional CDR sequence(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. An exemplary election would be an antibody comprising wherein: (A) the VH1 comprises: (i) a heavy chain complementarity-determining region 1 (CDRH1) of SEQ ID NO:121, (ii) a heavy chain complementarity-determining region 2 (CDRH2) of SEQ ID NO:141, (iii) a heavy chain complementarity-determining region 3 (CDRH3) of SEQ ID NO:161; and the VL1 comprises: (iv) a light chain complementarity-determining region 1 (CDRL1) of SEQ ID NO:221, (v) a light chain complementarity-determining region 2 (CDRL2) of SEQ ID NO:241; and (vi) a light chain complementarity-determining region 3 (CDRL3) of SEQ ID NO:261, and (B) the VH2 comprises: (i) a CDRH1 of SEQ ID NO:321; (ii) a CDRH2 of SEQ ID NO:341, and (iii) a CDRH3 of SEQ ID NO:361 (claim 1).

The inventions listed as Group I+ do not relate to a single special technical feature under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special technical features

The inventions of Groups I+ each include the special technical feature of a unique amino acid sequence. Each amino acid sequence comprises a unique peptide, and is considered a distinct technical feature.

Common technical features

No technical features are shared between the antibody amino acid sequences in each of Group I+ inventions and, accordingly, these inventions lack unity a priori.

----Please see continuation in first supplemental box-----

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. 1-3, 8-9, limited to SEQ ID NOs:121, 141, 161, 221, 241, 261, 321, 341, 361

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Box No. V Reasoned statement under Rule 43bis.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, 8-9	YES
	Claims	None	NO
Inventive step (IS)	Claims	1-3, 8-9	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1-3, 8-9	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-3, 8-9 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.

Regarding claim 1, WO 2019/126399A1 to Surrozen, Inc., (hereinafter 'Surrozen'399') teaches a multispecific antibody or antibody fragment (p12, in 14-17, - "Diabodies", multivalent or multispecific fragments constructed by gene fusion (W094/13804; P. Holliger et al., Proc. Natl. Acad. Sci. USA 906444-6448, 1993) are also a particular form of antibody contemplated herein') comprising at least:

(A) a first antigen-binding region which specifically binds to frizzled class receptor 4 (Fzd4) and comprises a first heavy chain variable domain (VH1) and a first light chain variable domain (VL1) (Claim 1 - 'An isolated antibody, or an antigen-binding fragment thereof, that binds to one or more Frizzled receptor, comprising a sequence comprising:

(i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 1A;

(ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 1A'),

(B) a second antigen-binding region which specifically binds to low density lipoprotein receptor-related protein 5 and/or 6 (LRP5 and/or LRP6) and comprises at least a second heavy chain variable domain (VH2) (p3, in 7-12, - 'In certain embodiments, any of the antibodies, or antigen-binding fragments thereof, are a fusion protein. In certain embodiments, the antibody, or antigen-binding fragment thereof, is fused to a polypeptide sequence that binds LRP5 or LRP6. In certain embodiments, the polypeptide sequence that binds LRP5 or LRP6 is an antibody, or an antigen-binding fragment thereof, that binds to LRP5 or LRP6.'), wherein:

(A) the VH1 comprises:

(i) a heavy chain complementarity-determining region 1 (CDRH1) which has an amino acid sequence which:

(i-1) has at least 80% identity to the amino acid sequence of SEQ ID NO: 121 or to the CDRH1 amino acid sequence contained in SEQ ID NO: 181, optionally defined according to Kabat; or

(i-2) comprises or consists of the amino acid sequence of SEQ ID NO: 121, or comprises or consists of the CDRH1 amino acid sequence contained in SEQ ID NO: 181, optionally defined according to Kabat;

(ii) a heavy chain complementarity-determining region 2 (CDRH2) which has an amino acid sequence which:

(ii-1) has at least 90% identity to the amino acid sequence of SEQ ID NO: 141 or to the CDRH2 amino acid sequence contained in SEQ ID NO: 181, optionally defined according to Kabat; or

(ii-2) comprises or consists of: the amino acid sequence of SEQ ID NO: 141; or comprises or consists of the CDRH2 amino acid sequence contained in SEQ ID NO: 181, optionally defined by Kabat; and

(iii) a heavy chain complementarity-determining region 3 (CDRH3) which has an amino acid sequence which:

(iii-1) has at least 90% identity to the amino acid sequence of SEQ ID NO: 161 or to the CDRH3 amino acid sequence contained in SEQ ID NO: 181, optionally defined by Kabat; or

(iii-2) comprises or consists of the amino acid sequence of SEQ ID NO: 161, or comprises or consists of the CDRH3 amino acid sequence contained in SEQ ID NO: 181, optionally defined by Kabat (Claim 2 - 'The isolated antibody, or antigen-binding fragment thereof, of claim 1, comprising a heavy chain variable region comprising an amino acid sequence having at least 90% identity to the amino acid sequence set forth in any of SEQ ID NOs: 1-37, 66, 68 or 1477.'; SEQ ID NO 66, aa 1-120 has 96.5% identity to VH1 of instant SEQ ID NO: 181,

wherein aa 31-35 has 80% identity to CDRH1 of claimed SEQ ID NO: 121, aa 50-66 has 94.1% identity to CDRH2 of claimed SEQ ID NO: 141, aa 99-109 has 100% identity to CDRH3 of claimed SEQ ID NO: 161). -----claim 1 continued-----

----Please see continuation in second supplemental box-----

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Supplemental Box

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

Continuation of:

Box No. IV. 3. Lack of unity of invention

Additionally, even if Group I+ inventions were considered to share the technical features of including:

a multispecific antibody or antibody fragment comprising at least: (A) a first antigen-binding region which specifically binds to frizzled class receptor 4 (Fzd4) and comprises a first heavy chain variable domain (VH1) and a first light chain variable domain (VL1), (B) a second antigen-binding region which specifically binds to low density lipoprotein receptor-related protein 5 and/or 6 (LRP5 and/or LRP6) and comprises at least a second heavy chain variable domain (VH2), wherein: (A) the VH1 comprises: CDRH1, CDRH2 and CDRH3 sequences, and the VL1 comprises: CDRL1, CDRL2 and CDRL3 sequences, and (B) the VH2 comprises: CDRH1, CDRH2 and CDRH3 sequences,

these shared technical features are previously disclosed by US 2021/0292422 A1 to Surrozen, Inc., (hereinafter 'Surrozen').

Surrozen teaches a multispecific antibody or antibody fragment comprising at least: (A) a first antigen-binding region which specifically binds to frizzled class receptor 4 (Fzd4) and comprises a first heavy chain variable domain (VH1) and a first light chain variable domain (VL1), (B) a second antigen-binding region which specifically binds to low density lipoprotein receptor-related protein 5 and/or 6 (LRP5 and/or LRP6) and comprises at least a second heavy chain variable domain (VH2), wherein: (A) the VH1 comprises: CDRH1, CDRH2 and CDRH3 sequences, and the VL1 comprises: CDRL1, CDRL2 and CDRL3 sequences, and (B) the VH2 comprises: CDRH1, CDRH2 and CDRH3 sequences (Claim 1 - 'A multispecific Wnt surrogate molecule, wherein the Wnt surrogate molecule comprises:

(i) a plurality of regions that each specifically bind to a set of one or more Frizzled (Fzd) receptor epitopes (Fzd binding regions), wherein at least two Fzd binding regions bind to different sets of one or more Fzd receptor epitopes; and

(ii) one or more regions that specifically bind to a Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) and/or a LDL receptor-related protein 6 (LRP6) (LRP5/6 binding regions).'; para [0020] - 'In some embodiments, at least one of the Fzd binding regions comprises one or more antigen-binding fragments of an antibody. In some embodiments, the one or more antigen-binding fragments are selected from the group consisting of: IgG, scFv, Fab, and VHH or sdAbs'; para [0083] - 'In this regard, an antigen-binding fragment of the herein described antibodies may comprise 1, 2, 3, 4, 5, or all 6 CDRs of a VH and VL sequence set forth herein from antibodies that bind one or more Fzd receptors or LRP5 and/or LRP6. In particular embodiments, an antigen-binding fragment may comprise all three VH CDRs or all three VL CDRs. Similarly, an antigen-binding fragment thereof may comprise all three CDRs of a VHH or sdAb'; para [0061] - 'FIGS. 12A-12E. The 2:2 tetraivalent bispecific molecules, consisting of the two F1 and two L2 binding arms, are highly potent in inducing Wnt signaling.').

As the technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups.

Therefore, Group I+ inventions lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.

continuation of item 4 above: claims 4-7, 10-34 are held unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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Supplemental Box

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

Continuation of:

Box No. V2. Citations and Explanations

-----continuation of claim 1 -----

Surrozen'399 fails to teach the amino acid sequence of CDRH1 and CDRH2 of claimed SEQ ID NOs: 121 and 141, respectively, and also fails to teach the VL1 comprises:

(iv) a light chain complementarity-determining region 1 (CDRL1) which has an amino acid sequence which:

(iv-1) has at least 90% identity to the amino acid sequence of SEQ ID NO:221 or to the CDRL1 amino acid sequence contained in SEQ ID NO: 281, optionally defined by Kabat; or

(iv-2) comprises or consists of the amino acid sequence of SEQ ID NO: 221, or comprises or consists of the CDRL1 amino acid sequence contained in SEQ ID NO: 281, optionally defined according to Kabat;

(v) a light chain complementarity-determining region 2 (CDRL2) which has an amino acid sequence which comprises or consists of:

(v-1) the amino acid sequence of SEQ ID NO: 241; or

(v-2) the CDRL2 amino acid sequence contained in SEQ ID NO: 281, optionally defined according to Kabat; and

(vi) a light chain complementarity-determining region 3 (CDRL3) which has an amino acid sequence which comprises or consists of:

(vi-1) the amino acid sequence of SEQ ID NO: 261; or

(vi-2) the CDRL3 amino acid sequence contained in SEQ ID NO: 281, optionally defined according to Kabat; and

(B) the VH2 comprises:

(i) a CDRH1 which has an amino acid sequence which comprises or consists of:

(i-1) the amino acid sequence of SEQ ID NO: 321; or

(i-2) the CDR141 amino acid sequence contained in SEQ ID NO: 381, optionally defined according to IMGT or Kabat;

(ii) a CDRH2 which has an amino acid sequence which:

(ii-1) has at least 90% identity to the amino acid sequence of SEQ ID NO: 341 or to the CDRH3 amino acid sequence contained in SEQ ID NO: 381, optionally defined according to IMGT or Kabat;

(ii-2) comprises or consists of the amino acid sequence of SEQ ID NO: 341; or

(ii-3) comprises or consists of the CDRH2 amino acid sequence contained in SEQ ID NO: 381, optionally defined according to IMGT or Kabat; and

(iii) a CDRH3 which has an amino acid sequence which:

(iii-1) has at least 90% identity to the amino acid sequence of SEQ ID NO:

361 or to the CDRH3 amino acid sequence contained in SEQ ID NO: 381, optionally defined according to IMGT or Kabat; or

(iii-2) comprises or consists of the amino acid sequence of any one of SEQ ID NOs: 361 and 363-366, or comprises or consists of the CDRH3 amino acid sequence contained in any one of SEQ ID NOS: 381 and 393-396, optionally defined according to IMGT or Kabat.

US 2005/0282252 A1 to Siegel (hereinafter 'Siegel') teaches Anti-Rh(D) light chain DPK9 JK4 with 100% identity to VL2 of instant SEQ ID NO:281, comprising CDRL1-CDRL3 sequences of claimed SEQ ID NOS:221, 241 and 261, respectively (para [0051] - 'FIG. 10 comprises FIGS. 10A and 10B. FIG. 10A is an alignment of anti-Rh(D) light chains to their nearest germline V and J genes, and indicates predominance of DPK-9 usage from the VI family.'; Example 2; Fig 10A, DPK9 JK4 sequence aa 1-107 has 100% identity to VL2 of instant SEQ ID NO:281, comprising CDRL1-CDRL3 sequences of claimed SEQ ID NOS:221, 241 and 261, respectively). Siegel does not teach Fzd4 binding antibody light chain.

WO 2019/126398 A1 to Surrozen, Inc., (hereinafter 'Surrozen'398') teaches Anti-LRP5 single domain antibody (VHH/sdAb), SEQ ID 133 with 93.1% identity to VH2 of instant SEQ ID NO:381 (Claim 13 - 'The Wnt surrogate molecule of any of claims 10-12, wherein the one or more LRP5/6 binding regions comprise an amino acid sequence having at least 90% identity to any of the sequences set forth in SEQ ID NOS:66-88 or 133, or an antigen-binding fragment thereof.'; SEQ ID NO 133, aa 1-117 has 93.1% identity to VH2 of instant SEQ ID NO:381, wherein 26-33 has 87.5% identity to CDRH1 of claimed SEQ ID NO:321, aa 50-57 has 100% identity to CDRH2 of claimed SEQ ID NO:341, aa 96-106 has 90.9% identity to CDRH3 of claimed SEQ ID NO:361). Surrozen'398 does not teach the sequence of CDRH1 and CDRH3 of claimed SEQ ID NOS: 321 and 361, respectively.

There is no prior art of record that, either alone or in combination with additional prior art, teaches or otherwise makes fairly obvious the sequence of claimed bispecific antibody comprising SEQ ID NOS: 121, 141, 321 and 361, respectively. Therefore, claim 1 meets the criteria set out in PCT Article 33(2)-(3) because the prior art does not teach or fairly suggest the claimed subject matter, specifically SEQ ID NOS: 121, 141, 321 and 361.

Regarding claims 2-3, 8-9, these claims are dependent on claim 1, and as such claims 2-3, 8-9, also meet the criteria set out in PCT Article 33(2)-(3) for substantially the same reasons.

Claims 1-3, 8-9 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.