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Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

(54) Title: ANTI-CLAUDIN 18.2 ANTIBODIES AND USES THEREOF

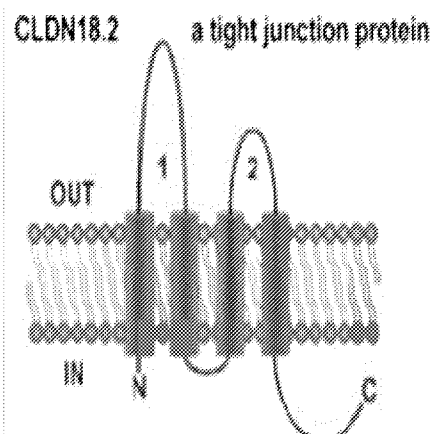
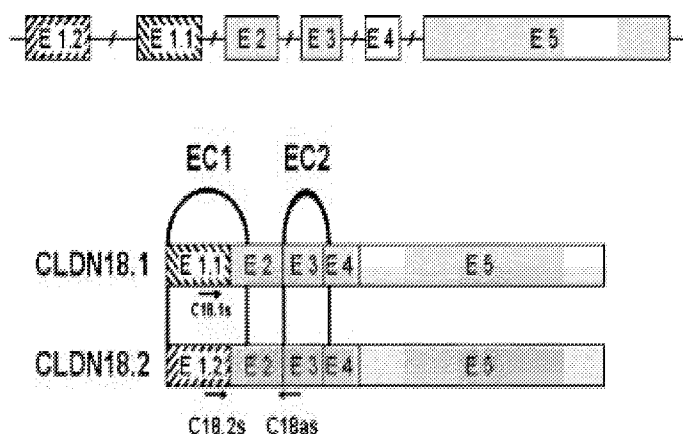


Figure 1

(57) **Abstract:** The present disclosure relates generally to immunoglobulin-related compositions (e.g., antibodies or antigen binding fragments thereof) that can bind to the Claudin 18.2 protein. The antibodies of the present technology are useful in methods for detecting and treating a Claudin 18.2-associated cancer in a subject in need thereof.

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/44800

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07K 16/28, C07K 16/30, A61P 35/00 (2022.01)

CPC - C07K 16/28, C07K 16/30, C07K 2317/56, C07K 16/3046, A61P 35/00

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)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2019/242505 A1 (L & L BIOPHARMA, CO. LTD) 26 December 2019 (26.12.2019); abstract; pg 24, para 2; para [0093]; claim 14, 16, 34	1, (3, 6)/(1), 7-8, 10, 11/(7-10)
A	WO 2010/137654 A1 (YOSHIDA et al.) 15 November 2012 (15.11.2012); para [0208]; claim 3, 5	2, (3, 6)/2, 9, 11/(9)
A	UniProt Accession No. A0A2S1YQL5, UniProtKB - A0A2S1YQL5 (A0A2S1YQL5_9FLAO), 18 July 2018 [online]. [Retrieved on 14 February 2022]. Retrieved from the internet: https://www.uniprot.org/uniprot/A0A2S1YQL5 ; entire document	1, 3/(1), 6/(1)
A	WO 2019/219089 A1 (BRIDGE HEALTH BIO-TECH CO., LTD) 21 November 2019; abstract; claim 13	1, 3/(1), 6/(1)
A	UniProt Accession No. Q920E8, UniProtKB - Q920E8 (Q920E8_MOUSE), 01 December 2001 [online]. [Retrieved on 14 February 2022]. Retrieved from the internet: https://www.uniprot.org/uniprot/Q920E8 ; entire document	2, 3/2, 6/2

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"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

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Name and mailing address of the ISA/US

Mall Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/44800

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:
 - 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 13ter.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 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
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 forming part of 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 21/44800

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.: 12-42
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 Supplemental Box ---

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.:
1-3, 6-11, limited as noted in extra sheet

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 21/44800

Box No. III Observations where unity of invention is lacking

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 1-11, directed to an antibody or antigen binding fragment thereof comprising a heavy chain immunoglobulin variable domain (VH) and a light chain immunoglobulin variable domain (VL). The antibody will be searched to the extent that the antibody encompasses (a) the VH comprises a VH-CDR1 sequence of SEQ ID NO: 6, a VH-CDR2 sequence of SEQ ID NO: 7, and a VH-CDR3 sequence of SEQ ID NO: 8, and/or the VL comprises a VL-CDR1 sequence of SEQ ID NO: 9, a VL-CDR2 sequence of SEQ ID NO: 10, and a VL-CDR3 sequence of SEQ ID NO: 11; further wherein the VH comprises an amino acid sequence of SEQ ID NO: 36; and/or (b) the VL comprises an amino acid sequence of SEQ ID NO: 37, further comprising a Fc domain of an isotype selected from the group consisting of IgG1, and comprising a HC amino acid sequence and a LC amino acid sequence selected from the group consisting of: SEQ ID NO: 64 and SEQ ID NO: 65, (note, these are the first claimed sequences for the inventive antibody embodiment). It is believed that claims 1-3, 6-11 encompass this first named invention, and thus these claims will be searched without fee to the extent that the antibody encompasses (a) the VH comprises a VH-CDR1 sequence of SEQ ID NO: 6, a VH-CDR2 sequence of SEQ ID NO: 7, and a VH-CDR3 sequence of SEQ ID NO: 8, and/or the VL comprises a VL-CDR1 sequence of SEQ ID NO: 9, a VL-CDR2 sequence of SEQ ID NO: 10, and a VL-CDR3 sequence of SEQ ID NO: 11; further wherein the VH comprises an amino acid sequence of SEQ ID NO: 36; and/or (b) the VL comprises an amino acid sequence of SEQ ID NO: 37, further comprising a Fc domain of an isotype selected from the group consisting of IgG1, and comprising a HC amino acid sequence and a LC amino acid sequence selected from the group consisting of: SEQ ID NO: 64 and SEQ ID NO: 65. Additional antibody polypeptide(s) comprising additional sequence(s) and/or variants of constant region will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected antibody polypeptide(s) comprising additional sequence(s) and/or variants of constant region. 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 (a) the VH comprises a VH-CDR1 sequence of SEQ ID NO: 6, a VH-CDR2 sequence of SEQ ID NO: 7, and a VH-CDR3 sequence of SEQ ID NO: 8, and/or the VL comprises a VL-CDR1 sequence of SEQ ID NO: 9, a VL-CDR2 sequence of SEQ ID NO: 10, and a VL-CDR3 sequence of SEQ ID NO: 11; further wherein the VH comprises an amino acid sequence of SEQ ID NO: 36; and/or (b) the VL comprises an amino acid sequence of SEQ ID NO: 37, further comprising a Fc domain of an isotype selected from the group consisting of IgG1 comprising a single amino acid substitutions consisting of N297A, and comprising a HC amino acid sequence and a LC amino acid sequence selected from the group consisting of: SEQ ID NO: 64 and SEQ ID NO: 65 (claims 1-4, 6-11).

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 Group I+ each include the special technical feature of a unique amino acid sequence. Each amino acid sequence encodes a unique peptide, and is considered a distinct technical feature.

Common technical features

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

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

An antibody or antigen binding fragment thereof comprising a heavy chain immunoglobulin variable domain (VH) and a light chain immunoglobulin variable domain (VL); wherein: (a) the VH comprises a VH-CDR1 sequence, a VH-CDR2 sequence, and a VH-CDR3 sequence, and/or the VL comprises a VL-CDR1 sequence, a VL-CDR2 sequence, and a VL-CDR3 sequence, these shared technical features are previously disclosed by US 2019/0076525 A1 to Ganymed Pharmaceuticals GmbH et al. (hereinafter "Ganymed").

Ganymed discloses an antibody or antigen binding fragment thereof (claim 1 - "A method of treating a cancer disease in a human patient, wherein the method comprises administering to the patient an antibody, said antibody having the ability of binding to CLDN18.2") comprising a heavy chain immunoglobulin variable domain, VH (claim 1 - "the antibody comprises a heavy chain variable region"), and a light chain immunoglobulin variable domain, VL (claim 1 - "a light chain variable region"), wherein: a. the VH comprises a VH-CDR1 sequence, a VH-CDR2 sequence, and a VH-CDR3 sequence (claim 1 - "the antibody comprises a heavy chain variable region (VH) having a CDR1 of positions 45-52 of SEQ ID NO: 17, a CDR2 of positions 70-77 of SEQ ID NO: 17, and a CDR3 of positions 116-126 of SEQ ID NO: 17"), and/or the VL comprises a VL-CDR1 sequence, a VL-CDR2 sequence and a VL-CDR3 sequence (claim 1 - "a light chain variable region (VL) having a CDR1 of positions 47-58 of SEQ ID NO: 24, a CDR2 of positions 76-78 of SEQ ID NO: 24, and a CDR3 of positions 115-123 of SEQ ID NO: 24").

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 12-42 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).