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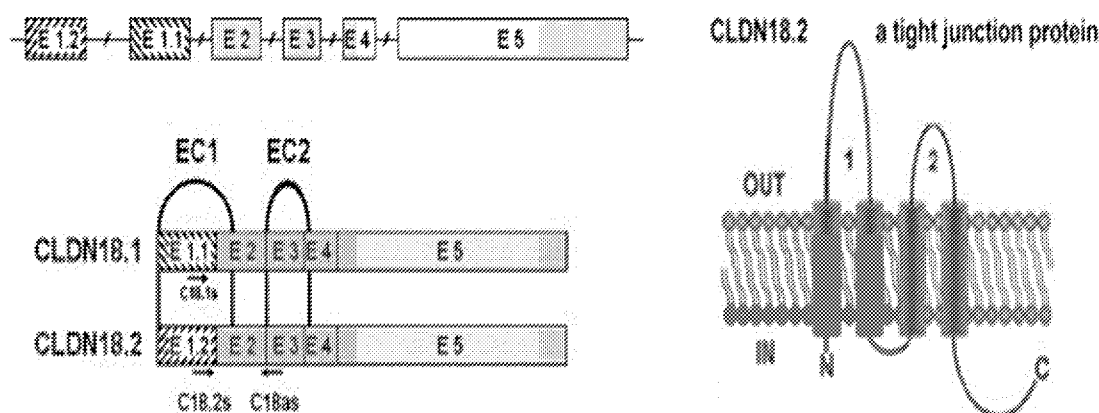
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Declarations under Rule 4.17:

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

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

FIG. 1



(57) Abstract: The present disclosure relates generally to immunoglobulin-related compositions (e.g. multi-specific antibodies or antigen binding fragments thereof) that can bind to the Claudin 18.2 protein. The multi-specific 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:

17 March 2022 (17.03.2022)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/44801

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07K 16/28; C07K 16/30; A61P 35/00 (2021.01)

CPC - C07K 16/28; C07K 16/30; C07K 2317/56; C07K 2317/565; C07K 2317/31; C07K 2317/2809; 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 2020/023679 A1 (ACCURUS BIOSCIENCES, INC.) 30 January 2020 (30.01.2020); especially abstract; para [0005]-[0006], [0223]; SEQ ID NOs: 61, 65, 100, 107	1-3, 7-10, 12-14
A	US 2017/0298120 A1 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 19 October 2017 (19.10.2017); especially SEQ ID NO: 96	1-3, 9, 12-14
A	US 2012/0141501 A1 (YOSHIDA et al.) 7 June 2012 (07.06.2012); especially SEQ ID NO: 8	1-3, 9, 12-14
A	US 2018/0362620 A1 (GENENTECH, INC.) 20 December 2018 (20.12.2018); especially SEQ ID NO: 75	7-8, 10
A	US 2018/0318437 A1 (BAYER PHARMA AKTIENGESELLSCHAFT) 8 November 2018 (08.11.2018); especially SEQ ID NO: 10	7-8, 10

☐ 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

21 December 2021

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/44801

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 21/44801

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.: 4-6, 15-42, 46-50, 52-60
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:
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.

Continued on 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.:
1-3, 7-10, 12-14, limited to the first named bispecific antibody (see details on 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 21/44801

Continued from Box No. III Observations where unity of invention is lacking

Group I+, Claims 1-3, 7-14, 43-45, 51, directed to a bispecific antibody or antigen binding fragment thereof comprising a first antigen binding moiety that binds a Claudin 18.2 epitope and a second antigen binding moiety that binds to a second epitope, wherein the first antigen binding moiety comprises a first heavy chain immunoglobulin variable domain (VH) and a first light chain immunoglobulin variable domain (VL), wherein the second antigen binding moiety comprises a second VH and a second VL. The bispecific antibody will be searched to the extent that the bispecific antibody encompasses (a) the first 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 first 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; and wherein the first VH comprises an amino acid sequence of SEQ ID NO: 36; and/or (b) the first VL comprises an amino acid sequence of SEQ ID NO: 37, wherein the bispecific antibody comprises a heavy chain (HC) amino acid sequence comprising SEQ ID NO: 64; and/or a light chain (LC) amino acid sequence comprising SEQ ID NO: 65, further wherein the second VH comprises an amino acid sequence of SEQ ID NO: 97; and/or (b) the second VL comprises an amino acid sequence of SEQ ID NO: 98; further comprising a Fc domain of an isotype IgG1; (note, these are the first claimed sequences for the inventive bispecific antibody). It is believed that claims 1-3, 7-10, 12-14 encompass this first named invention, and thus these claims will be searched without fee to the extent that the bispecific antibody encompasses (a) the first 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 first 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; and wherein the first VH comprises an amino acid sequence of SEQ ID NO: 36; and/or (b) the first VL comprises an amino acid sequence of SEQ ID NO: 37, wherein the bispecific antibody comprises a heavy chain (HC) amino acid sequence comprising SEQ ID NO: 64; and/or a light chain (LC) amino acid sequence comprising SEQ ID NO: 65, further wherein the second VH comprises an amino acid sequence of SEQ ID NO: 97; and/or (b) the second VL comprises an amino acid sequence of SEQ ID NO: 98; further comprising a Fc domain of an isotype IgG1. Additional antibody polypeptide(s) comprising additional sequence(s) and/or constant region variant(s) 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 constant region variant(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 a bispecific antibody encompassing (a) the first 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 first 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; and wherein the first VH comprises an amino acid sequence of SEQ ID NO: 36; and/or (b) the first VL comprises an amino acid sequence of SEQ ID NO: 37, wherein the bispecific antibody comprises a heavy chain (HC) amino acid sequence comprising SEQ ID NO: 64; and/or a light chain (LC) amino acid sequence comprising SEQ ID NO: 65, further wherein the second VH comprises an amino acid sequence of SEQ ID NO: 97; and/or (b) the second VL comprises an amino acid sequence of SEQ ID NO: 98; further comprising a Fc domain of an isotype IgG1 comprising a single amino acid substitution N297A (claims 1-3, 7-14).

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 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 of Groups I+ and, accordingly, these groups lack unity a priori.

Additionally, even if Group I+ inventions were considered to share the technical, these shared technical features are previously disclosed by the prior art, as further discussed below.

A feature shared by Group I+ is a bispecific antibody or antigen binding fragment thereof comprising a first antigen binding moiety that binds a Claudin 18.2 epitope and a second antigen binding moiety that binds to a second epitope, wherein the first antigen binding moiety comprises a first heavy chain immunoglobulin variable domain (VH) and a first light chain immunoglobulin variable domain (VL), wherein the second antigen binding moiety comprises a second VH and a second VL, and wherein: (a) the first VH comprises a VH-CDR1, a VH-CDR2 sequence, and a VH-CDR3 sequence and/or the first VL comprises a VL-CDR1 sequence, a VL-CDR2 sequence and a VL-CDR3 sequence;

(continued)

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(continued)

a bispecific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain are covalently bonded to one another, and wherein:

(a) each of the first polypeptide chain and the fourth polypeptide chain comprises in the N-terminal to C-terminal direction:

(i) a light chain variable domain of a first immunoglobulin that is capable of specifically binding to a first epitope;

(ii) a light chain constant domain of the first immunoglobulin;

(iii) a flexible peptide linker comprising the amino acid sequence (GGGGS)₃; and

(iv) a light chain variable domain of a second immunoglobulin that is linked to a complementary heavy chain variable domain of the second immunoglobulin, or a heavy chain variable domain of a second immunoglobulin that is linked to a complementary light chain variable domain of the second immunoglobulin, wherein the light chain and heavy chain variable domains of the second immunoglobulin are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence (GGGGS)₆ to form a single-chain variable fragment; and

(b) each of the second polypeptide chain and the third polypeptide chain comprises in the N-terminal to C-terminal direction:

(i) a heavy chain variable domain of the first immunoglobulin that is capable of specifically binding to the first epitope; and

(ii) a heavy chain constant domain of the first immunoglobulin.

However, this shared technical feature is previously disclosed by WO 2020/023679 A1 to Accurus Biosciences, Inc. (hereinafter 'Accurus').

Accurus discloses a bispecific antibody or antigen binding fragment thereof comprising a first antigen binding moiety that binds a Claudin 18.2 epitope and a second antigen binding moiety that binds to a second epitope (abstract - "Provided herein are novel anti-CLDN 18.2 antibodies and chimeric antigen receptors (CAR), cells or compositions comprising the same, vector or plasmid encoding... bispecific antibodies containing anti-CLDN 18.2 antibody, and methods for producing the same..."; para [0006] - "In some embodiments, the antibody is a bispecific antibody has a binding specificity to a second target protein."), wherein the first antigen binding moiety comprises a first heavy chain immunoglobulin variable domain (VH) and a first light chain immunoglobulin variable domain (VL), wherein the second antigen binding moiety comprises a second VH and a second VL, and wherein: (a) the first VH comprises a VH-CDR1, a VH-CDR2, and a VH-CDR3 sequence, and/or the first VL comprises a VL-CDR1, a VL-CDR2, and a VL-CDR3 sequence (para [0015] - "Also provided is an isolated cell comprising one or more polynucleotide encoding the antibody or fragment (e.g., VH1, VH2, VH3, VL1, VL2, VL3, heavy and light chain CDR 1, CDR 2, CDR3) thereof or the fusion protein or bispecific antibody of the present disclosure."). Accurus further discloses engineered antibodies such as scFv and multimerized versions comprising heavy and light chains linked via a linker (para [0210] - "Examples of antibodies include (but are not limited to) monoclonal, single chain, and functional fragments of antibodies."; para [0218] - "Alternatively, techniques for the production of single chain antibodies may be used. Single chain antibodies (scFvs) comprise a heavy chain variable region and a light chain variable region connected with a linker peptide (typically around 5 to 25 amino acids in length)."; para [0220] - "The antibodies of the present disclosure may be multimerized to increase the affinity for an antigen. The antibody to be multimerized may be one type of antibody or a plurality of antibodies which recognize a plurality of epitopes of the same antigen. As a method of multimerization of the antibody, binding of the IgG CH3 domain to two scFv molecules, binding to streptavidin, introduction of a helix-turn-helix motif and the like can be exemplified.").

Group I+ inventions further share the technical feature of: an anti-CD3 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 an amino acid sequence; and/or (b) the VL comprises an amino acid sequence. However, these shared technical features are previously disclosed by US 2018/0355038 A1 to Regeneron Pharmaceuticals, Inc. (hereinafter 'Regeneron').

Regeneron teaches an anti-CD3 antibody or antigen binding fragment thereof (para [0008] - "In a first aspect, the present invention provides antibodies and antigen-binding fragments thereof that bind human CD3 having weak or no detectable affinity for human and/or cynomolgus CD3. The antibodies according to this aspect of the invention are useful, inter alia, for targeting T cells expressing CD3, and for stimulating T cell activation, e.g., under circumstances where T cell-mediated killing is beneficial or desirable. The anti-CD3 antibodies of the invention, or antigen-binding portions thereof, may be included as part of a bispecific antibody that directs CD3-mediated T cell activation to specific cell types such as tumor cells or infectious agents.") comprising a heavy chain immunoglobulin variable domain (VH) and a light chain immunoglobulin variable domain (VL), wherein: (a) the VH comprises an amino acid sequence; and/or (b) the VL comprises an amino acid sequence (para [0009] - "Exemplary anti-CD3 antibodies of the present invention are listed in Tables 2 and 3 herein. Table 2 sets forth the amino acid sequence identifiers of the heavy chain variable regions (HCVRs), as well as heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3). Table 3 sets forth the sequence identifiers of the nucleic acid molecules encoding the HCVRs, HCDR1, HCDR2 and HCDR3 regions of the exemplary anti-CD3 antibodies. Tables 4 and 5 set forth light chain variable regions (LCVRs), as well as complementarity determining regions (LCDR1, LCDR2 and LCDR3) of the exemplary anti-CD3 antibodies."). Regeneron further teaches bispecific antibodies comprising anti-CD3 binding domain (Abstract - "The antibodies and bispecific antigen-binding molecules of the invention are useful for the treatment of diseases and disorders in which an upregulated or induced targeted immune response is desired and/or therapeutically beneficial").

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.