

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

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UNITED STATES OF AMERICA**

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) **29 January 2025 (29.01.2025)**

Applicant's or agent's file reference
55679-0009WO2

FOR FURTHER ACTION
See paragraph 2 below

International application No. PCT/US2024/037706	International filing date (day/month/year) 12 July 2024 (12.07.2024)	Priority date (day/month/year) 13 July 2023 (13.07.2023)
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International Patent Classification (IPC) or both national classification and IPC
IPC: **A61K 39/395** (2023.01); **A61P 35/00** (2023.01); **A61P 35/02** (2023.01); **A61P 37/06** (2023.01)
CPC: **A61K 39/39541**; **A61P 35/00**; **A61P 35/02**; **A61P 37/06**

Applicant
LTZ THERAPEUTICS 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
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Date of completion of this opinion
19 December 2024 (19.12.2024)

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2024/037706

Box No. I

Basis of the 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 43bis.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:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2024/037706

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. See claims listed below

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. 33, 38-42, 46-79 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 33, 38-42, and 46-79 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. 3-17, 20-31, 33, 35-79

- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing complying with WIPO Standard ST.26, and such listing was not available to the International Searching Authority in the form, language and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13~~ter~~.1(a).
 - ☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2024/037706

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 examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-32, 34-37, and 43-45 are drawn to anti-CLEC5A antibodies, and bispecific antibodies which bind CLEC5A and a tumor-associated antigen, or an autoimmune disease target.

The first invention of Group I+ is restricted to an antibody comprising a heavy chain variable chain region (VH) and a light chain variable region (VL), where the VH is selected to be SEQ ID NO:11, further comprising a HCDR1 (SEQ ID NO:3), HCDR2 (SEQ ID NO:5), HCDR3 (SEQ ID NO:7), and where the VL is selected to be SEQ ID NO:12, further comprising a LCDR1 (SEQ ID NO:8), LCDR2 (SEQ ID NO:9), and a LCDR3 (SEQ ID NO:10). The 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. Specifically, the first named invention was selected based on the VH and VL sequences listed in instant claim 18, and the CDR sequences listed in instant claim 1. It is believed that claims 1, 2, 18, 19, 32, and 34 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NOs 11 and 12.

Applicant is invited to elect additional VH, VL, and their respective, corresponding, SEQ ID NOs to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be an antibody comprising a heavy chain variable chain region (VH) and a light chain variable region (VL), where the VH is selected to be SEQ ID NO:21, further comprising a HCDR1 (SEQ ID NO:14), HCDR2 (SEQ ID NO:16), HCDR3 (SEQ ID NO:17), and where the VL is selected to be SEQ ID NO:22, further comprising a LCDR1 (SEQ ID NO:18), LCDR2 (SEQ ID NO:19), and a LCDR3 (SEQ ID NO:20). Additional VH, VL, and their respective, corresponding, SEQ ID NOs will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on 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/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulas do not share a significant structural element responsible for treating CLEC5A associated diseases, requiring the selection of alternative VH and VL where "An antibody or antigen-binding fragment thereof that binds to CLEC5A comprising a heavy chain variable region (VH) comprising an amino acid sequence that is at least 90% identical to a selected VH sequence, and a light chain variable region (VL) comprising an amino acid sequence that is at least 90% identical to a selected VL sequence, wherein the selected VH sequence and the selected VL sequence are one of the following: (1) the selected VH sequence is SEQ ID NO: 11, and the selected VL sequence is SEQ ID NO: 12; (2) the selected VH sequence is SEQ ID NO: 21, and the selected VL sequence is SEQ ID

Box No. IV Lack of unity of invention

NO: 22; (3) the selected VH sequence is SEQ ID NO: 31, and the selected VL sequence is SEQ ID NO: 32; (4) the selected VH sequence is SEQ ID NO: 41, and the selected VL sequence is SEQ ID NO: 42; (5) the selected VH sequence is SEQ ID NO: 51, and the selected VL sequence is SEQ ID NO: 52; (6) the selected VH sequence is SEQ ID NO: 61, and the selected VL sequence is SEQ ID NO: 62; (7) the selected VH sequence is SEQ ID NO: 71, and the selected VL sequence is SEQ ID NO: 72; (8) the selected VH sequence is SEQ ID NO: 81, and the selected VL sequence is SEQ ID NO: 82; (9) the selected VH sequence is SEQ ID NO: 83, and the selected VL sequence is SEQ ID NO: 84; (10) the selected VH sequence is SEQ ID NO: 85, and the selected VL sequence is SEQ ID NO: 86; (11) the selected VH sequence is SEQ ID NO: 87, and the selected VL sequence is SEQ ID NO: 88; (12) the selected VH sequence is SEQ ID NO: 89, and the selected VL sequence is SEQ ID NO: 90; and (13) the selected VH sequence is SEQ ID NO: 91, and the selected VL sequence is SEQ ID NO: 92.”

Additionally, even if Groups I+ were considered to share the technical features of an antibody or antigen-binding fragment thereof that binds to CLEC5A (C-type lectin domain family 5 member A) comprising: a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3; a light chain variable region (VL) comprising CDRs 1, 2, and 3; wherein the antibody or antigen-binding fragment thereof can mediate phagocytosis of macrophages (e.g., with a target cell killing efficacy that is at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 110%, at least 120%, at least 130%, at least 140%, or at least 150% as compared to that of a reference antibody (e.g., DX244)), and/or wherein the antibody or antigen-binding fragment thereof can induce a low level of cytokine (e.g., IL-6 or TNFα) release (e.g., less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, less than 5%, or less than 1% as compared to that induced by a reference antibody; and an antibody or antigen-binding fragment thereof, comprising: i) a first antigen-binding domain that specifically binds to a first antigen, wherein the first antigen is a tumor associated antigen (TAA); and ii) a second antigen-binding domain that specifically binds to C-type lectin domain family 5 member A (CLEC5A); or i) a first antigen-binding domain that specifically binds to a first antigen, wherein the first antigen is an autoimmune disease target; and ii) a second antigen-binding domain that specifically binds to CLEC5A. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2019/0336615 A1 to Silverback Therapeutics Inc. discloses an antibody or antigen-binding fragment thereof that binds to CLEC5A (C-type lectin domain family 5 member A) (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]) comprising: a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3; a light chain variable region (VL) comprising CDRs 1, 2, and 3 (HCDR1 ...HCDR2 ...HCDR3 ...VH ...LCDR1 ...LCDR2 ...LCDR3 ...VL, Para. [0008]); and an antibody or antigen-binding fragment thereof, comprising: i) a first antigen-binding domain that specifically binds to a first antigen (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]), wherein the first antigen is a tumor associated antigen (TAA) (when the recombinant bispecific antibody is bound to the tumor associated antigen, Para. [0008]); and ii) a second antigen-binding domain that specifically binds to C-type lectin domain family 5 member A (CLEC5A) (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]); or i) a first antigen-binding domain that specifically binds to a first antigen, wherein the first antigen is an autoimmune disease target (a cell surface marker recognized by the antigen binding domain can include macromolecules associated with viral and bacterial diseases or infections, autoimmune diseases and cancerous diseases, Para. [0255]); and ii) a second antigen-binding domain that specifically binds to CLEC5A (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]). Further, in regards to the limitation relating to, “wherein the antibody or antigen-binding fragment thereof can mediate phagocytosis of macrophages, and/or wherein the antibody or antigen-binding fragment thereof can induce a low level of cytokine release,” a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to distinguish the claimed invention from the prior art. If the prior art is capable of performing the intended use, it meets the claim.

**WRITTEN OPINION OF THE
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International application No.

PCT/US2024/037706

Box No. IV

Lack of unity of invention

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

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, 2, 18, 19, 32, 34

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2024/037706

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, 2, 18, 19, 32, 34	YES
	Claims	None	NO
Inventive step (IS)	Claims	1, 2, 18, 19, 32, 34	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1, 2, 18, 19, 32, 34	YES
	Claims	None	NO

2. Citations and explanations:

----- EXPLANATION -----

Claims 1, 2, 18, 19, 32, and 34 have been analyzed subject to the restriction that the claims read on an antibody comprising a heavy chain variable chain region (VH) and a light chain variable region (VL), where the VH is selected to be SEQ ID NO:11, further comprising a HCDR1 (SEQ ID NO:3), HCDR2 (SEQ ID NO:5), HCDR3 (SEQ ID NO:7), and where the VL is selected to be SEQ ID NO:12, further comprising a LCDR1 (SEQ ID NO:8), LCDR2 (SEQ ID NO:9), and a LCDR3 (SEQ ID NO:10).

Claims 1, 2, 18, 19, 32, and 34 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 to CLEC5A(C-type lectin domain family 5 member A) comprising: a heavy chain variable region (VH) of SEQ ID NO:11 comprising a VH CDR1 region of SEQ ID NO:3, the VH CDR2 region of SEQ ID NO:5, and the VH CDR3 region of SEQ ID NO:7; and a light chain variable region (VL) of SEQ ID NO:12, comprising VL CDR1 region of SEQ ID NO:8, the VL CDR2 region of SEQ ID NO:9, and the VL CDR3 region of SEQ ID NO:10.

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

(i) US 2019/0336615 A1 to Silverback Therapeutics Inc. (hereinafter, "Silverback") teaches an antibody or antigen-binding fragment thereof that binds to CLEC5A (C-type lectin domain family 5 member A) (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]) comprising: a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3; a light chain variable region (VL) comprising CDRs 1, 2, and 3 (HCDR1 ...HCDR2 ...HCDR3 ...VH ...LCDR1 ...LCDR2 ...LCDR3 ...VL, Para. [0008]); and an antibody or antigen-binding fragment thereof, comprising: i) a first antigen-binding domain that specifically binds to a first antigen (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]), wherein the first antigen is a tumor associated antigen (TAA) (hen the recombinant bispecific antibody is bound to the tumor associated antigen, Para. [0008]); and ii) a second antigen-binding domain that specifically binds to C-type lectin domain family 5 member A (CLEC5A) (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]); or i) a first antigen-binding domain that specifically binds to a first antigen, wherein the first antigen is an autoimmune disease target (a cell surface marker recognized by the antigen binding domain can include macromolecules associated with viral and bacterial diseases or infections, autoimmune diseases and cancerous diseases, Para. [0255]); and ii) a second antigen-binding domain that specifically binds to CLEC5A (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]).

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

None of the prior art taken alone or in combination fairly teach or suggest an antibody that binds to CLEC5A(C-type lectin domain family 5 member A) comprising: a heavy chain variable region (VH) of SEQ ID NO:11 comprising a VH CDR1 region of SEQ ID NO:3, the VH CDR2 region of SEQ ID NO:5, and the VH CDR3 region of SEQ ID NO:7; and a light chain variable region (VL) of SEQ ID NO:12, comprising VL CDR1 region of SEQ ID NO:8, the VL CDR2 region of SEQ ID NO:9, and the VL CDR3 region of SEQ ID NO:10.

Claims 2 and 32 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 18, the prior art of record, individually or in combination, does not teach or fairly suggest an antibody that binds to CLEC5A comprising a heavy chain variable region (VH) of SEQ ID NO:11 comprising a VH CDR1 region of SEQ ID NO:3, the VH CDR2 region of SEQ ID NO:5, and the VH CDR3 region of SEQ ID NO:7; and a light chain variable region (VL) of SEQ ID NO:12, comprising VL CDR1 region of SEQ ID NO:8, the VL CDR2 region of SEQ ID NO:9, and the VL CDR3 region of SEQ ID NO:10.

The following prior art is made of record to support and further define the reasons why claim 18 meets the criteria set out in PCT Article 33(2)-(3):

(i) Silverback teaches an antibody or antigen-binding fragment thereof that binds to CLEC5A (C-type lectin domain family 5 member A) (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]) comprising: a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3; a light chain variable region (VL) comprising CDRs 1, 2, and 3 (HCDR1 ...HCDR2 ...HCDR3 ...VH ...LCDR1 ...LCDR2 ...LCDR3 ...VL, Para. [0008]); and an antibody or antigen-binding fragment thereof, comprising: i) a first antigen-binding domain that specifically binds to a first antigen (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]), wherein the first antigen is a tumor associated antigen (TAA) (hen the recombinant bispecific antibody is bound to the tumor associated antigen, Para. [0008]); and ii) a second antigen-binding domain that specifically binds to C-type lectin domain family 5 member A (CLEC5A) (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]); or i) a first antigen-binding domain that specifically binds to a first antigen, wherein the first antigen is an autoimmune disease target (a cell surface marker recognized by the antigen binding domain can include macromolecules associated with viral and bacterial diseases or infections, autoimmune diseases and cancerous diseases, Para. [0255]); and ii) a second antigen-binding domain that specifically binds to CLEC5A (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]).

None of the prior art taken alone or in combination fairly teach or suggest an antibody that binds to CLEC5A(C-type lectin domain family 5 member A) comprising: a heavy chain variable region (VH) of SEQ ID NO:11 comprising a VH CDR1 region of SEQ ID NO:3, the VH CDR2 region of SEQ ID NO:5, and the VH CDR3 region of SEQ ID NO:7; and a light chain variable region (VL) of SEQ ID NO:12, comprising VL CDR1 region of SEQ ID NO:8, the VL CDR2 region of SEQ ID NO:9, and the VL CDR3 region of SEQ ID NO:10.

Claims 19 and 32 depend from claim 18, and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 18.

Regarding claim 34, the prior art of record, individually or in combination, does not teach or fairly suggest an antibody or antigen-binding fragment thereof that binds to CLEC5A, comprising a heavy chain variable region (VH) of SEQ ID NO:11 comprising a VH CDR1 region of SEQ ID NO:3, the VH CDR2 region of SEQ ID NO:5, and the VH CDR3 region of SEQ ID NO:7; and a light chain variable region (VL) of SEQ ID NO:12, comprising VL CDR1 region of SEQ ID NO:8, the VL CDR2 region of SEQ ID NO:9, and the VL CDR3 region of SEQ ID NO:10; wherein the antibody or antigen-binding fragment thereof can

Box No. V	Reasoned statement under Rule 43<i>bis</i>.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
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mediate phagocytosis of macrophages, and/or wherein the antibody or antigen-binding fragment thereof can induce a low level of cytokine release.

The following prior art is made of record to support and further define the reasons why claim 34 meets the criteria set out in PCT Article 33(2)-(3):

(i) Silverback teaches an antibody or antigen-binding fragment thereof that binds to CLEC5A (C-type lectin domain family 5 member A) (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]) comprising: a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3; a light chain variable region (VL) comprising CDRs 1, 2, and 3 (HCDR1 ...HCDR2 ...HCDR3 ...VH ...LCDR1 ...LCDR2 ...LCDR3 ...VL, Para. [0008]); and an antibody or antigen-binding fragment thereof, comprising: i) a first antigen-binding domain that specifically binds to a first antigen (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]), wherein the first antigen is a tumor associated antigen (TAA) (hen the recombinant bispecific antibody is bound to the tumor associated antigen, Para. [0008]); and ii) a second antigen-binding domain that specifically binds to C-type lectin domain family 5 member A (CLEC5A) (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]); or i) a first antigen-binding domain that specifically binds to a first antigen, wherein the first antigen is an autoimmune disease target (a cell surface marker recognized by the antigen binding domain can include macromolecules associated with viral and bacterial diseases or infections, autoimmune diseases and cancerous diseases, Para. [0255]); and ii) a second antigen-binding domain that specifically binds to CLEC5A (a recombinant bispecific antibody, comprises: a) a target antigen binding domain, Para. [0005]; an antigen selected from the group consisting of...CLEC5A, Para. [0017]).

None of the prior art taken alone or in combination fairly teach or suggest an antibody or antigen-binding fragment thereof that binds to CLEC5A, comprising a heavy chain variable region (VH) of SEQ ID NO:11 comprising a VH CDR1 region of SEQ ID NO:3, the VH CDR2 region of SEQ ID NO:5, and the VH CDR3 region of SEQ ID NO:7; and a light chain variable region (VL) of SEQ ID NO:12, comprising VL CDR1 region of SEQ ID NO:8, the VL CDR2 region of SEQ ID NO:9, and the VL CDR3 region of SEQ ID NO:10; wherein the antibody or antigen-binding fragment thereof can mediate phagocytosis of macrophages, and/or wherein the antibody or antigen-binding fragment thereof can induce a low level of cytokine release.

Claims 1, 2, 18, 19, 32, and 34 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.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2024/037706

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 33 contains exemplary claim language (e.g.), which renders the intended scope of the claim unclear. Herein, claim 33 has been interpreted without the exemplary claim language.

Claims 34 and 36 contain exemplary claim language (e.g.), which renders the intended scope of the claim unclear. For the purposes of this written opinion, claims 34 and 36 have been interpreted without the exemplary claim language.