

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 55679-0009WO2		FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2024/037706	International filing date (<i>day/month/year</i>) 12 July 2024 (12.07.2024)	(Earliest) Priority Date (<i>day/month/year</i>) 13 July 2023 (13.07.2023)
Applicant LTZ THERAPEUTICS INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out 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)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 9A
☐ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☒ as selected by this Authority, because this figure better characterizes the invention.
- b. ☐ none of the figures is to be published with the abstract.

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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.
 - 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.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

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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.: **33, 38-42, 46-79**
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 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:

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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 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 TNFa) 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

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Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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.

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

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, 2, 18, 19, 32, 34**

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.

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A. CLASSIFICATION OF SUBJECT MATTERIPC: **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**

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	US 2020/0289631 A1 (IMMATICS BIOTECHNOLOGIES GMBH) 17 September 2020 (17.09.2020) entire document	1, 2, 18, 19, 32, 34
A	WO 2023/012356 A2 (INSERM (INSTITUT NATIONAL DE LA SANTÉ ET DE LA RECHERCHE MÉDICALE) et al.) 09 February 2023 (09.02.2023) entire document	1, 2, 18, 19, 32, 34
A	US 2019/0336615 A1 (SILVERBACK THERAPEUTICS INC.) 07 November 2019 (07.11.2019) entire document	1, 2, 18, 19, 32, 34
A	US 2020/0206357 A1 (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY et al.) 02 July 2020 (02.07.2020) entire document	1, 2, 18, 19, 32, 34
A	KEDAGE et al. "CLEC5a-directed bispecific antibody for effective cellular phagocytosis," mAbs, 16 March 2022 (16.03.2022), Vol. 14, Iss. 1, Pgs. 1-12. entire document	1, 2, 18, 19, 32, 34



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

19 December 2024 (19.12.2024)

Date of mailing of the international search report

29 January 2025 (29.01.2025)

Name and mailing address of the ISA/US

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