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(54) Title: COMPOSITION AND METHODS OF TARGETING THE PRE-B CELL RECEPTOR FOR THE TREATMENT OF LEUKEMIAS AND LYMPHOMAS

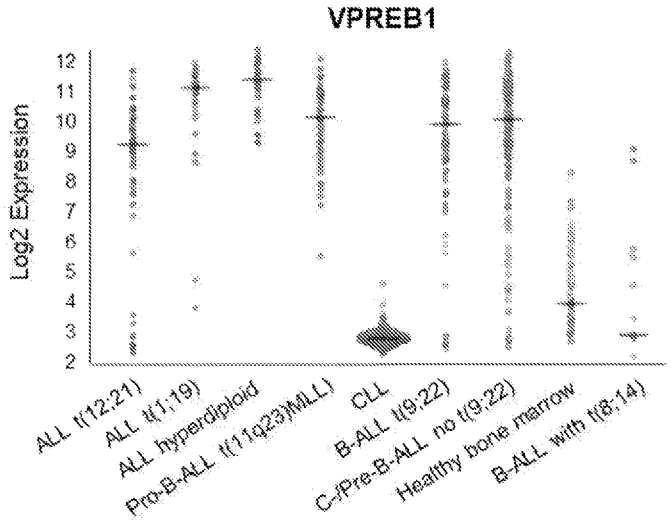


Figure 1A

(57) Abstract: The present invention relates to antibodies that bind the pre-B cell receptor components VpreB and lambda-5, and compositions comprising such antibodies for use in diagnosing and eliminating pre-BCR-expressing leukemia and lymphoma cells. In one aspect, the present invention provides isolated antibodies or an antigen-binding fragment thereof capable of specifically binding to a SLC. The SLC is composed of two noncovalently-linked polypeptides, VpreB and lambda-5.

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[Continued on next page]

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11 March 2021 (11.03.2021)

# INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/00; A61K 39/395; A61K 45/06 (2020.01)
CPC - A61K 39/3955; A61K 39/39558; A61K 45/06; A61K 2039/505 (2020.08)

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. |
|---|---|---|
| X<br>--<br>Y | US 2015/0004162 A1 (SEA LANE BIOTECHNOLOGIES, LLC) 01 January 2015 (01.01.2015) entire document | 1, 2, 38, 39<br>----------<br>40 |
| Y | WANG et al. "Differential surrogate light chain expression governs B-cell differentiation," Blood, 01 April 2002, (01.04.2002), Vol. 99, Iss. 7, Pgs. 2459-2467. entire document | 40 |
| A | US 2019/0004033 A1 (CELGENE CORPORATION) 03 January 2019 (03.01.2019) entire document | 1-3, 5, 38-40 |
| A | US 2018/0282761 A1 (KYMAB LIMITED) 04 October 2018 (04.10.2018) entire document | 1-3, 5, 38-40 |
| A | US 2018/0022805 A1 (WILSON et al) 25 January 2018 (25.01.2018) entire document | 1-3, 5, 38-40 |

☐ 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 | Date of mailing of the international search report |
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| 30 November 2020 | 04 JAN 2021 |
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**INTERNATIONAL SEARCH REPORT**

International application No.
PCT/US2020/042529

**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 13*ter*.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 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.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:

SEQ ID NOs: 1-17, 19, 21, 23, 42, 44, 46, 64, and 70 were searched.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/042529

**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.: 6-9, 12-37, 41, 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 extra sheet(s).

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, 5, and 38-40 to the extent that they read on an antibody of SEQ ID NOs: 6, 12, 19, 21, 23, 42, 44, 46, 64, and 70.

**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/US2020/042529

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

Group I+: claims 1-5, 10, 11, and 38-40 are drawn to anti-pre-B cell receptor antibodies, and methods comprising the same.

The first invention of Group I+ is restricted to an anti-pre-B cell receptor (pre-BCR) antibody, and methods comprising the same, wherein the anti-pre-BCR antibody is selected to be 5-2D7, 5-2D7 comprising a heavy chain variable region, wherein in the heavy chain variable region is selected to be SEQ ID NO:6, encoded by SEQ ID NO:64, the heavy chain further comprising heavy chain complementarity determining regions CDR1, CDR2, and CDR3, wherein CDR1 is selected to be SEQ ID NO:19, CDR2 is selected to be SEQ ID NO:21, and CDR3 is selected to be SEQ ID NO:23; and a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:12, encoded by SEQ ID NO:70, the light chain further comprising light chain complementarity determining regions CDR1, CDR2, and CDR3, wherein CDR1 is selected to be SEQ ID NO:42, CDR2 is selected to be SEQ ID NO:44, and CDR3 is selected to be SEQ ID NO:46. It is believed that claims 1-3, 5, and 38-40 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: 6, 12, 19, 21, 23, 42, 44, 46, 64, and 70.

Applicant is invited to elect additional anti-pre-BCR antibodies, each with a specified SEQ ID NO for each heavy chain variable region and light chain variable region, to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be an anti-pre-B cell receptor (pre-BCR) antibody, and methods comprising the same, wherein the anti-pre-BCR antibody is selected to be 5-4A9, 5-4A9 comprising a heavy chain variable region, wherein in the heavy chain variable region is selected to be SEQ ID NO:7, encoded by SEQ ID NO:65, the heavy chain further comprising heavy chain complementarity determining regions CDR1, CDR2, and CDR3, wherein CDR1 is selected to be SEQ ID NO:19, CDR2 is selected to be SEQ ID NO:26, and CDR3 is selected to be SEQ ID NO:23; and a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:13, encoded by SEQ ID NO:71, the light chain further comprising light chain complementarity determining regions CDR1, CDR2, and CDR3, wherein CDR1 is selected to be SEQ ID NO:48, CDR2 is selected to be SEQ ID NO:44, and CDR3 is selected to be SEQ ID NO:46. Additional anti-pre-BCR antibodies 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 recognizing and binding to a pre-B cell receptor, requiring the selection of alternatives for the amino acid sequences of the heavy and light chain variable regions of the anti-pre-BCR antibodies, where "...[the] VH compris[es] one or more heavy chain CDRs comprising at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identity to any of SEQ ID NO:19, 21, 23, 26, 30,32, 34, 37, or 39 and/or ...[the] VL compris[es] one or more light chain CDRs comprising at least 80%, 85%, 90%, 95%, 98%, 99% or 100% identity to any of SEQ ID NO:42, 44, 46, 48, 53, 55, or 56".

Additionally, even if Groups I+ were considered to share the technical features of an isolated antibody specific for pre-BCR, or antigen-binding fragment thereof, that specifically binds to human pre-BCR, optionally as part of a sterile composition comprising pharmaceutically acceptable excipients; an isolated antibody, or antigen-binding fragment that specifically binds to the VpreB subunit of the SLC of human pre-BCR, a VH comprising a HC CDR1, a HC CDR2, a HC CDR3, and/or a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3; an isolated antibody, or antigen-binding fragment that specifically binds to the lambda-5 subunit of the SLC of human pre-BCR; and a method of treating a leukemia or lymphoma in a companion animal, such as a dog or a cat, comprising administering a therapeutically effective amount of a monoclonal antibody or antigen-binding fragment thereof that specifically binds to cells expressing pre-BCR; these shared technical features do not represent a contribution over the prior art.

Specifically, US 2015/0004162 A1 to Sea Lane Biotechnologies, LLC discloses an isolated antibody specific for pre-BCR (antibodies isolated, Para. [0100]), or antigen-binding fragment thereof, that specifically binds to human pre-BCR (anti-VpreB antibody, Para. [0321]); an isolated antibody (antibodies isolated, Para. [0100]), or antigen-binding fragment that specifically binds to the VpreB subunit of the SLC of human pre-BCR (anti-VpreB antibody, Para. [0321]), a VH comprising a HC CDR1, a HC CDR2, a HC CDR3, and/or a VL comprising a LC CDR1, a LC CDR2, and a LC CDR3 (antibody that includes at least one humanized immunoglobulin or antibody chain (i.e., at least one humanized light or heavy chain). The term "humanized immunoglobulin chain" or "humanized antibody chain" (i.e., a "humanized immunoglobulin light chain" or "humanized immunoglobulin heavy chain") refers to an immunoglobulin or antibody chain (i.e., a light or heavy chain, respectively) having a variable region that includes a variable framework region substantially from a human immunoglobulin or antibody and complementarity determining regions (CDRs), Para. [0104]; CDR is CDR1, CDR2, or CDR3, Para. [0122]); a method of treating a leukemia or lymphoma in a companion animal, such as a dog or a cat, (a method of treating cancer is provided, Para. [0017]; subject can be an animal, including but not limited to ...cats and dogs, Para. [0263]) comprising administering a therapeutically effective amount of a monoclonal antibody or antigen-binding fragment thereof that specifically binds to cells expressing pre-BCR (antibodies in an amount effective to treat the disease, Para. [0253]; antibodies disclosed herein are administered to patients, Para. [0255]; monoclonal antibody ...anti-VpreB antibody, Para. [0321]; cells expressing or overexpressing target molecules in vivo, Para. [0295]).

"Differential surrogate light chain expression governs B-cell differentiation," to Wang et al. discloses an antibody, or antigen-binding fragment that specifically binds to the lambda-5 subunit of the SLC of human pre-BCR (monoclonal anti-VpreB/5 antibodies to readdress the issue of SLC expression during B lineage differentiation, Pg. 2460, left-hand column, first paragraph).

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