(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 September 2016 (15.09.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/144728 A3

(51) International Patent Classification:
A61K 38/18 (2006.01) *A61K 38/07* (2006.01)
A61K 35/15 (2015.01)

(21) International Application Number:
PCT/US2016/020838

(22) International Filing Date:
4 March 2016 (04.03.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/129,572 6 March 2015 (06.03.2015) US

(71) Applicant: **THE BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM** [US/US]; 201 West 7th Street, Austin, TX 78701 (US).

(72) Inventors: **ZHANG, Chengcheng**; 4501 Druid Lane, Apt. 117, Dallas, TX 75205 (US). **DENG, Mi**; 4712 Bull Run Drive, Plano, TX 75093 (US). **AN, Zhiqiang**; C/o Ut Health Science Center At Houston, 7000 Fannin Street, Suite 720, Houston, TX 77030 (US). **XIONG, Wei**; 3618 Abbeywood Drive, Pearland, TX 77584 (US). **ZHANG, Ningyan**; C/o Ut Health Science Center At Houston, 7000 Fannin Street, Suite 720, Houston, TX 77030 (US). **ZHENG, Junke**; C/o Shanghai Jiao-tong University School Of Medici, Chongqing South Road 280, Shanghai, 200025 (CN). **GUI, Xun**; C/o Ut Health Science Center At Houston, 7000 Fannin Street, Suite 720, Houston, TX 77030 (US).

(74) Agent: **HIGHLANDER, Steven, L.**; Parker Highlander PLLC, 1120 S. Capital Of Texas Highway, Building One, Suite 200, Austin, TX 78746 (US).

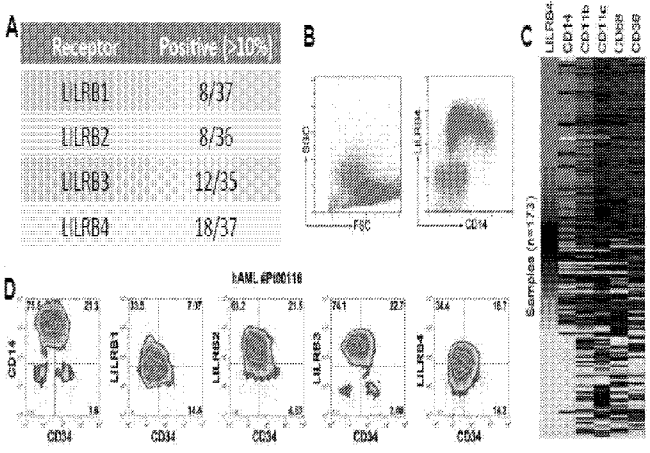
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,

[Continued on next page]

(54) Title: ANTI-LILRB ANTIBODIES AND THEIR USE IN DETECTING AND TREATING CANCER

(57) Abstract: The present disclosure is directed to antibodies binding to LILRBs and methods of detecting and treating cancer therewith.



FIGS. 1A-D

WO 2016/144728 A3

LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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:
27 October 2016

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/20838

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:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/20838

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.: 6-8, 12-15, 22-25, 32-35
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:

Claims 6-8, 12-15, 22-25 and 32-35 are unsearchable under Article 34(4)(a)(ii). In particular, the claims, in referring to an illegible drawing, are so unclear that no meaningful opinion can be formed on the novelty, inventive step or industrial applicability of the claimed invention(s).

3. ☐ Claims Nos.:
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:

-***-Continued Within the Next 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.:
1-5, 9-11, 16-21, 26-31; restricted to SEQ ID NOs: 160-165

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/US16/20838

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/18, 35/15, 38/07 (2016.01)
CPC - A61K 45/06, 38/16, 31/713; C07K 16/2803
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)
IPC(8) Classifications: A61K 38/18, 35/15, 38/07 (2016.01)
CPC Classifications: A61K 45/06, 38/16, 31/713; C07K 16/2803

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO); USPTO Web Page; Google; Google Scholar; EBSCO: Entrez Pubmed; NCBI BLAST; Lens.org; ENA; Search terms -- cancer, detection, antibody, 'clone-paired, 'heavy chain', 'light chain', CDR, treatment, AML, sample, humanized antibody, chimeric antibody, IgG, intravenous

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2011/0044894 A1 (KARSUNKY, H) February 24, 2011; abstract; paragraphs [0015], [0018], [0019], [0023], [0028], [0035], [0036], [0046], [0056], [0083], [0104], [0176], [0178], [0198], [0202]	1-5, 9-11, 16-21, 26-31
A	US 2012/0328616 A1 (LI, Y et al.) December 27, 2012; paragraphs [0117], [0120]	1-5, 9-11, 16-21, 26-31
A	US 2006/0223096 A1 (UMANA, P et al.) October 05, 2006; paragraphs [0016], [0130]; SEQ ID NO: 72	1-5, 9-11, 16-21, 26-31
A	US 2005/0287538 A1 (CHEUNG, W-T, et al.) December 29, 2005; SEQ ID NO: 121	1-5, 9-11, 16-21, 26-31
A	US 2009/0041783 A1 (TAKAYAMA, H, et al.) February 12, 2009; paragraphs [0026], [0084], SEQ ID NO: 35	1-5, 9-11, 16-21, 26-31
A	WO 2014/059028 A1 (INGENCIA, INC.) April 17, 2014; page 5, lines 10-20; page 38, line 2; page 39, line 9; SEQ ID NO: 256	1-5, 9-11, 16-21, 26-31
A	US 2002/0176855 A1 (CO, MS et al.) November 28, 2002; paragraphs [0004], [0005]; SEQ ID NO: 18	1-5, 9-11, 16-21, 26-31
A	US 2014/0356364 A1 (LANGERMANN, S et al.) December 04, 2014; paragraphs [0155], [0267]; SEQ ID NO: 18	1-5, 9-11, 16-21, 26-31

☐ 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
"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
16 August 2016 (16.08.2016)	08 SEP 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US16/20838

-***-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 must be paid.

Groups I+, Claims 1-5, 9-11, 16-21, 26-31 and SEQ ID NOs: 160, 161, 162, 163, 164 and 165 are directed toward a monoclonal antibody for methods for detecting a cancer cell or cancer stem cell in a sample and for treating a subject having cancer; and a hybridoma comprising a nucleic acid encoding said antibody.

The antibody, methods and hybridoma will be searched to the extent that the antibody comprises a heavy chain variable region comprising a CDR1 encompassing SEQ ID NO: 160 (first exemplary HCDR1), a CDR2 encompassing SEQ ID NO: 161 (first exemplary HCDR2) and a CDR3 encompassing SEQ ID NO: 162 (first exemplary HCDR3); and a light chain variable region comprising a CDR1 encompassing SEQ ID NO: 163 (first exemplary LCDR1), a CDR2 encompassing SEQ ID NO: 164 (first exemplary LCDR2) and a CDR3 encompassing SEQ ID NO: 165 (first exemplary LCDR3). Applicant is invited to elect additional antibody(ies) comprising set(s) of heavy and light chain CDRs, with specified set(s) of SEQ ID NOs: for each antibody, to be searched. Additional set(s) of antibody CDR sequences will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 2 (in-part), 3 (in-part), 4 (in-part), 5 (in-part), 9 (in-part), 10 (in-part), 11 (in-part), 16 (in-part), 17 (in-part), 18 (in-part), 19 (in-part), 20 (in-part), 21 (in-part), 26 (in-part), 27 (in-part), 28 (in-part), 29 (in-part), 30 (in-part) and 31 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 160 (HCDR1), SEQ ID NO: 161 (HCDR2) SEQ ID NO: 162 (HCDR3), SEQ ID NO: 163 (LCDR1), SEQ ID NO: 164 (LCDR2) and SEQ ID NO: 165 (LCDR3). 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. An exemplary election would be an antibody a heavy chain variable region comprising a CDR1 encompassing SEQ ID NO: 166 (first exemplary elected HCDR1), a CDR2 encompassing SEQ ID NO: 167 (first exemplary elected HCDR2) and a CDR3 encompassing SEQ ID NO: 168 (first exemplary elected HCDR3); and a light chain variable region comprising a CDR1 encompassing SEQ ID NO: 169 (first exemplary elected LCDR1), a CDR2 encompassing SEQ ID NO: 170 (first exemplary elected LCDR2) and a CDR3 encompassing SEQ ID NO: 171 (first exemplary elected LCDR3).

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

Groups I+ share the technical features including: a method of detecting a cancer cell or cancer stem cell in a sample or subject comprising: (a) contacting a subject or a sample from said subject with an antibody or antibody fragment having heavy and light chain CDR sequences; and (b) detecting binding of said antibody to a cancer cell or cancer stem cell in said subject or sample; a method of treating a subject having cancer comprising administering to said subject an antibody or antibody fragment having heavy and light chain CDR sequences; a monoclonal antibody or antibody fragment, wherein the antibody is characterized by heavy and light chain CDR sequences; and a hybridoma comprising a nucleic acid encoding an antibody characterized by heavy and light chain CDR sequences.

However, these shared technical features are previously disclosed by US 2010/0104509 A1 to King et al. (hereinafter 'King').

King discloses a method of detecting a cancer cell or cancer stem cell in a sample or subject (detecting CD19 expressed on the surface of cells, including tumor cells (a method of detecting a cancer cell in a sample or subject); paragraphs [0005], [0744], [0747]) comprising: (a) contacting a subject or a sample from said subject (comprising: (a) contacting a subject or a sample from said subject; paragraphs [0005], [0747]) with an antibody or antibody fragment (with an antibody or antibody fragment; paragraphs [0005], [0747]) having heavy and light chain CDR sequences (having heavy and light chain CDR sequences; paragraph [0026]); and (b) detecting binding of said antibody to a cancer cell or cancer stem cell in said subject or sample (detecting binding of said antibody to a cancer cell or cancer stem cell in said subject or sample; paragraphs [0005], [0744], [0747]); a method of treating a subject having cancer comprising administering to said subject an antibody or antibody fragment (a method of treating a subject having cancer comprising administering to said subject an antibody or antibody fragment; paragraphs [0180], [0184]) having heavy and light chain CDR sequences (having heavy and light chain CDR sequences; paragraph [0026]); a monoclonal antibody or antibody fragment (a monoclonal antibody or antibody fragment; paragraph [0026]), wherein the antibody is characterized by heavy and light chain CDR sequences (wherein the antibody is characterized by heavy and light chain CDR sequences; paragraph [0026]); and a hybridoma comprising a nucleic acid encoding an antibody (a hybridoma comprising a nucleic acid encoding an antibody; paragraphs [0255], [0477]) characterized by heavy and light chain CDR sequences (characterized by heavy and light chain CDR sequences; paragraph [0026]).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the King reference, unity of invention is lacking.